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GABAergic Interneurons in Severe Early Epileptic Encephalopathy with a Suppression-Burst Pattern: A Continuum of Pathology

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Additional information is available at the end of the chapter

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Abstract

Early infantile epileptic encephalopathy (EIEE) and early myoclonic encephalopathy (EME) are catastrophic epilepsies starting in the neonatal period. The International League Against Epilepsy classifies both of them as generalized symptomatic epilepsies of nonspecific etiology, characterized by early onset, presence of burst-suppression EEG pattern and serious prognosis. The critical difference lies in their presumed etiologies and the prevailing clinical seizure type at onset: EIEE (known as Ohtahara syndrome) usually manifests with tonic seizures, while EME is mainly associated with myoclonic seizures. However, the distinction between those two pathologies is not always easy due to clinical and etiological overlap. Both mutations in the ARX gene for EIEE (OMIM 308350) and disruption in the neuregulin receptor ErbB4 for EME (OMIM 609304) impair interneuron migration and alter the number of GABAergic interneurons in the postnatal cortex. These findings could explain the occurrence of severe epileptic encephalopathy with a burst-suppression pattern and represent a continuum of progressive pathology. In the present chapter we review the genes involved in EIEE and EME including their possible mechanisms of action, particularly via GABAergic interneurons. Their clinical manifestations are myoclonic or tonic seizures, which represent the expression of the underlying pathology and correlate with degree of brain damage.

Keywords: ARX gene, burst-suppression EEG pattern, early infantile epileptic encephalopathy, early myoclonic encephalopathy, early-onset epileptic encephalopathy, encephalopathy, epilepsy, ErbB4, GABA, interneurons, genetics, development, children, neonatal epilepsies, newborn, Ohtahara syndrome, seizures

1. Introduction

Neonatal seizures are the most characteristic sign of neurological disease and the most frequent neurological events during the neonatal period (babies less than 28 days old), often reflecting a variety of different pre-, peri-, or postnatal disorders of the central nervous system (CNS). The incidence of seizures is highest during the neonatal period. The overall risk of neonatal seizures in the United States was 2.84 per 1000 live births, and risk estimates were consistently higher in low-birth-weight infants (relative risk of 3.9) [1]. We have found an absolute incidence of neonatal convulsions in newborns (NBs) infants of 2‰ in live births (in full term of 1.4‰, in preterm of 13.4‰, and in immature NBs (with a gestational age of <29 weeks) of 27.8‰) [2]. Besides, higher incidence and prevalence rates of epilepsy have been found in developing countries [3]. They may be symptomatic or cryptogenic, precursory or subsequent epilepsies, and acquired causes are the most frequent. Thus, in our study the etiology was distributed as follows: hypoxic-ischemic encephalopathy (HIE, 32%), brain malformations or cerebral dysgenesis (24%), intracranial hemorrhage (16%), and, less frequently, infections, metabolic disorders and pharmacological changes (8%), and epileptogenic diagnosis (4%). Notwithstanding, we are currently observing a decrease down to 7.9% in brain malformations as a cause of neonatal seizures due to the impact of the implementation of the legal termination of pregnancy due to congenital anomalies or birth defects.

The neonatal period is the most vulnerable time for the occurrence of seizures. Overall, neonatal seizures are the expression of a serious neurological condition that requires urgently both etiological and symptomatic treatment, because by themselves can aggravate brain damage. The study of neonatal seizures also allows us to better understand the mechanisms that affect the developing brain [4]. The burden of acute recurrent seizures in neonates may also impact chronic outcomes independently from the etiology [5].

The developing brain has a higher incidence of seizures in both animal and human models. These neonatal seizures can produce long-lasting consequences that are stage-dependent [6]. The nervous system (NS) of the newborn presents singularities related to the lower maturation of its structures. The neonatal brain has an increased neuronal metabolism, and, therefore, a high rate of oxygen consumption. Such energetic costs seem also to exert a selective pressure toward a metabolically efficient neural morphology, leading to a metabolically efficient patterning of dendritic arborizations, neural codes, and brain-wiring patterns [7]. However, the theory of energy failure has largely been disproved. Brains of immature animals have been shown to be capable of using anaerobic metabolism and require less adenosine triphosphate (ATP) when aerobic energy production ceases, even during status convulsivus. Recent explanations for the injurious consequences of prolonged convulsions postulate that neuronal damage occurs from excessive release of excitatory amino acids (EAA) which, by binding to their ligand-gated ionic receptors, cause a large influx of Ca^{2+} , resulting in acute excitotoxic cell death and neuronal apoptosis [8].

On the other hand, neurotransmitters (NTs)—especially γ -aminobutyric acid (GABA) and glutamate—as well as N-methyl-D-aspartate receptors (NMDARs) play key roles in successive

steps of brain development, including the proliferation, migration, survival, and differentiation of neurons. Cerebral cortical circuits are composed of both excitatory (glutamatergic) projection and local inhibitory (GABAergic) neurons. The NMDA receptor subunits in the developing brain are more permeable and less susceptible to block than mature forms, with the result that immature brains are far more excitable and epileptogenic than the adult brain (9). Although in general the neonatal brain is more resistant to hypoxia than the adult brain, the former seems to be more vulnerable to the neurotoxic amino acids that occur during seizures [9].

Although early-onset epileptic syndromes are a rare and not a common cause for neonatal seizures, they have aroused increasing interest since they generally involve genetic diseases. Thus, it is very important to establish the diagnosis in order to allow adequate genetic counseling. The study of these syndromes has also helped to clarify the role of NTs and receptors, signal transduction, intracellular transporters, and enzymes in the origin of seizures. More accurate molecular genetics diagnostic tools will allow diagnosing a larger number of cases previously considered of unknown etiology and open the door to pharmacogenomics.

2. Neonatal epileptic encephalopathy (EE) with suppression-burst EEG pattern

2.1. Concept of epileptic encephalopathies

The International League Against Epilepsy (ILAE) defines epileptic encephalopathies (EEs) as follows: they “are a group of diseases in which epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. These impairments can worsen over time” [10]. This means that not only refractory seizures but also that serious epileptiform discharges observed in the electroencephalogram (EEG) background contribute to the progressive decline in brain function. The three main features of EEs are refractory seizures, severe EEG abnormalities, developmental delay, and/or intellectual disability. Around 40% of seizures that occur during the first 3 years of life are due to EEs. A few syndromes are considered epileptic encephalopathies, also known as early-onset epileptic encephalopathies (EOEEs) (for a review, see [11, 12]):

- Early myoclonic encephalopathy (EME) and Ohtahara syndrome (OS) in the neonatal period;
- West syndrome (WS), epilepsy of infancy with migrating focal seizures (EIMFS), and Dravet’s syndrome (DS) during infancy;
- Lennox-Gastaut syndrome (LGS), epileptic encephalopathy with continuous spikes and waves during sleep (CSWS), and Landau-Kleffner syndrome (LKS) during childhood.

2.2. Classification epilepsy syndromes

In the last International Classification of the Epilepsies (ILAE classification), the epilepsy syndromes are classified by reliably identified common clinical and electrical characteristics. Such “electro-clinical” syndromes have a typical age of seizure onset, specific seizure types, and EEG characteristics, and often other features, which when taken together allow the diagnosis of every specific epilepsy syndrome [13]. The classification, which has been updated on an ongoing basis by the ILAE Commission on Classification and Terminology in Epilepsy Diagnosis [14] (a cutting-edge online diagnostic manual of the epilepsies), includes within the *electro-clinical syndromes* of neonatal/infantile onset the following syndromes (arranged by age at onset):

2.2.1. Neonatal period

- Self-limited neonatal seizures and self-limited familial neonatal epilepsy
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome (OS) or early infantile epileptic encephalopathy (EIEE)

2.2.2. Infancy

- Self-limited familial and nonfamilial infantile epilepsy
- West syndrome (WS)
- Dravet’s syndrome (DS)
- Myoclonic epilepsy in infancy (MEI)
- Epilepsy of infancy with migrating focal seizures (EIMFS)
- Myoclonic encephalopathy in nonprogressive disorders
- Febrile seizures plus, genetic epilepsy with febrile seizures plus

“Early myoclonic encephalopathy” (EME) and “Ohtahara syndrome” (OS), are listed as two separate syndromes in the classification of epilepsies. Both are characterized by early onset (EIEE may also occur later), presence of “burst-suppression” (BS) EEG pattern, seizures that do not respond to anti-seizure medication, and serious prognosis. EEG pattern is the most important diagnostic feature for both clinical entities. BS means that the EEG tends to display periods of very little electrical brain activity or flattening of the brain waves, followed by a burst of high spiky activity before returning to very low activity again. The BS is characterized by high-voltage bursts (multifocal spikes of 150–350 mV, and 1–3-s duration) alternating regular rate with almost flat suppression phases (2–5 s). These changes can be seen both during sleep and when the child is awake [15]. The differential diagnosis is based mainly on the different types of seizures: fragmentary myoclonus, erratic focal seizures, and massive myoclonias for EME, and tonic seizures and predominantly tonic spasms (flexor or extensor/stiffening of arms or legs, uni-, or bilateral) for EIEE [16, 17] (see **Table 1**).

	Early myoclonic encephalopathy (EME)	Early infantile epileptic encephalopathy (EIEE) Ohtahara syndrome
General description	<ul style="list-style-type: none"> Both entities are syndromes consisting of frequent intractable seizures and severe early encephalopathy resulting in limited development and reduced life expectancy. They are considered “epileptic encephalopathies”. This term implies that the epileptic activity itself might be directly implicated in additional neurodevelopmental impairments besides those expected from the underlying etiology alone, and that suppression of epileptic activity might minimize this additional disability. Treatable <i>metabolic etiologies</i> (especially pyridoxine and pyridoxal-5-phosphate disorders) should be excluded early. Both sexes are affected equally. 	
Age of occurrence	Onset of seizures in the first 2 months of life (during the first week in 76% of the cases, with 96% occurring by the first month)	The onset of seizures is in the first month of life (range 1–3 months).
Different seizure types	<p>Myoclonic seizures are frequent: fragmentary myoclonus, erratic focal seizures, and massive myoclonias.</p> <p>Tonic seizures are observed later, usually around 3–4 months of age.</p>	<p>Tonic seizures predominate.</p> <p>Many seizure types may occur, but myoclonic seizures are rare.</p>
Electroencephalograph	Suppression-burst pattern: <i>Consisting of alternating periods of slow waves of high amplitude (the burst) and periods of so-called flat EEGs (the suppression)</i>	
Clinical course	Severe developmental delay is seen, with or without regression.	Children with this syndrome may evolve to West or Lennox Gastaut syndrome.
Antecedent and birth history	Typically normal	
Neurological examination	Abnormal neurological behavior may be present prior to onset of seizures.	
	Abnormal in keeping with the presence of severe neurological impairment. <i>Head size is typically normal at onset; microcephaly may develop over time.</i>	Abnormal in keeping with underlying brain structure abnormalities and the presence of severe neurological impairment. Head size is typically normal; however, microcephaly may occur.
Causes: There is overlap in the etiologies that cause Ohtahara syndrome and early myoclonic encephalopathy.	Metabolic etiologies are common (nonketotic hyperglycinemia is the commonest cause, amino and organic acidopathies, urea cycle disorders, mitochondrial disorders, pyridoxine and pyridoxal-5-phosphate disorders, molybdenum cofactor deficiency,	Structural brain etiologies are common Metabolic etiologies (mitochondrial disorders, nonketotic hyperglycinemia, pyridoxine/pyridoxal-5-phosphate disorders, carnitine palmitoyl transferase deficiency, and others).

	Early myoclonic encephalopathy (EME)	Early infantile epileptic encephalopathy (EIEE) Ohtahara syndrome
	sulfite oxidase deficiency, Menke syndrome, Zellweger syndrome, and other disorders are also seen). Structural brain abnormalities are rare.	
Genetic causes	SLC25A22, ErbB4, etc.	ARX, STXBP1, KCNQ2, SCN2A, GNAO1, etc.

Table 1. Epilepsy syndromes with debut neonatal/infantile and suppression-burst EEG pattern.

2.3. Early myoclonic encephalopathy (EME)

EME was first reported in 1978 by Aicardi and Goutieres [18], as “Encephalopathie myoclonique neonatale”. It is characterized by early-onset fragmentary myoclonus, erratic focal seizures, and massive myoclonias during the neonatal period (before the first week 76% of the cases, and 96% occurring within the first month). Tonic seizures are observed later, generally around 3–4 months of age [16, 19]. Suppression-burst pattern (SBP) becomes more apparent in sleep in EME. The prognosis is grave [20] and evolves into hypsarrhythmia in 41% of patients [21].

2.4. Early infantile epileptic encephalopathy (EIEE), and Ohtahara syndrome (OS)

OS is also known as “early infantile epileptic encephalopathy” (EIEE) or “early infantile epileptic encephalopathy with burst-suppression pattern”. EIEE was first described by Ohtahara and contributors in 1976 [22], mainly characterized by tonic spasms that start during the first month of life (range of 1–3 months, but may occur within the first 10 days of life or during the first hour after delivery). The epileptic spasms may be either generalized and symmetrical or lateralized, and may occur in clusters or singly, while awake and during sleep alike. The duration of tonic spasms is up to 10 s, and the interval between spasms within cluster ranges from 9 to 15 s. In one-third of cases, other seizure types include partial motor seizures or hemiconvulsions, but myoclonic seizures are rare [23]. Interictal EEG shows a BS with high-voltage paroxysmal discharges separated by prolonged periods of nearly flat tracing that last for up to 18 s. OS is considered to be the result of developmental static structural brain damage. Patients show a poor outcome with severe psychomotor retardation or death. In the majority of patients (76%), EIEE evolves to infantile spasms (ISS) [21].

2.5. Severe early-onset epileptic encephalopathy (EOEEs) with a suppression-burst pattern: a continuum of pathology

Ohtahara and Yamatogi in 2006 [24] explain the differential diagnosis of EME versus EIEE/OS. Etiologically, structural brain lesions are most likely in OS, and nonstructural/metabolic disorders in EME. Clinically, tonic spasms are the main seizures in OS, while myoclonia and frequent partial motor seizures in EME. Another difference is noted in the EEG findings: SBP is consistently observed in both waking and sleeping states in OS, but SBP becomes more

apparent during sleep in EME. In OS, the SBP evolves to hypsarrhythmia around 3–4 months of age, and sometimes it progresses further to diffuse slow spike waves; by contrast, in EME the SBP may persist up to late childhood after a transient evolution to hypsarrhythmia in the middle to late infancy. The evolution of the two syndromes is also different: OS evolves to West syndrome (WS), and further to Lennox-Gastaut syndrome (LGS) with age, but EME persists long without such an evolution except a transient phase of West syndrome.

Nevertheless, the border between the two syndromes unfortunately is not always clear since they share many common features (age of onset, BS-EEG pattern, grave prognosis), but also each of them can evolve from one to the other. Due to this overlap, the classification is sometimes questionable even among the published cases. Thus, they have also been generally referred to as “neonatal epileptic encephalopathy” [25]. To the point that Aicardi and Ohtahara finally recognized that they may be one single epileptic syndrome, and they proposed the designation of “severe neonatal epilepsies with suppression-burst pattern” [16]. Various authors have also suggested that both entities constitute a single syndrome that has a predictable age-related evolution and its clinical manifestations express a continuum of the progressive brainstem dysfunction, with frequent evolution toward West and Lennox-Gastaut syndromes [21, 26, 27].

The severe epileptic encephalopathies (EIEE, WS, late infantile epileptic encephalopathy, and LGS) share many common clinical features and in certain individuals there is a progression from one syndrome to the next. Ohtahara proposed that these epilepsies occur on an electro-clinical spectrum and that the clinical and EEG features depend on the maturity of the NS [28]. However, there are differences between the disorders that may not be explained by the concept of “age-dependent encephalopathy” [29]. Other authors such as Lombroso [30] conclude that there is some justification to provisionally support a nosological place for the EME syndrome, whereas a nosologically separate position for the EIEE syndrome seems to be less justified, and it would be safer to consider it for now as an early variant of the West syndrome (WS).

Most of the cases of EIEE are associated with structural brain anomalies while the better part of EME with metabolic disorders (including nonketotic hyperglycinemia) [16, 20, 30–33]. Nevertheless, the etiology of EIEE is heterogeneous, and patients with EIEE often have acquired causes (e.g., HIE), structural brain defects (e.g., cortical brain malformations), or metabolic disorders [34, 35]. Thereby, the recognition is that multiple etiologies can produce under certain circumstances either syndrome, and there is an overlap in both severe early-onset epileptic encephalopathies (EOEEs) that may share a common mechanism. On the other hand, recent molecular genetics studies have shown that these encephalopathies are genetically heterogeneous and phenotypically diverse disorders, such that similar gene mutations have been found in several different epileptic encephalopathies syndromes, reinforcing the notion that these epilepsies are unlikely to be distinguished on the basis of cause alone. Thus, the ILAE emphasizes in its classification the symptomatic nature and nonspecific etiology of these syndromes.

Lombroso et al. found that asphyxiated babies meeting EME criteria exhibited both erratic myoclonia and BS, while presenting clinical and EEG parameters and evolutions differing from others who had homogeneous enough profiles to justify their inclusion in a provisional EME

syndrome [8]. However, since HIE can be the common cause of neonatal seizures, brain damage, and BS pattern (BS is caused in 44.1% of cases by HIE) [36], it may serve as a model to study the correlation of progressive brain damage and evolution of the crisis. In our clinical experience, we have observed that the two entities (EME and EIEE) may be present in the evolutionary course of an epileptogenic encephalopathy neonatal secondary to HIE. As an illustrative example, we report the case of a newborn infant admitted to the Pediatrics Department at the Albacete General Hospital (Spain), who initially presented early neonatal seizures as tonic extension of the limbs, eye deviation, as well as sucking, pedaling, and swimming movements. Their initial EEG showed severe depression of brain bioelectrical activity, which progressed into EME at 15 days, with myoclonic convulsions and a BS-EEG pattern. Neuroimaging studies objectified a deep ischemia with the involvement of basal ganglia. Within 2 months of life, the clinical picture changed and it was suggestive of EIEE: flexion spasms appeared together with radiological progression toward a “multicystic encephalomalacia”. In our patient, the presence of myoclonic seizures with subsequent flexion spasms associated with the appearance of brain structural abnormalities and the persistence of a BS-EEG pattern also support the notion of one epileptic syndrome with different clinical manifestations depending on age at presentation and brain damage/maturational status of the patient.

We have also observed the clinical course and EEG evolution of an extreme low-birth-weight preterm neonate with glycine encephalopathy (already published [37]), in which the BS pattern and seizures did not appear until the third month after birth (40 weeks corrected gestational age). An immature brain could have been responsible, at least in part, for the long asymptomatic period before the onset of convulsions in our patient. This suggests that an adequate maturation and organization of the brain development—particularly regarding GABAergic interneurons—is required for the onset of EME.

The most prominent distinctive points between both epilepsy syndromes are the observation that patients with OS exhibit predominantly tonic seizures, their crises evolve to ISS, and the outlook is often worse than in patients with EME. Although both syndromes may have different courses, the differentiation at the beginning may be impossible, since both myoclonus and tonic convulsions may coexist and present the same electrical pattern, although some specialists report to be able to find distinctive features between the EEG patterns. Tonic seizures are considered to be a manifestation of brainstem dysfunction and it is possible that this is more prominent in OS. Thereby, in a review article Djukic and collaborators [21] analyze preliminary studies that would suggest the following:

- Evidence that the brainstem is involved in the expression of tonic seizures;
- Evidence of increased excitability/epileptogenicity in the immature brainstem;
- Evidence of decreased seizure-controlling substrate in the immature brainstem;
- Clinical evidence supporting the notion that tonic seizures are associated with the severity of brainstem dysfunction in EIEE and EME;

- For the Ohtahara syndrome, some mothers retrospectively reported movements consistent with seizures in utero [38]. Unable to rule out that the myoclonic component had occurred in utero.

The standard notion is that when the brain is intact and a strong harmful event happens leading to acute excitotoxic cell death and neuronal apoptosis (e.g., acute cerebral injury in HIE and metabolic disorders), a BS-EEG pattern is acutely developed. However, the newborn shows a first stage of frequent and diverse seizure types: fragmentary myoclonus, erratic focal seizures, and massive myoclonias compatible with the specific epilepsy syndrome EME. Conversely, when there is brain damage established—nonprogressive static structural developing brain damage (e.g., brain injury such as multicystic encephalomalacia in HIE, cortical brain malformations, brainstem dysfunction, and metabolic disorders with intrauterine brain damage, among others)—also a BS-EEG pattern may occur that can be demonstrated, but the infant is more likely to show tonic intractable seizures that are typical of EIEE. In view of these evidences, we believe that these syndromes do not correspond so much to an “age-dependent encephalopathy” but rather to a “damage-dependent encephalopathy”. Thereby, it is possible that these syndromes represent successive stages of “a continuum and progressive neuronal injury” from an epileptic process.

3. Genetic factors in severe early-onset epileptic encephalopathy

3.1. Genome instability and neurotransmitter signaling

The genetic factors are thought to play a role in at least 70% of patients with epilepsy [39]. Genetic analysis for copy number variants (CNVs) and single EOEEs candidate genes have become increasingly important investigations in clinical practice. Data suggest that mutations causing EE are often sporadic, mostly due from de novo dominant mutations in a single autosomal gene, although inherited autosomal recessive and X-linked forms also exist [40].

Over recent years, huge steps have been made to clarify the genetics of epilepsy, and the amount of reports on novel genetic causes of EOEEs has increased due to fast developments and dramatically reduced costs in molecular genetic techniques, especially the “next-generation sequencing” (NGS) technologies (for a review, see [41–43]).

Mutations have been identified in several genes in infants with severe EOEEs, clustering in several biological pathways that are often shared by patients with similar mutations. But the complexity of phenotype/genotype correlations—one syndrome having multiple genetic causes (genetic heterogeneity) and one gene being associated with different phenotypes (pleiotropy)—has been progressively unraveled for both EIEE and EME. To date, the genetic origin of up to 36 genetic phenotypes (EIEE 1 to EIEE36), as referred in the Online Catalog of Human Genes and Genetic Disorders “Online Mendelian Inheritance in Man” (OMIM), has been identified [44]. Many of them are related to mutations in NT receptors, transporters, or associated proteins.

Title (OMIM)	Gene	Phenotype Clinical	Age	Seizures predominate	EEG
EIEE1 (308350)	ARX	Ohtahara syndrome	1–3 months	Tonic seizures	SBP
EIEE2 (300672)	CDKL5	X-linked dominant infantile spasm syndrome-2 (ISSX2). Dysmorphic.	1–10 weeks	Infantile spasms. Atypical Rett syndrome	H
EIEE3 (609304)	SLC25A22	Early myoclonic encephalopathy (EME)	Neonatal period	Myoclonic seizures	SBP
EIEE4 (612164)	STXBP1	Ohtahara and West syndrome with cerebral hypomyelination	3 days to 4.5 months	Tonic seizures	SBP/H
EIEE5 (613477)	SPTAN1	West syndrome with pontocerebellar atrophy and hypomyelination	3 months	Infantile spasms.	H
EIEE6 (607208)	SCN1A	Dravet S. and FEB3A, MHP3	Mean 6 months	Multiple types.	GSWD
EIEE7 (613720)	KCNQ2	Ohtahara Syndrome and BFNS1	Neonatal period	Tonic seizures	SBP
EIEE8 (300607)	ARHGEF9	Hyperekplexia and epilepsy	Neonatal period	Tonic seizures provoked by tactile stimulation	Varies
EIEE9 (300088)	PCDH19	EFMR. Juberg-Hellman syndrome	6–36 months	Multiple types	Varies
EIEE10 (613402)	PNKP	Microcephaly, seizures, and developmental delay (MCSZ)	<6 months	Complex partial type	Varies
EIEE11 (613721)	SCN2A	EIEE and benign familial infantile seizures-3 (BFIS3)	Neonatal period	Tonic-clonic seizures. Infantile spasms	SBP GSWD
EIEE12 (613722)	PLCB1	West Syndrome and MMPSI	10 weeks to 6 months	Tonic seizures/infantile spasms	MF/H
EIEE13 (614558)	SCN8A	Intractable seizures	First days to 6 months	Multiple types	Varies/H
EIEE14 (614959)	KCNT1	Refractory focal seizures. MMPSI	<6 months	Multiple types	MF
EIEE15 (615006)	ST3GAL3	West syndrome	3–7 months	Infantile spasms	H
EIEE16 (615338)	TBC1D24	Familial infantile myoclonic epilepsy (FIME) and MMPSI	First weeks or months	Myoclonic seizures. Multiple types	Varies
EIEE17 (615473)	GNAO1	Intractable seizures	First weeks or months	Tonic seizures	SBP

Title (OMIM)	Gene	Phenotype Clinical	Age	Seizures predominate	EEG
EIEE18 (615463)	SZT2	Dysmorphic feature and thick corpus callosum	First months or years	Tonic-clonic seizures	Varies
EIEE19 (615744)	GABRA1	Dravet syndrome	8–11 months	Multiple types	GSWD
EIEE20 (300868)	PIGA	Multiple congenital anomalies—hypotonia-seizures, Syndrome 2	First days to 9 months	Myoclonic seizures	SBP/H
EIEE21 (615833)	NECAP1	Intractable seizures	First years	Multiple types	Varies
EIEE22 (300896)	SLC35A2	Congenital disorder of glycosylation type II _m (CDG2M)	First days to 3 months	Tonic seizures. Infantile spasms	Varies/H
EIEE23 (615859)	DOCK7	Intractable seizures. Dysmorphic feature and cortical blindness	2–6 months	Tonic seizures. Multiple types	MF/H
EIEE24 (615871)	HCN1	Resembling Dravet syndrome with pharmaco-resistant febrile seizures	4–13 months	Tonic-clonic, progress to atypical absences	Varies
EIEE25 (615905)	SLC13A5	Developmental delay and tooth hypoplasia	First 7 days	Focal clonic seizures. Status epilepticus	Focal MF
EIEE26 (616056)	KCNB1	Intractable seizures	First years	Multiple types	H/MF
EIEE27 (616139)	GRIN2B	West syndrome	First months	Infantile spasms	H
EIEE28 (616211)	WWOX	Lethal microcephaly syndrome. Simplified gyral pattern	Mean 2 months	Multiple types	Varies
EIEE29 (616339)	AARS	Hypomyelination. Charcot-Marie-Tooth disease, axonal, type 2N	3–6 months	Myoclonic seizures	MF
EIEE30 (616341)	SIK1	Intractable seizures	Neonatal period	Myoclonic. Tonic and infantile spasms	SBPMF H
EIEE31 (616346)	DNM1	Intractable seizures. West syndrome	2–13 months	Multiple types. Infantile spasms	Varies/H
EIEE32 (616366)	KCNA2	Ataxia and myoclonic epilepsy	5–17 months	Myoclonic seizures. Multiple types	Varies
EIEE33 (616409)	EEF1A2	West syndrome	First week or month	Myoclonic seizures. Infantile spasms	MF/H
EIEE34 (616645)	SLC12A5	Refractory migrating focal seizures	First weeks or months	Focal seizures	Varies

Title (OMIM)	Gene	Phenotype Clinical	Age	Seizures predominate	EEG
EIEE35 (616647)	ITPA	Lack of myelination of early structures	Neonatal period	Multiple types	Varies
EIEE36 (300884)	ALG13	Congenital disorder of glycosylation Is	First week or month	Infantile spasms	MF/H

SBP: suppression-burst pattern on EEG. **H:** hypsarrhythmia. **GSWD:** generalized spike-wave discharges. **MF:** multifocal epileptogenic foci. **MMPSI:** malignant migrating partial seizures of infancy. **FEB3A:** febrile seizures, familial, 3A. **MHP3:** migraine, familial hemiplegic, 3. **BFNS1:** benign familial neonatal seizure 1. **EFMR:** epilepsy, female-restricted, with mental retardation.

Table 2. EIEE following the classification of OMIM.

Despite these evidences, in the last International Classification of epilepsies these entities are included as epilepsy syndromes and they are classified according to the age of onset and their electro-clinical features, for example, Ohtahara and West syndromes. However, in OMIM these syndromes are included in the so-called “epileptic encephalopathy, early infantile”, or “early infantile epileptic encephalopathy” (EIEE), paying great attention to their genetic origin and less so to their phenotype. Thus, epileptic encephalopathy, early infantile 1 (EIEE1) is Ohtahara syndrome (OMIM 308350) caused by a mutation in the “aristaless-related homeobox gene” (ARX; 300382) on chromosome Xp22. Whereas early myoclonic encephalopathy (EME; OMIM 609304) caused by mutation in the “solute carrier family 25 (mitochondrial carrier, glutamate), member 22 gene” (SLC25A22; 609302), is named EIEE3 (609304) Dravet’s syndrome, caused by mutation in SCN1A gene (182389), is named EIEE6 (6070208) (see **Table 2**).

Nevertheless, the heterogeneity of the epileptic features is often the rule for most of the reported genes, and, inversely, the same gene mutation can cause several seizure types, even in the same patient across ages. Therefore, in many cases, clinical prediction of causative genes is challenging for some patients, since the association between phenotypic pleiotropy and genetic heterogeneity phenotype is not sufficiently distinctive. Sequential single-gene analysis (by direct Sanger sequencing) is costly, time consuming, and often unsuccessful. With the current development of the NGS technologies—via gene panel analysis—diagnostic rates improve. NGS can also help to clarify and broaden the phenotypic spectrum of the genes involved. In a recent study, Trump et al. [45], in a 400 series of patients with early-onset seizure disorders and/or severe developmental delay, identified causative mutations in 18% of the individuals with seizures. The diagnostic rate was highest among those with seizure onset within the first 2 months of life (39%). The most frequently mutated gene was SCN2A (11 patients). Other recurrently mutated genes included CDKL5, KCNQ2, SCN8A (six patients each), FOXP1, MECP2, SCN1A, STXBP1 (five patients each), KCNT1, PCDH19, TCF4 (three patients each), and ATP1A3, PRRT2, and SLC9A6 (two patients each). Mutations in EHMT1, GABRB3, LGI1, MBD5, PIGA, UBE3A, and ZEB2 were each found in single patients. These authors also pointed out that only in 15% of them, the clinician had sufficient clinical certainty for a specific mutated gene as the probable cause prior to genetic testing. Neurometabolic disorders and frequent major structural brain anomalies were not included in the panel, which may explain the absence of the ARX gene.

3.2. Genetic mutations in Ohtahara syndrome

A phenotype relatively similar to that of Ohtahara syndrome can be a consequence of various mutations on a single gene, with special mention to the ARX gene, but also to KCNQ2, SCN2A, STXBP1, and GNAO1 among other genes.

3.2.1. The homeobox gene ARX (MIM 300382)

One of the most important and well studied is the mutation in the ARX gene, which is the one responsible for OS named EIEE1 (OMIM 308350) that causes severe disorganization of forebrain with aberrant migration and differentiation of interneurons containing gamma-aminobutyric acid (GABAergic interneurons) [46–49] via the Dlx pathway [50]. Additionally, the ARX gene modifies glutamatergic neurons excitability and morphology. Pyramidal neurons show a dramatic rise in the frequency of excitatory inputs associated with a redevelopment of their axonal arborization resulting from glutamate network remodeling. Thus, secondary alterations are instrumental for the development of disease-specific phenotypes and should be regarded to explain the “phenotypic pleiotropy” associated with epileptogenic mutations [51].

The homeobox gene ARX is one of the most frequently mutated genes in “phenotypic spectrum of disorders”, comprising a nearly continuous series of X-linked developmental disorders with intellectual disability (ID), ranging from syndromic (S-XLMR) and nonsyndromic X-linked mental retardation (XLMR), to lissencephaly and infantile spasms without brain malformations. At least seven well-defined clinical entities have been described including [47, 52, 53].

- Ohtahara syndrome (308350),
- Nonsyndromic X-linked mental retardation with or without seizures, ARX-related (OMIM 300419),
- Partington syndrome, characterized by the association of mild to moderate intellectual deficit, dysarthria, and variable movement disturbances—dystonic hand movements— (OMIM 309510),
- Proud syndrome or microcephaly—corpus callosum agenesis—abnormal genitalia syndrome (OMIM 300004),
- X-linked lissencephaly with ambiguous genitalia (LISX2, XLAG), as well as hydranencephaly and abnormal genitalia (OMIM 300215).

The genetic heterogeneity (same clinical entities being associated with several mutations in ARX) together with intra- and interfamilial pleiotropy is becoming a hallmark of ARX mutations [53]. It appears to be a consistent genotype-phenotype correlation and both intra- and interfamilial variability of expression of some of the mutations, particularly the common 428-451dup (24 bp) mutation [54]. On the other hand, brain-imaging abnormalities can also be highly variable, ranging from lissencephaly/hydranencephaly and cortical dysplasia (among others) to normal brain. Microarray analysis has identified a total of 1006 gene promoters bound by ARX, and around 24% of Arx-bound genes were found to show expression changes

following ARX overexpression or knock-down. Several of the ARX target genes are known to be important for a variety of functions in brain development and some of them suggest new functions for ARX [55]. Phenotype/genotype studies in humans suggest that truncating mutations cause X-linked lissencephaly, and insertion/missense mutations result in epilepsy and intellectual deficit without cortical dysplasia [56].

3.2.2. Dysfunctions of potassium (K⁺) channels

Several epileptic phenotypes have been associated to dysfunctions of potassium (K⁺) channels, and it has been recently proposed to name such epilepsies as “K⁺ channelepsies” [57]. Based on their structures, biophysical characteristics, pharmacological sensitivities, and physiology, these channels are classified as (for a review, see [58]) follows:

- Voltage-gated (K_v 1-12): Regulation of outward K⁺ currents and action potentials, modulation of NT release, control of both excitability and electrical properties of neurons.
- Inwardly rectifying (Kir1-7): Maintenance of the resting membrane potentials and regulation of the cell excitability.
- Sodium-activated channels (K_{Na}): Regulation of delayed outward currents IK_{Na} and contribution to adaptation of firing rate.
- Ca²⁺-activated channels (K_{Ca}): Regulation of neuronal firing properties and circuit excitability.

3.2.2.1. KCNQ2 (# 602235)

As an example of phenotypic diversity, reference is made to mutation in the KCNQ2 gene on chromosome 20q13.3 (encoding the K_v7.2 channel), characterized by benign familial neonatal seizures-1 (BFNS1) that can also cause early infantile epileptic encephalopathy-7 (EIEE7, OMIM 613720). Reported genotype-phenotype observations for KCNQ2 with truncating mutations are associated with the benign, inherited phenotype and missense mutations affecting key residues with the severe, sporadic phenotype [45]. Cellular experiments indicate that these latter mutations may have a dominant negative effect on cellular function [59].

The EIEE7 is an atypical severe early-onset epilepsy with refractory seizures and prominent tonic component. Most patients showed a BS-EEG pattern and were diagnosed clinically with Ohtahara syndrome (but with an earlier start during the neonatal period), infrequent evolution to West syndrome, and good response to sodium channel blockers (phenytoin, carbamazepine, zonisamide,...), topiramate (TPM), or valproic acid, but poor developmental prognosis [60]. Weckhuysen et al. in 2012 [61] reported eight unrelated patients with EIEE7 confirmed by genetic analysis. All patients had the onset of seizures during the first week of life, and two mothers retrospectively noted intrauterine jerking during the last 2 months of pregnancy. Early magnetic resonance imaging (MRI) of the brain showed characteristic hyperintensities in the basal ganglia and thalamus. These evidence supports (as we mentioned above) that the myoclonic component had occurred in utero while tonic crises may be a manifestation of brainstem dysfunction [21].

3.2.2.2. *KCNT1*

The *KCNT1* gene encodes the K_{Na} channel subunit *KCNT1*, called Slack (sequence such as a calcium-activated potassium channel). Mutations in *KCNT1* gene have been found in different epilepsy syndromes (EIEE 14): autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), epilepsy of infancy with migrating focal seizures (EIMFS), and other types of EOEEs, including OS [62]. Patients displaying *KCNT1* mutations have a very high occurrence of severe mental and intellectual disability.

3.2.3. *SCN2A* (MIM 182390)

The three isoforms of the brain sodium channel alpha subunit are encoded by three distinct sodium channel, voltage-gated genes (*SCN1A*, *SCN2A*, and *SCN3A*) that share a common ancestral origin [63].

De novo mutations in *SCN2A* are increasingly recognized as a cause of an early-onset seizure and developmental delay. The clinical spectrum named EIEE11 (MIM 613721) includes OS and benign familial infantile seizures-3 (BFIS3) [64]. While inherited *SCN2A* mutations have been identified in multiple mild epilepsy cases, by contrast in cases with EIEE and severe or profound developmental delay, the majority of mutations were de novo missense variants, similarly to the abovementioned findings for *KCNQ2* [45, 65].

3.2.4. *STXBP1* (MIM 602926)

STXBP1 (mapping to 9q34.1) encodes the n-Sec1 (neural-specific, syntaxin-binding protein), which participates in the constitutive secretory pathway between the Golgi apparatus and the plasma membrane, and implicated in vesicle trafficking and NT release [66]. The mutation in *STXBP1* (named EIEE4, MIM 612164) shows a relatively similar phenotype to OS but with frequent evolution to West syndrome [67] and cerebral hypomyelination in MRI brain imaging. Mutations in *STXBP1* are not limited to patients with Ohtahara or West syndrome, but are also present in about 10% of patients with an EOEE without a specific recognized epilepsy syndrome [68].

A *de novo* heterozygous missense mutation in the *STXBP1* gene was found for the severe phenotype of early infantile epileptic encephalopathy with suppression burst (EIEE4) [69, 70]. By contrast, a *de novo* truncating mutation in *STXBP1* was identified in nonsyndromic intellectual disability (NSID) with/without history of epilepsy [71, 72].

3.2.5. *GNAO1* (139311)

The *GNAO1* gene encodes an alpha subunit (Go, alpha subunit) of the heterotrimeric guanine nucleotide-binding proteins (G proteins), a large family of signal-transducing molecules. Go-alpha has been implicated in ion channel regulation. Most of the reported cases present EIEE17 (OMIM 615473), characterized by OS with intractable tonic seizures in the first weeks of life associated with BS pattern on EEG, involuntary movements, and progressive cerebral atrophy. Delayed myelination and thin corpus callosum were common features in brain images [73].

A novel heterozygous missense pathogenic GNAO1 variant is reported in an EIEE presented at birth with twitching movements and convulsions, with nonspecific electro-clinical signs, and no radiological abnormalities [74]. Other reports demonstrated that GNAO1 variants can cause involuntary movements and severe developmental delay with/without seizures, suggesting that GNAO1 variants can cause various neurological phenotypes [75].

3.3. Genetic mutations in EME

On a genetic point of view, several genes have been associated with EME.

3.3.1. *SLC25A22* gene

As referred to above, the SLC25A22 gene is most often associated with EME (or EIEE 3) and encodes mitochondrial carriers that transport a variety of metabolites across the inner mitochondrial membrane (it is one of the two mitochondrial glutamate/H⁺ symporters), with strong expression in the developing brain. Mutated SLC25A22 expression in areas of the brain decreased glutamate transport activity and contributed to the genesis and control of myoclonic seizures [76]. Malignant migrating partial seizures in infancy (MMPSI, or EIEE14, OMIM 614959) that may occur as a result of heterozygous mutation in the KCNT1 gene (608167) on chromosome 9q34 can also be caused by a SLC25A22 gene mutation, expanded the phenotypic spectrum associated with this gene [77].

3.3.2. *PIGA*

Phosphatidylinositol glycan class A (PIGA, OMIM 311770) is involved in the first step of glycosylphosphatidylinositol (GPI) biosynthesis, a glycolipid that attaches dozens of different proteins to the cell surface. Many proteins, including CD55 and CD59, are anchored to the cell by GPI. The loss of CD55 and CD59 on erythrocytes causes complement-mediated lysis in paroxysmal nocturnal hemoglobinuria (PNH).

Multiple congenital anomalies-hypotonia-seizures syndrome-2 (MCAHS2, or EIEE20, OMIM 300868) is an X-linked recessive neurodevelopmental disorder characterized by neonatal hypotonia, myoclonic seizures, dysmorphic features, and variable congenital anomalies involving the central nervous, cardiac, and urinary systems. EEG, in the most severe cases, showed hypsarrhythmia or BS pattern. Some affected individuals die in infancy [78].

3.3.3. *SIK1*

SIK1 (OMIM 605705) is a member of the AMP kinase subfamily with several roles in the CNS and is involved in the regulation of corticotropin-releasing hormone in the hypothalamus. SIK1 abundance and activity are also increased by stimulation with ACTH (adrenocorticotrophic hormone), which is a first-line treatment for ISS [79].

The mutations in SIK1 gene have been associated with a spectrum of developmental epilepsies [80], mainly EME (EIEE30, 616341), and also with OS and ISS. Brain was either normal, mild hypoplasia of the frontal lobes. Interestingly, one of the patients described in

this work that developed intermittent myoclonic jerking movements did not respond to anticonvulsants. Their EEG on day 14 of life showed BS pattern, and at 8 months of age the EEG had not improved, with continued BS associated with both myoclonic and tonic seizures. Brain MRI showed no structural malformations. In another OS patient with tonic seizures, the brain exhibited “a simplification of the gyral pattern”, and asymmetric thinning of the WM. This evidence also supports the idea that tonic seizures in OS are associated with structural and static brain damage, while the EME requires a good cerebral cortical development.

3.3.4. Neuregulin-1 receptor ErbB4

The neuregulins (NRGs) are cell-cell signaling proteins that are ligands for receptor tyrosine kinases of the ErbB family. Recently, it has been known also that disruption in the neuregulin-1 receptor ErbB4 (family members of tyrosine kinase receptors, OMIM 600543) also contributes to EME (OMIM 609304) [81] by impairing interneuron migration [82] and altering the number of GABAergic interneurons in the postnatal cortex [83]. NRG1 is crucial for maintaining a normal radial glial scaffold and signals allowing neuronal migration. It also induces the expression of brain lipid-binding protein (BLBP), a well-known marker of radial glia [84]. NRGs also regulate the timing of astrogenesis in the developing brain [85], as well as in the myelination of Schwann cells [86].

3.4. Genetic analysis for copy number variants (CNVs)

Advances in molecular genetic testing have greatly improved diagnostic rates in EIEE, with an important role of array-comparative genomic hybridization (array-CGH) investigation in this group of disorders. Array CGH can readily detect micro-chromosomal aberrations at a much finer resolution than the 5-Mb limit of the conventional karyotype. There are over 200 disorders where epilepsy is or can be part of the clinical condition, but not the primary feature (Online Mendelian Inheritance in Man, OMIM). Many of these can be associated with various micro-chromosomal anomalies; therefore, the array CGH is more widely applied as a frontline diagnostic tool, especially for children with syndromic epilepsy.

CNVs can be recurrent due to non-allelic homologous recombination (NAHR) in “hotspots” regions of segmental duplication (SD) or low-copy repeats (LCRs). The most common of the recurrent microdeletions associated with generalized epilepsy are typically seen at a frequency close to 1% at 15q13.3, 16p13.11, and 15q11.2. These loci also confer susceptibility to ID, autism spectrum disorders (ASDs), and schizophrenia (for a review, see [87]). Rare copy number variants—deletions and duplications—have recently been established as important cause of epileptic encephalopathies. Pathogenic CNVs play an important role in the genetic etiology of unknown cause EOEEs: 7.9% of affected individuals carried at least one rare CNV [88], and in at least 3.4% [89] to 4.1% [88] of patients, CNVs were clearly pathogenic.

4. GABAergic neurons in the developing brain

To accomplish stability, neurons must maintain a homeostatic balance between adjustment output (to meet new requirements) and preservation output within a satisfactory performance range. This balancing act is performed through the combination of synaptic plasticity and changes in intrinsic neuronal excitability. The neuronal components of brain circuitry are generally considered to be “stable” across an animal’s life, excepting the growth and degeneration phases that happen during development, aging, or pathology. The periods of greatest neuronal instability occur during the early ontogenesis and CNS development. The EEA (glutamate and especially GABA acting like an excitatory) plays a fundamental role in the developing brain. The hypothesis of a “homeostatic-like” regulation [90] (by NT and receptors) of neuronal migration that controls final position, timing, and number of cells at destination depends on the following:

- the type of migration: radial, tangential, or chain migration;
- the type of cells: principal glutamatergic neurons versus GABAergic interneurons; and
- the brain area: neocortex, cerebellum, rostral migratory stream.

4.1. Distinct modes of migration in the developing cortex

The newly specified neurons migrate long distances before they differentiate and form synapses. Neuron migration routes in the developing mammalian brain are generally a long and complex process, but it can be summarized in the following: (for a review, see [91, 92])

- a. Radial-type migration: postmitotic neurons migrate away from the germinal ventricular zone to their positions in the developing cortex, using two forms of radial movement: somal translocation, which is adopted by the early-generated neurons, and glia-guided locomotion, which is used predominantly by pyramidal cells.
- b. Tangential-type migration: cortical interneurons migrate tangentially into the cortex and then seek the ventricular zone before moving radially to take up their positions in the cortical anlage.

4.2. Transient and permanent circuitry elements

In lower mammals, all hippocampal and almost all neocortical neurons are born in a specific region named ganglionic eminence in the ventral (basal) part of the telencephalon. The glutamatergic principal cells (i.e., projection neurons) migrate from the proliferative layer to their target region following a radial orientation. Meanwhile, GABAergic interneurons via long-distance tangential migration (parallel to pial surface) move from the ganglionic eminence to their target layer in the cerebral cortex. A substantial body of evidence indicates that in humans neocortical GABAergic interneurons of local cortical circuitry are likely to originate in two different areas: 65% are born in the ventricular/subventricular zone of the dorsal telencephalon, and 35% originate from the ganglionic eminences (proliferative zones of the subpallium) [93].

The subplate zone (SPZ) is a transient cytoarchitectonic compartment of the fetal telencephalic wall, situated between the fetal white matter (WM) (i.e., intermediate zone) and the cortical plate, and it is the crucial laminar compartment for the development of the human cerebral cortex. The subplate contains numerous neurons of various morphological types and molecular phenotypes, including differentiated projection (glutamatergic) neurons and local (GABA and peptidergic) interneurons [94]. The developing human cortex goes through three major early stages of functional development: (1) between 13 and 15 postconceptional weeks (PCW): initial-transient fetal circuitry, centered at the SPZ, which is endogeneously (spontaneously) driven; (2) 15 and 30 PCW: perinatal dual circuitry (coexistence of endogeneously driven subplate-centered transient circuitry with developing cortical plate-centered permanent circuitry) that slowly disappears toward the end of gestation and during the early postnatal period; and (3) postnatally established permanent (externally driven) cortical circuitry, centered at the cortical plate (i.e., developing cortical layers I–VI). While the SPZ disappears during the perinatal and early postnatal period, numerous subplate neurons survive and remain embedded in the superficial (gyral) WM of adolescent and adult brain as the so-called *interstitial neurons* [95]. There is also a prolonged coexistence of transient and permanent circuitry elements in the developing cerebral cortex. Therefore, the neuronal elements in transient fetal zones form a developmental potential for plasticity after perinatal cerebral lesions [96].

The subpallium also generates oligodendrocytes (OLs) that migrate in a similarly tangential path to the cortex. These are the cells that give rise to myelin, a major component of WM, and play an important role in assuring fast neuronal signaling in the CNS [97]. The proliferation and differentiation of developing oligodendroglial cells and their myelination of axons are partly controlled by NT (glutamate, GABA, glycine, etc.) (for a review, see [98]). Numerous studies refer connections among this OLs and the GABAergic system [99, 100]. The growth of the axonal pathways in preterm newborn explains their vulnerability and plasticity, while conversely in neonates the vulnerability is related to the intracortical circuitry. In addition to OLs loss, axonal disruption, and excess apoptosis, a significant loss of telencephalon GABAergic subplate neurons expression was found in neonatal brains with WM lesions, compared with neonatal brains without WM lesions, which could contribute to the pathogenesis of neurological deficits in children [101]. On the other hand, innate immunity mediated by microglia plays a crucial role in initiating and propagating seizure-induced inflammatory responses, as long-term epileptogenic effects of early-life seizure, such that seizure-induced microglia activation primes the central immune response to overreact and to increase the susceptibility to a second seizure later in life [102].

4.3. GABAergic interneurons

GABAergic neurons in cerebral cortex mostly correspond to local circuit neurons (interneurons), which release GABA as their output, and are the major inhibitory cells of the mature CNS. Despite including only 20–30% of the cerebral cortical neuronal population, these cells play an essential part and mighty role in modulating the electrical activity in the synapse of the excitatory pyramidal cells. In the epileptogenic neocortex, there is preferential loss of GA-

BAergic neurons, namely “basket cells” (BCs) and chandelier cells (ChCs) (for a review, see [103, 104]).

The interest in developing human cortex and GABAergic neurons has increased in the past decade. GABAergic interneurons develop early in the cortical anlage during embryonic development, whereas glutamatergic activity arises later. Although interneurons are present in all regions of the mature telencephalon, many studies have shown that during embryogenesis these cells are generated in specific compartments of the subcortical telencephalon and migrate across WM to reach their final destinations in the mature brain. Studies of histological sections of progressively more developed embryonic brains revealed that GABAergic cells were firstly present in the preplate, subventricular, and ventricular proliferative zones, migrated later to the subplate, marginal zone, and intermediate zones and finally reached the cortical plate (for a review, see [93, 105]).

Despite progress toward understanding the genetic determinants that specify the fate of neural progenitors, much remains unknown about the complex molecular machinery that directs the migration of immature neurons to specific regions of the cerebrum. Interestingly, in addition to its function in synaptic transmission, NTs have been shown to promote several developmental processes that contribute to the creation and maintenance of the CNS. In this regard, a growing body of literature has highlighted a role for NT through the activation of its receptors in the regulation of cell migration in the telencephalon during development and in adulthood [106, 107]. Thus, it seems that the activation of GABA_AR regulates neuronal proliferation, migration, and differentiation of GABAergic interneurons in the developing cerebral cortex [108]. Most interestingly, GABAergic interneuron dysfunction may contribute to a subset of genetic developmental epilepsies [104]. It is also worth noting that, in experimental animals, it has been shown that status epilepticus altered neurogenesis and decreased the number of GABAergic neurons in the septal dentate gyrus at the early phase of epileptogenesis. This could modify the connectivity between these cells and disturb the maturation of the GABAergic neurotransmission in the immature brain [109].

Lévesque et al. [110] described the interneurons spark seizure-like activity in the cortex in an *in vitro* model of epileptiform synchronization:

- Interneurons (66.7%) are more likely to fire in association with interictal discharges than principal cells (35.3%).
- The pre-ictal period is characterized by increased interneuron firing that reaches its peak at ictal onset, while the activity of principal cells does not change.
- The tonic phase of the ictal discharges is associated with high firing from interneurons that fire in a phase-locking relationship with low-voltage fast (LVF) oscillations.
- Interneurons continue to generate action potentials in association with the interictal discharges occurring during blockade of ionotropic glutamatergic transmission.

Their results illustrate the major role of interneurons in interictal discharge generation and in the transition to ictal activity.

5. Excitotoxicity in developing brain

Amino acids are among the most abundant NTs in the CNS, and most neurons use GABA and glutamate, both primary regulators of the excitability of most neurons in the brain (glutamate is an excitatory NT, while GABA is an inhibitory NT in the adult mammalian brain), and are therefore involved in important physiological processes and in pathophysiologic events.

Receptor families of EAA are overexpressed in the immature brain. Due to the abundance of EAA receptors in early ontogenesis and age-dependent changes in intrinsic neuronal excitability, an excitotoxic hypothesis as the source of neonatal seizures seems plausible, even though some observations do not support this theory [8]. Many reports reviewed here aimed to demonstrate that both NTs (GABA and glutamate) modulate neuronal migration and brain maturation in humans by early paracrine actions, and cytoskeletal dynamic changes are regulated by intracellular calcium. Thus, there is evidence that the activation of specific GABA and glutamate receptors is instrumental in cell migration by promoting motility and acting as an acceleratory or stop signal. Therefore, the modification of glutamate and GABAergic systems, among other mechanisms, can trigger disorders in cortical migration of neurons, the most common CNS developmental alteration observed in human patients and a significant cause of seizures [9].

5.1. The amino acid glutamate

Glutamate is the major excitatory NT in the CNS, released from both neurons and glial cells. During neurotransmission, glutamate is released from presynaptic neurons by means of depolarization of the presynaptic neuronal end plate and then diffuses across the synaptic cleft to activate postsynaptic glutamatergic receptors.

The mammalian genome contains five glutamate transporter genes—“solute carrier family”—(EAAT1, slc1a3; EAAT2, slc1a2; EAAT3, slc1a1; EAAT4, slc1a6; EAAT5, slc1a7). The most important and most abundant transporters for the removal of transmitter glutamate in the brain are EAAT2 (GLT-1) and EAAT1 (GLAST). These transporters keep the extracellular level excitatory amino acids low and provide amino acids for metabolic purposes (for a review, see [111]).

Glutamate is one of the NTs with the most receptors; therefore, its classification is complex. There are two known groups of glutamate receptors: ionotropic (iGluRs, ligand-gated ion channels) and metabotropic (G-protein-coupled) receptors. iGluRs are further divided into the following subgroups with respect to their pharmacological properties: GluN (the N-methyl-D-aspartic acid), GluA (AMPA, the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), GluK (kainate), and GluD (δ) receptors [112]. NMDA receptors are named “slow” (slow transmission, synaptic currents are typically very slow) and non-NMDAs “fast” (fast transmission, synaptic currents are typically very fast) [113].

Metabotropic glutamate (mGlu) receptors are further subdivided into three groups of eight subtypes: group I with components mGlu1 and mGlu5 (coupled to Gq/G11), group II consist-

ing of mGlu2 and mGlu3; and group III composed of mGlu4, mGlu6, mGlu7, and mGlu8 (members of both latter groups are coupled to Gi/Go) [114].

Glutamate receptors are regulated in both neuronal and glial cells within the developing brain. Rapid synaptic excitation in the CNS is mediated primarily by the activation of postsynaptic ionotropic (AMPA and NMDA) glutamate receptors. Both of these receptors play different, well-defined roles in excitation: AMPA receptors (AMPA receptors) are considered to be the primary mediators of fast neurotransmission under resting conditions, whereas NMDA receptors, based on their unique properties, detect the coincidence of glutamate release and postsynaptic depolarization and are involved in the induction of long-term synaptic changes [115, 116]. Several studies indicate that glutamate receptor-mediated excitotoxicity is a key player in neuronal and glial cell death and that its involvement in the developing brain is more critical than in the adult brain [117, 118]. Other studies have shown a dual effect of glutamate on GABAergic interneuron survival during cerebral cortex development, expressed as either excitotoxicity lesions or antiapoptotic effects depending on the cortical layers. In layer VI, NMDA led to excitotoxicity, sustained calcium mobilization and necrosis; conversely, in the immature layers II–IV, NMDA decreased apoptosis and induced transient calcium mobilization [119].

5.1.1. NMDA receptors

The NMDA receptor is an essential executive and integrative element of the glutamatergic system and crucial for proper functioning of neuronal circuits. NMDA receptors have received a great deal of attention over the last few decades, due to their key role in neuronal excitotoxicity (their hypofunction or overactivation can result in neuronal disturbances and neurotoxicity) and their involvement in many types of neural plasticity (for a review, see [120, 121]).

The NMDA receptor subunits in the developing brain create populations of receptors that flux more calcium, open more easily, and block less frequently than mature forms, allowing these receptors to fulfill their special role in development. However, this makes the immature brain more susceptible to excitotoxic injury if energy levels are compromised. For instance, neurotoxicity mediated by NMDA is more enhanced in the neonatal brain than in the adult brain. Therefore, development-dependent changes in the expression of NMDA receptor subunits and their composition are, at least, partially responsible for the fact that immature brains are far more excitable and epileptogenic than the adult brain. Nevertheless, the important role that NMDA receptors play in activity-dependent neuronal plasticity during development contraindicates treatments that block NMDA receptors at specific neurodevelopmental stages due to their potential adverse effects on brain development [122].

5.1.2. AMPA receptors

AMPA receptors are Na⁺ and K⁺ (in some cases Ca²⁺) permeable ion channels constituted by four subunits (GluA1–GluA4), playing the major determinants of the rapid component of excitatory synaptic currents in the brain. They exhibit fast activation and deactivation kinetics aside from rapid desensitization. The receptor subunits interact with transmembrane AMPA

regulatory proteins (TARPs), exerting its influence on the synthesis, trafficking and localization of AMPA receptors at the cell surface, aside from their functional properties such as open probability, channel conductance, activation, deactivation, and desensitization [121].

In the developing brain, early alterations of the AMPA receptors (AMPA receptors) play a significant role in epileptogenesis, seizure susceptibility, and seizure-induced neuronal injury, and mediate synaptic potentiation induced by neonatal seizures [123]. Changes in AMPA receptor number are of great significance for CNS function, for instance, in shaping mechanisms underlying synaptic plasticity in cognitive aging [124]. Several studies have thrown light on the role of AMPA receptor maturation in perinatal seizures and brain injury. In immature subjects, AMPA receptors are relatively overexpressed in WM OLs, while after maturation those receptors predominate in neurons of cortex and hippocampus. Besides, in rodent models, it has been observed that hypoxia/ischemia causes neuronal damage at postnatal day 7 and seizures at postnatal days 10–12, but not at younger or older ages. These effects were found to be reversible by the administration of an AMPA receptor antagonist [125].

5.2. The amino acid GABA

GABA is a major NT expressed from the embryonic phase and throughout life. GABA is a versatile molecule with multiple functions during neocortical development and plays an important role in the developing brain even prior to synaptogenesis: stem cell proliferation, migration, synaptogenesis, and circuit formation. These diverse roles of GABA seem to depend both on cell-intrinsic properties (particularly high intracellular Cl^- gradient in immature neurons) and on extrinsic factors [126]. By changing the excitatory/inhibitory balance, GABAergic plasticity can regulate excitability, neural circuit function, and contribute to learning and memory [127]. GABA exerts depolarizing effects mostly contributing to the expression of spontaneous activities that are instructive for the construction of neural networks but GABA also acts as a potent trophic factor (for a review of metabolism and transport, see [128, 129]). The mammalian genome contains four genes encoding GABA transporters—“solute carrier family”—(GAT1, slc6a1; GAT2, slc6a13; GAT3, slc6a11; and the Betain/GABA transporter type 1 (BGT-1), slc6a12). GABA transporter types 1 and 3 (GAT-1 and GAT-3, respectively) are the two main subtypes of GATs responsible for the regulation of extracellular GABA levels in the central nervous system [111, 130]. GABA is actively taken up by neuron and astrocyte carrier proteins and broken down into succinic acid semialdehyde by glutamic acid decarboxylase (GAD) or repackaged into a vesicle that is released again at the next synaptic transmission [131].

There are two main types of GABA receptors: the ionotropic GABA subtype A receptor and the metabotropic GABA subtype B receptor [93]. The GABA receptor type A (GABA_A receptor) is a ligand-gated chloride channel that mediates major inhibitory functions in the adult CNS. GABA_A receptors function mainly as pentamers containing α , β , and either γ or δ subunits. At an early developmental stage, GABA, acting at GABA_A receptors, produces a rapid synaptic excitatory response and is implicated in most processes of neurogenesis, including neuronal migration, proliferation, differentiation, and preliminary circuit building. In the mature CNS, GABA acts in an inhibitory manner, a switch mediated by chloride/cation transporter expres-

sion. In contrast to the ionotropic GABA_A receptors, GABAB receptors are responsible for the latter and slower component of inhibitory transmission [132]. The composition of GABA_A receptors is different in newborns, with less $\alpha 1$ and more $\alpha 2/3$ subunits, rendering them less responsive to benzodiazepines [133].

In the adult NS, due to low intracellular levels of neuronal chloride [Cl⁻] gradients, GABA inhibits most neurons by the activation of GABA subtype A receptor channel chloride currents (GABA_ARs), causing Cl⁻ influx, membrane hyperpolarization, and inhibition. During development, GABAergic neurotransmission undergoes a switch from excitatory to inhibitory due to a reversal of [Cl⁻] gradients [134]. In immature neurons, high levels of expression and robust activity of the chloride-importing Na-K-2Cl cotransporter NKCC1 cause the accumulation of intracellular [Cl⁻] and, therefore, a depolarized Cl⁻ equilibrium potential, responsible for an excitatory effect in the developing brain; besides the Cl⁻ exporting activity of KCC2 is lower than in mature neurons, and in the context of NKCC1 expression, neuronal [Cl⁻] is higher and GABA_A reversal potential (EGABA) is more depolarized, such that the binding of GABA to ligand-gated GABA_A receptor-associated Cl⁻ channels triggers Cl⁻ efflux and depolarizing excitation. This results in the outward flux of [Cl⁻] through GABA_A channels, the opposite direction compared with mature neurons. In adults, NKCC1 expression decreases and the expression of the genetically related chloride-extruding K-Cl cotransporter KCC2 increases, which turns GABA_A receptor activation inhibitory because Cl⁻ flows into the cell (for a review, see [135]).

6. GABAergic system in early-life epilepsies

The incidence of seizures classified as reactive, symptomatic, or idiopathic is particularly high in the early ages of life. The most common reactive seizures in early life are febrile convulsions, although they must be differentiated from symptomatic seizures precipitated by fever. Symptomatic seizures are often associated with different levels of CNS insults, including HIE, metabolic storage diseases gray matter, and brain congenital malformations. In the neuronal migration disorders and idiopathic seizures, increasingly a genetic defect can be identified (e.g., LIS1 mutations for lissencephaly). In all these instances, the GABAergic system has been proposed as a key player in “age-dependent vulnerability to seizures” [136, 137].

During seizures, the release of GABA occurs, and this outward flow of Cl⁻ in neonatal neurons is excitatory. The immaturity of GABAergic inhibitory systems has been implicated in the heightened susceptibility of neonates to seizures in early-life epilepsies, and contributes to a greater seizure propensity and poor electroencephalographic response to GABAergic anti-convulsants such as phenobarbital (PB) and benzodiazepine [133]. This is thought to be due to shunting inhibition or inhibition via excitatory effects upon inhibitory interneurons [138]. During seizures, the excessive GABAergic stimulation of the substantia nigra reticulata that is believed to occur has been reported to be proconvulsant in neonatal animals while it would be anticonvulsant at older ages [139]. This developmental switch seems to occur earlier in female rats [140]. But in addition to GABA synapses, also the intact glutamatergic transmission

has been linked to the appearance of a BS pattern [141]. Therefore, certain neocortical cell types may act as EEG burst-suppression pacemakers, in particular the “fast-rhythmic-bursting” neurons described in neocortex [142].

Gene symbol	Titles	Locus	OMIM	EIEE
Genes impair interneuron migration				
ARX	Aristaless-related homeobox, X-linked	Xp21.3	300382	EIEE 1/LISX2
HER4/ERBB4	Tyrosine kinase-type cell surface receptor HER4 (Neuregulin-1receptor ErbB4)	2q34	600543	EIEE 3 (EME)
Genes encoding ion channels				
SCN1A	Sodium channel, neuronal type 1a subunit;	2q24.3	182389	EIEE 6 or Dravet Synd. GEFSP2/FEB3A/MHP3
SCN2A	Sodium channel neuronal type 2a subunit	2q24.3	182390	EIEE 11/BFIS3
SCN8A	Sodium channel neuronal type 8a subunit	12q13	600702	EIEE 13
KCNA2	Potassium channel, voltage-gated, shaker-related subfamily, member 2	1p13.3	176262	EIEE 32
KCNQ2	Potassium channel, voltage-gated, KQT-like subfamily, member 2	20q13.3	602235	EIEE 7/BFNS1
KCNB1	Potassium channel, voltage-gated, Shab-related subfamily, member 1	20q13.13	600397	EIEE 26
KCNT1	Potassium channel, subfamily t, member 1	9q34.3	608167	EIEE 14
CACNA2D2	Calcium channel, voltage-dependent, alpha 2/delta subunit 2	3p21.31	607082	VUS
HCN1	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1	5p12	602780	EIEE 24
Genes encoding regulators of synaptic vesicles release				
DNM1	Dynamin-1	9q34.11	602377	EIEE 31
NECAP1	Necap endocytosis-associated protein 1	12p13.31	611623	EIEE 21
TBC1D24	Tbc1 domain family, member 24	16p13.3	613577	EIEE 16
STXBP1	Syntaxin-binding protein 1	9q34.1	602926	EIEE 4
Genes encoding regulators of intracellular/intercellular signal transduction				
DOCK7	Dedicator of cytokinesis 7	1p31.1	615730	EIEE 23
GNAO1	Guanine nucleotide-binding protein, alpha-activating activity polypeptide 1	16q13	139311	EIEE 17
ARHGEF9	Rho guanine nucleotide exchange factor 9	Xq11.1	300429	EIEE 8/hyperekplexia
ST3Gal III	St3 beta-galactoside alpha-2,3-sialyltransferase 3	1p34.1	606494	EIEE 15

Gene symbol	Titles	Locus	OMIM	EIEE
WWOX	Ww domain-containing oxidoreductase	16q23	605131	EIEE 28
SPTAN1	Spectrin, alpha, nonerythrocytic 1	9q34.11	182810	EIEE 5
PCDH19	Protocadherin 19	Xq22.1	300460	EIEE 9
PLCB1	Phospholipase c, beta-1	20p12.3	607120	EIEE 12
PIGA	Phosphatidylinositol glycan, class A	Xp22.2	311770	EIEE 20
AARS	Alanyl-tRNA synthetase	16q22.1	601065	EIEE 29
SIK1	Salt-inducible kinase 1	21q22.3	605705	EIEE 30
ALG13	Asparagine-linked glycosylation 13	Xq23	300776	EIEE 36
Genes encoding neurotransmitters membrane receptors				
GRIN 2A	Glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2 ^a	16p13.2	138253	FESD
GRIN2 B	Glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2b	12p13.1	138252	EIEE 27
GABRA 1	Gamma-aminobutyric acid receptor, alpha-1	5q34	137160	EIEE 19
Genes encoding intracellular transporters				
SLC12A5	Solute carrier family 12 (potassium/chloride transporter), member 5	20q13.12	606726	EIEE 34
SLC13A5	Solute carrier family 13 (sodium-dependent citrate transporter)	17p13.1	137160	EIEE 25
SLC25A22	Solute carrier family 25 (mitochondrial carrier, glutamate) member 22	11p15.5	609302	EIEE 3 (EME)
SLC35A2	Solute carrier family 35 (UDP-galactose transporter), member 2	Xp11.23	314375	EIEE 22
EEF1A2	Eukaryotic translation elongation factor 1, alpha-2	20q13.33	602959	EIEE 33
Genes encoding enzymes				
SZT2	Seizure threshold 2	1p34.2	615463	EIEE 18
CDKL5	Cyclin-dependent kinase-like 5	Xp22.13	300203	EIEE 2
PNKP	Polynucleotide kinase 3-prime phosphatase	19q13.4	605610	EIEE 10
ITPA	Inosine triphosphate pyrophosphohydrolase	20p13	147520	EIEE 35

EIEE: early infantile epileptic encephalopathy. LISX2: lissencephaly, X-linked 2. EME: early myoclonic encephalopathy. GEFSP2: epilepsy, generalized, febrile plus, type 2. FEB3A: febrile seizures, familial, 3A. MHP3: migraine, familial hemiplegic, 3. BFIS3: benign familial infantile seizures-3. BFNS1: benign familial neonatal seizures. VUS: variant of uncertain significance because its contribution to EIEE has not been confirmed. FESD: focal epilepsy and speech disorder.

Table 3. Genes of early-onset epileptic encephalopathies.

Mutations or genetic variations of the genes encoding the $\alpha 1$, $\alpha 6$, $\beta 2$, $\beta 3$, $\gamma 2$, or δ subunits (GABRA1, GABRA6, GABRB2, GABRB3, GABRG2, and GABRD, respectively) of the GABA_A receptor have been associated with the pathomechanisms of human epilepsy and genetic epilepsy syndromes, both with and without febrile seizures syndromes, including pure febrile seizures (FSs), generalized epilepsy with febrile seizures plus (GEFS+), Dravet's syndrome (DS, also known as severe myoclonic epilepsy in infancy, SMEI), childhood absence epilepsy (CAE), and juvenile myoclonic epilepsy (JME). Related genotypic and phenotypic spectra of mutations of GABA_A receptor are changeful, thus, mutations of GABRA1 (137160) in 5q34 were associated with EIEE19 or DS. Recently, mutations of GABRA1, GABRB2, and GABRB3 were associated with ISS and Lennox-Gastaut syndrome, and also GABRB3-related EOEE [143]. These mutations that compromise hyperpolarization through GABA_A receptors are found in both translated and untranslated gene regions. Interestingly, most of the insufficiencies are not caused by receptor-gating abnormalities, but by multiple mechanisms, including (I) endoplasmic reticulum (ER)-associated degradation; (II) reducing subunit mRNA transcription or stability, impairing subunit folding, stability, or oligomerization; (III) intracellular-trafficking defects; and (IV) ER stress [144, 145].

While ion channel genes were considered for a long time as the only major group of genes involved in genetic epilepsies, at present, an increasing number of non-ion-channel genes and new pathways have been identified and it is difficult to find a common mechanism to explain EOEE. In 2015, Mario Mastrangelo [43] summarized clinical presentations, genotype-phenotype relationships, and genes involved in the pathogenesis of EOEE comprising genes encoding ion channels, regulators of synaptic vesicles release, regulators of intracellular/intercellular signal transduction, NT, membrane receptors, intracellular transporters, and enzymes (see **Table 3**).

The study of epilepsy due to single gene defects has helped to clarify certain seizure mechanisms. The role of ARX mutations is well defined on downstream targets of this interneuron-expressed transcription factor as well as their effects on cell migration and maturation of GABAergic interneurons, which can help to explain the phenotype of ISS and electrographic seizures [146]. During the early stages of development, ARX is expressed in a significant proportion of neurons in the cortex, striatum, ganglionic eminences, and the spinal cord. In the adult, the expression of ARX is still present but restricted to regions that are known to be rich in GABAergic neurons, such as the amygdala and olfactory bulb [47]. SCN1A mutations also implicate a predominant role for GABA interneurons due to disturbed GABAergic function [147].

A variety of the named "epilepsy-age-dependent epileptic encephalopathies" is considered to share a common pathological mechanism connected with the structural and functional disturbance of interneurons, and therefore they have been designated with a new term "interneuronopathies" [55, 148, 149, 150]. However, not only interneurons but also pyramidal neurons could be at the origin of these encephalopathies. Therefore, those genes that disrupt the glutamate metabolism via mitochondrial respiratory chain damage (i.e., mitochondrial glutamate carrier SLC25A22) should also be considered as an important cause of the neonatal epileptic encephalopathy (EME, EIEE3) [151].

Another example of a gene that presents mutations related to EIEE23 is DOCK7 (Dedicator of cytokinesis 7, locus 1p31.3). Overexpression of human DOCK7 in transfected embryonic rat hippocampal neurons induced the formation of multiple axons, whereas knockdown of Dock7 inhibited axon formation. DOCK7 is an important regulator of microtubule assembly both in the context of neurogenesis and in the establishment of neuronal polarity in newborn pyramidal neurons. It also promotes the development of nascent axons by activating Rac1 (a Rac guanine nucleotide exchange factor). In addition, DOCK7 controls the development and the morphological differentiation of GABAergic interneurons in the developing cortex. In human, the loss of DOCK7 function causes a syndromic form of epileptic encephalopathy and cortical blindness (EIEE23) by affecting multiple neuronal processes, with different types of seizures, including tonic seizures, infantile spasms myoclonus, partial complex seizures with rotation of the head, drop attacks, and tonic seizures among other crises [152]. Thus, some genes may be involved in several pathways of cortical development.

Quoting the words of Connie Wu [93], “the so called “GABA shift” is a fascinating change in the effect of GABA from depolarizing action in the developing brain to hyperpolarizing action in the adult brain”. The depolarizing action of the GABAergic system would be governed by glutamate with an inhibitory effect on this early excitatory activity of the GABA in the early neocortex [153], and by GABA_B receptors-mediated inhibition of GABA_A receptor calcium elevations in the developing hypothalamus, providing a mechanism for excitatory-inhibitory balance during development [154].

Additionally, the full maturation of the GABAergic system in humans occurs after the neonatal period. In the human cerebral cortex and WM, there is evidence that an important part of the development of the GABAergic system takes place during the latter half of gestation and into the first few years of infancy [155]. In point of fact, it is possible that the human GABAergic system does not completely mature until adolescence [156]. The interruption of any aspect of this sequence of events during development, due to either an environmental insult or genetic mutations, could have devastating consequences on normal brain function [157], and may interfere neuronal morphology, differentiation, and connectivity, manifesting as cognitive or neurodevelopmental deficits. In the same vein, further dysregulation of inhibitory GABA systems has been shown to play a major role in facilitating seizures, particularly marked in the early neonatal ages [158].

One hypothesis that has been presented is that the normal variability in the number of interneurons could explain the propensity of some individuals to develop epilepsy more than others as a result of an injury or any other trigger that could lead to neuron loss. Particularly, if chandelier cells (which are considered to be the most powerful cortical GABAergic inhibitory interneuron) were affected, it would have serious consequences for the inhibitory control of the pyramidal cells [159]. Recent data have shown that early postnatal transplantation of interneuronal precursor cells increased GABAergic inhibition in the host brain and dramatically suppressed seizure activity in epileptic mice [160]. These data create future expectations for “the Promise of an Interneuron-based Cell Therapy for patients with intractable forms of epilepsy” [161].

7. Antiepileptic drugs (AEDs) in EIEE

As we mentioned previously, epilepsy in children represents a symptom of complex brain diseases, presenting with a variety of syndromes, with many treatment options and disparing results. The prognosis is generally good, with a large proportion responding well to the first treatment given. But a substantial share (particularly children with epileptogenic encephalopathies), however, will not respond well to AEDs, despite aggressive and often off-label use of a variety of drugs. For these patients, the clinical goal is to find an optimal balance between the benefits and side effects of a particular medication.

Before 1993, the management of epilepsy was limited to six major AEDs consisting of phenobarbital, primidone, phenytoin, valproate, carbamazepine, and ethosuximide (ESM). These were referred to as the “first-generation AEDs” or traditional AEDs. Since the 1990s new drugs were introduced and called “second-generation” antiepileptic drugs, including felbamate, gabapentin (GBP), lamotrigine, topiramate, tiagabine (TGB), levetiracetam (LEV), oxcarbazepine, zonisamide, vigabatrin (VGB), and pregabalin [162]. Newly published evidence-based treatment guidelines have helped physicians to choose the most effective AED in pediatric epilepsy, although data do not always fully support new antiepileptic drugs due to lack of well-designed, randomized controlled trials [163].

At present, there are about 20 novel antiepileptic drugs, categorized as “third generation”. Some of these drugs are derived from others that can be found in today’s market place. Among the most representative include brivaracetam and seletracetam (analogs of levetiracetam), pregabalin, ganaxolone (GNX) (belong to neurosteroids), carisbamate and fluorofelbamate (analog of felbamate), rufinamide, safinamide (inhibit the release of glutamate), lacosamide, eslicarbazepine (analog of the antiepileptic drug oxcarbazepine), and talampanel (glutamate antagonist). Some of these drugs are recommended only in adults, but it is expected that they would also be included for therapy in children in the future, as it happened with the second-generation AEDs (see **Table 4**).

The second-generation AEDs have less effect on hepatic metabolism and cytochrome P450 induction, fewer drug interactions, and lower protein binding. Their off-label use in pediatric patients is fairly widespread and has given new options for the treatment of patients with epileptic encephalopathy and refractory epilepsy, despite most of these agents not having US Food and Drug Administration (FDA) indications for use [164, 165]. However, the newer AEDs are not more efficacious than the older-generation AEDs. In particular, there is no clinical evidence to suggest that the newer agents should be considered as a first-choice treatment in any form of epilepsy in children [166].

The Task Force Report for the ILAE Commission of Pediatrics, in a recent report [167], summarizes the recommendations for the management of infantile seizures. For focal seizures, levetiracetam is effective (strong evidence); for generalized seizures, weak evidence supports levetiracetam, valproate, lamotrigine, topiramate, and clobazam (CLB); for Dravet’s syndrome, strong evidence supports that stiripentol is effective (in combination with valproate and clobazam), whereas weak evidence supports that topiramate, zonisamide, valproate, bromide,

and the ketogenic diet are possibly effective; and for Ohtahara syndrome, there is weak evidence that most antiepileptic drugs are poorly effective.

Main mechanism of action	Main groups		AEDs	
Factors that influence excitatory postsynaptic potential (EPSP): - Na ⁺ influx - Ca ⁺⁺ currents - Paroxysmal Depolarization	Sodium Influx	Sodium channel blockers	Phenytoin (PHT) Carbamazepine(CBZ) Oxcarbazepine (OXC) Eslicarbazepine Zonisamide (ZNS) Lamotrigine(LTG) Lacosamide	
	Calcium Channel	Calcium current inhibitors	Ethosuximide(ESM)	
Factors that influence inhibitory postsynaptic potential (IPSP). - K ⁺ efflux - Cl ⁻ influx - Pumps - Low pH	GABA-A receptor by Cl influx.	GABA enhancers	GABA A agonist (enhanced by binding directly to GABA-A receptors) Barbiturates Primidone Benzodiazepines Progesterone Ganaxalone	
		Uptake inhibitor (by blocking presynaptic GABA uptake)	Tiagabine(TGB)	
		GABA-transaminase inhibitor (by inhibiting the metabolism)	Vigabatrine (VGB)	
		GAD modulation (increasing the synthesis of GABA)	Gabapentin(GBP) Valproate (VPA) Pregabalin Progabide(Prodrug)	
	GABA-B receptor by K efflux		GABA-B receptors antagonist CGP35348	
	Glutamate receptors facilitate the flow of both Na and Ca ions into the cell, while K ions flow out of the cell, resulting in excitation	Glutamate blockers	NMDA	Felbamate
			AMPA/KAINATE	Topiramate (TPM) Parampanel
Neuronal Potassium Channel Openers			Ezogabine (known as retigabine)	
Carbonic anhydrase inhibitors (decreases the pH)			Acetazolamide	
Unknown	Binds the Synaptic vesicle protein 2A (SV2A) (function has not been clearly defined; by Ca ⁺⁺ ?)		Levetiracetam (LEV) (Glycine?) Brivaracetam Rufinamide	

AEDs Main Group Classification, basis in main mechanism of action: excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP). Several mechanisms of action are indicated by arrows

Table 4. Mechanism of action of antiepileptic drugs (AEDs).

Research on the molecular basis and pathways of some epilepsy syndromes has become practical clinical task and has a clear value for both the patient and his family. It is now possible for some cases to make therapeutic decisions made based on genetic findings of EIEE. This capacity for precision therapy is expected to become more usual in the near future [168].

An extensive knowledge of the genes involved in EIEE may allow a more appropriate use of AEDs based on their mechanism of action. The AEDs can also be grouped according to their primary mechanism of action, although many of them have various actions and others have unknown mechanisms of action. The main groups include (1) GABA enhancers and (2) non-GABAergic antiepileptic drugs: sodium channel blockers, calcium current inhibitors, glutamate blockers, neuronal potassium channel openers, carbonic anhydrase (CA) inhibitors, and drugs with unknown mechanisms of action (see **Table 4**).

7.1. AEDs and GABAergic system

The current GABAergic antiepileptic drugs (especially GABA receptor agonists), while often effective for adults, are not always capable of stopping seizures and preventing their sequelae in neonates. The GABAergic drugs mainly include phenobarbital, benzodiazepines, tiagabine, vigabatrin, gabapentin, valproate, and pregabalin.

7.1.1. GABA receptor agonists: drugs that enhance the actions of the neurotransmitter GABA

A number of antiepileptic drugs (AEDs) have agonistic effects on GABA subtype A ($GABA_A$) receptors. Currently, the first-line medical treatment for neonatal seizures is composed of drugs that increase $GABA_A$ Rs, such as phenobarbital and benzodiazepines (clobazam, clonazepam); another treatment strategy is the indirect manipulation of the GABAergic system, via the modulation of neuronal Cl^- gradients, by targeting the cation- Cl^- cotransporters (NKCC1 and KCC2) or their regulatory signaling molecules [169].

- **Phenobarbital (PB)** increases $GABA_A$ Rs. PB has been the gold standard and remains the preferred drug for the management of neonatal seizures for the treatment of seizures in neonates [170]; however, PB controls seizures in less than half of newborns [171]. This reduced efficacy of GABA-enhancing AEDs has been linked to neuronal chloride transport in the developing brain. It is also intriguing to consider that recent insights regarding the impact of maturational changes in neuronal chloride transporter expression on GABA receptor function may provide strategies for adjunctive therapies of neonatal seizures, and could improve the neuroprotective efficacy of PB in the neonate.

Specifically, blocking the neonatal neuronal chloride transporter with **bumetanide** (a specific inhibitor of the NaC-KC- 2Cl cotransporter NKCC1) can augment the inhibitory activity of GABA agonists such as PB [172, 173]. Low concentrations of the diuretic bumetanide have been shown to alter the ion gradient that underlies the excitatory effects of GABA. Blocking the NKCC1 transporter with bumetanide prevents outward Cl^- flux and causes a more negative GABA equilibrium potential in immature neurons. While several studies have reported anticonvulsant effects of bumetanide [174], others have found no significant anticonvulsant effect. The alteration of Cl^- transport by bumetanide reduces electrographic seizures, and the

combination of bumetanide and PB is significantly more effective than PB alone on seizure occurrence, frequency, and duration [172].

- **Stiripentol (STP):** STP enhances central GABA transmission through a barbiturate-like effect, since it increases the duration of opening of GABA-A receptor channels, and also may increase the GABA levels by interfering with its uptake and its metabolism. In 2007, the European Medicines Agency granted STP a marketing authorization for Dravet's syndrome whose seizures are not adequately controlled with clobazam and valproate. The combination of STP with clobazam (CLB) and valproate seems promising for therapy of severe myoclonic epilepsy in infancy (SMEN) with a responder rate of 54% [175], as well as to suppress convulsive status epilepticus [176].
- **Benzodiazepines:** The benzodiazepines most often used for the treatment of epilepsy are diazepam, midazolam, lorazepam, clonazepam, and clobazam. The first three drugs are used primarily in protocols for emergency treatment of seizures and status epilepticus due to their rapid onset of action, the availability of intravenous (IV) forms, and anticonvulsant effects. Its use for long-term treatment is limited due to the development of tolerance. Benzodiazepines are used in (phenobarbital) refractory cases of neonatal seizures [177].
 - **Clonazepam** has higher affinity for the GABA_A receptor site than diazepam and binds to GABA_A receptors that do not bind other benzodiazepines. Clonazepam is the drug of choice for myoclonic seizures and subcortical myoclonus.
 - **Clobazam (CLB):** In addition to its agonist action at the GABA_A receptor, clobazam may affect voltage-sensitive conductance of calcium ions and the function of sodium channels, which makes CLB a potent anticonvulsant for partial epilepsy.

7.1.2. Uptake inhibitor (by blocking presynaptic GABA uptake)

Tiagabine (TGB) represents a new generation of AEDs. It is a derivative of nipecotic acid, with a unique mechanism of action: uptake inhibitor, by blocking presynaptic GABA uptake. TGB was approved for use by the FDA in 1997 as an adjunct agent for adults and children past 12 years of age with epilepsy, suffering from partial seizures, with and without secondary generalization. Following a period of great enthusiasm for the use of TGB, it was put aside. The FDA on 18 February 2005 issued a warning about the possible occurrence of nonconvulsive as well as convulsive status epilepticus in a subset of nonepileptic and epileptic patients treated with TGB [178], and should be under surveillance of frequency and severity of TGB overdoses and reported to the American Association of Poison Control Centers (AAPCC).

There are very little data on TGB use in children, but this agent appears to be effective and have a good tolerability profile and it still has its place in the treatment of drug-resistant epilepsy.

7.1.3. GABA transaminase inhibitors (inhibition of the GABA-degrading enzyme)

- **The Vigabatrin (VGB)** has been widely used for the treatment of refractory epilepsies in epileptic encephalopathies. The anti-seizure effect of VGB is a result of enhanced brain

extracellular GABA levels by irreversible inhibition of the GABA-degrading enzyme GABA aminotransferase (GABA-T) [179]. VGB inhibits GABA-T and elevates GABA in the subthalamic nucleus (STN) [180].

ACTH, corticosteroids, and VGB are the first-line drugs for the treatment of ISS. However, the detection of an irreversible visual field defect observed in as high as 30–50% of children treated with VGB has contraindicated its use as first-line drug. Regarding West syndrome, there is some evidence for the preference of hormonal treatments over VGB, except for children under 3 months. In children with tuberous sclerosis complex (TSC), VGB is the treatment of first choice. Around 30% of patients who present with ISS respond well to treatment with VGB. VGB should be considered as an early treatment option in early-onset epileptic encephalopathies (EIEE and EME) [181]. Patients with mutation in STXBP1 gene could especially benefit from treatment with VGB [182]. Interestingly, VGB can cause swelling and loss of myelin, suggesting that excessive activation of GABA_A receptors while oligodendrocytes are undergoing myelination may be deleterious for that process [183].

7.1.4. GAD modulation

GAD modulation increases GABA turnover/synthesis of GABA.

- **Gabapentin (GBP)** was approved on January 1994 as an adjunctive treatment in patients 12 years or older with partial seizures, with or devoid of secondary generalization, which were resistant to the traditional AEDs. GBP is an anticonvulsant GABA-mimetic and considered as a structural analog of the inhibitory NT GABA. However, preliminary studies proposed that GBP did not bind to either GABA_A or GABA_B receptors, nor was it transformed metabolically into GABA. GBP prevents voltage-dependent sodium currents, and it is also claimed to reduce presynaptic glutamate release and binding to postsynaptic calcium channels and prevent central desensitization due to glutamate neurotransmission in the dorsal horn of the spinal canal [184].

GBP has been used in both adults and children for numerous neurologic conditions, including management of epilepsy, neuropathic pain (control of pain and irritability attributed to neurologic impairment), refractory insomnia, and occasionally movement disorders (e.g., restless legs syndrome, dystonia, and nystagmus) [185]. GBP use for seizure has been limited as a result of inconsistent efficacy and concern about seizure exacerbation (in particular, aggravation of myoclonic seizures) [186]. GBP may significantly ameliorate dystonia severity and improve activities of daily living and quality of life in children [187].

- **Sodium valproate (VPA)** acts through a combination of several mechanisms. Among the mechanisms through which valproate exerts its anticonvulsant properties, an increase in GABA turnover is included by significantly enhanced GABA inhibition in the cerebral cortex, an action which is independent of its effect on spontaneous activity [188]. Thereby, it potentiates GABAergic functions in some specific brain regions, such as substantia nigra, thought to be involved in the control of seizure generation and propagation [189]. In children, and especially in infants with epileptic encephalopathies, treatment with valproate is preferred when proper diagnosis is not achieved [190].

- **Pregabalin:** GBP and pregabalin are structurally related to the inhibitory neurotransmitter GABA, and can modulate voltage-activated Ca^{2+} channels. The pharmacological activity of pregabalin is similar but not identical to that of GBP. Pregabalin reduces excitatory properties by modulating voltage-activated Ca^{2+} and K^{+} channels. The actions of pregabalin may involve both extracellular and intracellular drug target sites and modulation of a variety of neuronal conductances, by direct interactions and through intracellular signaling involving protein kinase A [191]. Pregabalin is remarkable for seizure control in children with intractable epilepsy, and reduced more than 50% of seizure intensity in 40.2% of patients [192], although there are no references to support the use of pregabalin in Ohtahara syndrome.

7.2. Non-GABAergic antiepileptic drugs

7.2.1. Sodium channel blockers

With the increasing knowledge of the involvement of ion channels in the origin of epilepsy, a greater number of publications that establish optimal treatment based on the genetic defect have been appearing. This evidence may allow in the future to establish a "treatment on demand." This is particularly important for genes encoding ion channels and sodium channel blockers, such as:

- First generation: phenytoin (PHT), carbamazepine (CBZ);
- Second generation: oxcarbazepine (OXC), zonisamide (ZNS), lamotrigine (LTG);
- Third generation: eslicarbazepine, lacosamide.

Concerning Dravet's syndrome (caused in 80% of cases by mutations in *SCN1A*), there is some evidence showing that early aggressive therapy improves outcome, so genetic testing should be considered early. The *SCN1A* protein appears to be mainly on inhibitory interneurons, and treatment with sodium channel blockers such as lamotrigine and carbamazepine should be avoided, whereas valproic acid, topiramate, clobazam, and stiripentol appear to be beneficial [193, 194]. By contrast, in the epileptic encephalopathies associated with mutations in *SCN2A* and *SCN8A*, their profile of drug responsiveness may be different since the proteins encoded by these genes are localized in excitatory neurons. In fact, for *SCN8A* encephalopathy, sodium channel blockers may be effective in some cases [195].

Regarding the Ohtahara syndrome caused by mutations in the *KCNQ2* channel, recent experience suggests that sodium channel blockers, carbamazepine, and phenytoin (40 and 33%, respectively, were seizure-free), are effective in this disorder. An effective treatment may be important for reducing the neurodevelopmental impairment associated with this disorder [60, 196].

Besides the known use of phenytoin for the treatment of neonatal seizures, other AEDs second generation such as oxcarbazepine and zonisamide have been relatively well studied in pediatric seizure patients, including their use as monotherapy. Both agents have demonstrated good efficacy and tolerability for patients as young as 1 month old. Zonisamide is efficacious

in pediatric epilepsy syndromes, including LGS, WS, OS [197], and for seizure control in children with intractable epilepsy [192].

7.2.2. Calcium current inhibitors

- In addition to ethosuximide (ESM), other drugs such as topiramate (TPM) and LTG also act as calcium currents inhibitors. Childhood absence epilepsy (CAE) is one of the most common types of pediatric epilepsy. It is generally treated with ESM, VPA, or LTG. VPA-LTG combination therapy has a good efficacy and fewer side effects than other treatments, and it should thus be considered as a first-line therapy in absence of epilepsy [198]. ESM next to clobazam and sulthiame is the most commonly used treatment in patients with Landau-Kleffner syndrome (LKS), but it has no use in EIEE.

7.2.3. Glutamate blockers

7.2.3.1. NMDA antagonist

- **Felbamate:** Although felbamate has multiple mechanisms of action, it is thought to have its most potent antiepileptic effects through the inhibition of the N-methyl-D-aspartate receptor (NMDAR). Felbamate was approved in 1993 as a novel antiepileptic drug to be used both as monotherapy and as an adjunctive therapy to treat partial seizures with and without generalization in adults and as an adjunctive therapy for LGS. Despite its favorable efficacy, there has been restricted approval of felbamate only for adjunctive therapy in patients with LGS because of the occurrence of felbamate-related hepatotoxicity and idiosyncratic aplastic anemia. Our current understanding of clinical data on the risk: benefit of felbamate therapy supports its use as an important therapeutic option for some patients with refractory epilepsy [199]. Early initiation of felbamate is recommended for children with refractory epilepsy [200]. Felbamate monotherapy was able to achieve relevant antiepileptic effects in a unique patient with neurofibromatosis type 1 (NF1) and tuberous sclerosis complex (TSC) [201].
- **Memantine:** In a patient with a mutation in GRIN2A, encoding a glutamate NMDA receptor subunit, memantine therapy (acting on the glutamatergic system by blocking NMDA receptors) appeared effective [202]. This case exemplifies the potential for personalized genomics and therapeutics to be utilized for early diagnosis and treatment of infantile-onset neurological diseases.

7.2.3.2. AMPA/KAINATE antagonist

- **Topiramate (TPM)** exerts an antiepileptic effect via four mechanisms: (1) blockade of voltage-dependent sodium channels, (2) GABA_A agonist, (3) AMPA/kainate glutamate receptor subtype, and (4) inhibition of carbonic anhydrase isoenzymes type I and IV. In the United States, topiramate currently is approved for (1) partial-onset and secondarily GTCs, (2) primary GTCs, and (3) LGS. Currently, its use for the EOEE has not been established. Although TPM is well studied in adults and older children, limited data exist for the

application to neonates. The use of TPM in neonates has met with two significant challenges: first, to date no intravenous formulation is commercially available, and second, there is significant concern that TPM adversely affects language development [203]. TPM is a good add-on drug in patients with epileptic encephalopathies such as LGS and myoclonic astatic epilepsy. Regarding treatment options for ISS, TPM can be used when first-line drugs have proven ineffective. Cessation of all spasms occurred in 32 [204] to 48% infants treated with TPM [205]. In our experience (unpublished data), initial polytherapy with low dose of ACTH and TPM was effective to suppress ISS in most patients, allowing to leave TPM—after removal of ACTH—as AEDs of choice to prevent recurrence of the ISS. This combined treatment has been endorsed by other authors [206, 207].

- **Perampanel (PER):** PER is a newer antiepileptic drug, first-in-class orally active, selective noncompetitive AMPA receptor antagonist. In 2012, the European Union approved usage for adjunctive therapy in partial-onset seizures (for patients age >12 years), with US approval following in 2013 [208]. PER seems to be effective also in children and adolescents with pharmaco-refractory epilepsies. Tolerability was acceptable [209]. But randomized controlled trials in children are necessary to support its use.

7.2.4. Neuronal potassium channel openers

- **Retigabine (RTG)/ezogabine:** The new-generation drugs retigabine (RTG (international nonproprietary name)) and ezogabine (EZG (US adopted name)) are the first neuronal potassium ($K_V7_2-7_5$) channel openers (act uniquely by enhancing the M-type potassium current), and they are used as an adjunctive treatment for partial epilepsies in adult patients. Mutations in KCNQ2 and KCNQ3, encoding the voltage-gated potassium channels KV 7.2 and KV 7.3, are known to cause BFNS1 and severe epileptic encephalopathy with pharmaco-resistant seizures. Application of RTG partially reversed these effects for the majority of the analyzed mutations. Thus, RTG or similar drugs have been proposed for use as a personalized therapy for this severe disease [210]. But unfortunately toxicity may limit its use, and there are few data available on its effectiveness in KCNQ2 encephalopathy.

7.2.5. Carbonic anhydrase inhibitors

In humans, 16 different isozymes of the zinc enzyme carbonic anhydrases (CA) have been described and are considered as drug targets, some of them being involved in various pathological disorders such as glaucoma, epilepsy, and cancer.

Triggering mechanisms of seizures includes an increase of intracellular potassium concentration and a pH shift within the brain. pH buffering of extra- and intracellular spaces is mainly carried out by the CO_2/HCO_3^- buffer, the equilibration of the two species being assured by the zinc enzyme CA [211]. Neuronal excitability is related to GABAergic depolarization via $GABA_A$ receptor and contributed by HCO_3^- efflux, playing a role in initiating ictal-like epileptiform events in several cortical structures. HCO_3^- -dependent depolarization can be suppressed by membrane-permeable inhibitors of CA such as acetazolamide, methazolamide, zonisamide, topiramate, and sulthiame, which can reduce seizures through perturbation of

the CO₂ equilibrium and/or the inhibition of ion channels [212], leading to diminished depolarization of principal cells and, perhaps, interneurons [213].

- **Acetazolamide** has been approved for the treatment of epilepsy since 1953, and should be considered when there is a poor response to conventional antiepileptic drugs or refractory epilepsy. They have been used in various diseases including LKS [214], dominant paroxysmal ataxia, juvenile myoclonic epilepsy, newborn with Arnold-Chiari malformation with central apneas, or in epileptic apnea in MMPSI resulting in complete disappearance of epileptic seizures [215].
- **Sulthiame** is an inhibitor of CA and a widely used add-on antiepileptic drug for the treatment of intractable epilepsy, WS, status epilepticus during sleep (ESES), continuous spikes and waves during slow sleep (CSWS) syndrome, and LKS, which was refractory to other AEDs. Sulthiame may lead to a cessation of seizures when used as an add-on therapy to pyridoxine in patients with WS. No evidence exists for the use of sulthiame as an add-on therapy in patients with epilepsy outside WS. Large, multicenter randomized controlled trials are necessary to inform clinical practice if sulthiame is to be used as an add-on therapy for epilepsy [216]. Sulthiame was associated with deterioration in cognitive function in children with benign epilepsy of childhood with central temporal spikes [217].

7.3. Others

7.3.1. *Drugs with unknown mechanisms of action*

- **Levetiracetam (LEV):** Although the mechanism of action of LEV is still not well defined, new hypotheses propose that LEV and brivaracetam act by accelerating the induction of supply rate depression in synaptic vesicle trafficking, mainly synaptic vesicle glycoprotein 2a (SV2a) during incipient epileptic activity [218]. SV2 (encoded by the SV2A gene -OMIM 185860-) might mediate the uptake of NTs into vesicles. Loss of SV2A leads to a reduction in action potential-dependent gamma-aminobutyric acid (GABA)ergic neurotransmission [219]. LEV is utilized for the treatment of seizures, including neonatal seizures. There is strong evidence that LEV is effective in the treatment of focal seizures, whereas for generalized seizures, there is weak evidence to support the use of levetiracetam, valproate, lamotrigine, topiramate, and clobazam uses [167]. Treatment with intravenous levetiracetam is the new option for patients with refractory status epilepticus, even in patients younger than 2 years old (off-label use) [220]. Status epilepticus is characterized by downregulation of the inhibitory gamma-aminobutyric acid system, and LEV acting via different mechanisms could slow the epileptogenesis. Lately, LEV has been considered as the first-choice treatment for patients with early-onset epileptic encephalopathy due to an STXBP1 mutation and refractory to other antiepileptic drugs [221, 222].
- **Rufinamide** is a triazole derivative that is structurally unrelated to any currently marketed AEDs. It was approved by the FDA in December 2008 for adjunctive treatment of seizures associated with LGS for children 4 years or older and for adults. The precise mechanism by which rufinamide exerts its antiepileptic effect is unknown. In vitro studies suggest that the

principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Placebo-controlled studies for rufinamide that have efficacy data include studies involving (1) patients with LGS in children aged 1 year or older, (2) pediatric partial-onset seizures as adjunctive therapy, (3) adult partial-onset seizures (for both monotherapy and adjunctive therapy), and (4) patients with refractory GTCs [223]. Few studies in children with epileptic encephalopathies (EE) aged <4 years show that RUF is efficacious (60% were responders) and well tolerated. Therefore, for controlling seizures in this very severe form of epilepsy, the off-label use of RUF is justified [224].

7.3.2. Steroid hormones and neurosteroids

Steroid hormones and neurosteroids play an important role in children and adults with epilepsy, and act on both synaptic and extrasynaptic GABA_A receptors. Corticosteroids, progesterone, estrogens, and neurosteroids have been shown to affect seizure activity in animal models and in clinical studies (for a review, see [225]).

- **Sex-steroid hormones** influence brain excitability and could explain sex differences in seizure susceptibility. Androgens are mainly anticonvulsant (mainly enhance GABA-activated currents), but the effects are more varied. For the female gender, progesterone and its metabolites are anticonvulsant, while estrogens are mainly proconvulsant (e.g., catamenial epilepsy). Estrogens reduce chloride conductance and potentiate glutamate receptor-mediated excitotoxicity responses (by potentiating NMDA receptor activity), but also affect GABAergic mechanisms and alter brain morphology by enhancing the density dendrite spine. Progesterone is a natural endogenous anticonvulsant hormone with substantial impact on seizure susceptibility that acts mainly to enhance postsynaptic GABAergic activity by increasing chloride conductance at GABA_A receptors and attenuates the glutamate excitatory response. It also alters messenger RNA for glutamic acid decarboxylase and GABA_A receptor subunits (for a review, see [226]).
- **Adrenocorticotrophic hormone and oral corticosteroids:** Pituitary-adrenal hormones have long been known to affect epileptogenesis. Even though the mechanism behind the efficacy of ACTH is mediated by biochemical processes that remain unknown, a reduction in glutamine/glutamate levels in the cerebral cortex after ACTH therapy in patients with WS has been shown [227]. Systemic administration of ACTH causes an increase in midbrain and striatal GABA receptor binding [228]. ACTH, oral corticosteroids, and VGB are now first-line treatments for IS in the United States and Europe. The current literature suggests that short-term, low-dose ACTH (versus high dose) should be considered first-line treatment of IS [229], and is more effective than oral corticosteroids and VGB for the cessation of spasms. ACTH is preferred for short-term control of epileptic spasms not due to tuberous sclerosis (level B recommendation). Oral steroids are probably effective in short-term control of spasms (level C recommendation), and a shorter interval from the onset of spasms to treatment initiation may improve long-term neurodevelopmental outcome (level C recommendation) [167]. Nevertheless, some clinicians use corticosteroids, VGB, and TPM as first-line treatments for this group. As we have already mentioned above, initial combined

treatment with low-dose ACTH and TPM was effective in treating ISS in most patients. After removing ACTH from the treatment regimen, TPM can be left as the AED of choice to prevent recurrence of the ISS. For refractory infantile spasms, other antiepileptic drugs have been used (i.e., valproate, zonisamide, sulthiame, levetiracetam, lamotrigine, pyridoxine, and ganaxolone) as well as adjunctive flunarizine and novel drugs not yet in clinical use (i.e., pulse rapamycin and melanocortin receptor agonists) [230].

- **Neurosteroids: Ganaxolone (GNX)** is the 3-beta-methylated synthetic analog of allopregnanolone; it belongs to a class of compounds referred to as neurosteroids. GNX is an allosteric modulator of GABA(A) receptors, acting through binding sites, which are distinct from the benzodiazepine-binding site [231]. In children with refractory ISS, or with continuing seizures after a prior history of ISS, ganaxolone has been used as a second-line drug [232].

7.3.3. Other drugs

- **Quinidine** reverses the in vitro functional gain seen with KCNT1 mutations implicated in EIEE 14, and a clinical response to quinidine has been observed [233, 234].
- **Rapamycin:** The recent discovery of the importance of mutations in DEPDC5 (OMIM 614191, “Dep domain-containing protein 5”) for familial focal epilepsy with variable foci (OMIM 604364), associated with both lesional (focal cortical dysplasia, band heterotopia, hemimegalencephaly, etc.) and non-lesional epilepsies, whose expression occurred throughout neurons and GABAergic interneurons in brain development, has provided a new source for therapeutic targets. Since DEPDC5 is now known to be a regulator of the mTOR (mammalian target of rapamycin) pathway, this raises the possibility of treatment with rapamycin analogs [235]. Modulation of the mammalian target of rapamycin pathway may hold promise for malformation-associated epilepsy. All of these observations will need careful double-blind trials to establish efficacy [236].
- **Potassium bromide**, an old antiepileptic drug, should have a place as a drug of tertiary choice in the treatment of children with refractory epilepsy. Its main use is in the treatment of MMPS [237] and Dravet’s syndrome [238].

8. Conclusion

The distinction between early infantile epileptic encephalopathy (EIEE) —mostly known as Ohtahara syndrome—and early myoclonic encephalopathy (EME), unfortunately, is not always easy due to clinical and etiological overlap. Thus, different authors suggest that both entities are actually the same entity.

The main differences lie in the type of crisis, which may correspond with the underlying activity of the GABAergic system. Acute noxa in the newborn with a still immature cortical brain produces a strong release of GABA. Due to the more depolarized Cl^- reversal potential in the neonatal neurons, the binding of GABA to ligand-gated GABA_A receptor-associated Cl^-

Ca^{2+} channels triggers Cl^- efflux and a depolarizing excitation leading to severe and early myoclonic seizures. However, when impairments in the proper migration of GABAergic interneurons occur, a longer period without epileptogenic activity would be expected. Tonic seizures would appear later associated with the severity of the brainstem dysfunction. According to this view, this second type would not be so much an “age-dependent encephalopathy” but rather a “damage-dependent encephalopathy”. Therefore, it is possible that these syndromes represent different stages of a progressive neuronal-dysfunction epileptic “continuum of pathology” with a suppression-burst pattern.

A greater knowledge of the genes involved in the origins of epilepsy may lead to a future with improved treatments for patients with early encephalopathies.

Nomenclature/abbreviations

ACTH	adrenocorticotrophic hormone
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy
AEDs	antiepileptic drugs
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ARX	aristaless-related homeobox gene
Array-CGH	array-comparative genomic hybridization
ASDs	autism spectrum disorders
BFNS1	benign familial neonatal seizures-1
BFIS3	benign familial infantile seizures-3
BLBP	brain lipid-binding protein
BS	burst suppression
CA	carbonic anhydrases
CAE	childhood absence epilepsy
CBZ	carbamazepine
CLB	clobazam
CNS	central nervous system
CNVs	copy number variations
CSWS	continuous spikes and waves during sleep
DS	Dravet’s syndrome
EAA	excitatory amino acids
EEG	electroencephalogram
EES	epileptic encephalopathies
EIEE	early infantile epileptic encephalopathy

EEIE	early <i>epileptic</i> infantile <i>encephalopathy</i>
EIMFS	epilepsy of infancy with migrating focal seizures
EME	early myoclonic encephalopathy
EOEEs	early-onset epileptic encephalopathies
ESES	status epilepticus during sleep
ESM	ethosuximide
EZG	ezogabine
GABA	gamma-aminobutyric acid
GABA _A Rs	GABA subtype A receptor channel chloride currents
GABA-T	GABA aminotransferase
GBP	gabapentin
GNX	ganaxolone
GPI	glycosylphosphatidylinositol
GTCs	generalized tonic-clonic seizures
HIE	hypoxic-ischemic encephalopathy
iGluRs	ionotropic glutamate receptors
ID	intellectual disability
ILAE	International League Against Epilepsy
ISS	infantile spasms
LCRs	low-copy repeats
LGS	Lennox-Gastaut syndrome
LKS	Landau-Kleffner syndrome
LTG	lamotrigine
MEI	myoclonic epilepsy in infancy
mGlu	metabotropic glutamate
MMPSI	malignant migrating partial seizures in infancy
MRI	magnetic resonance imaging
NAHR	non-allelic homologous recombination
NBs	newborns
NMDA	N-methyl-D-aspartic acid
NS	nervous system
NSID	nonsyndromic intellectual disability
NT	neurotransmitters
OLs	oligodendrocytes

OMIM	online Mendelian inheritance in man
OS	Ohtahara syndrome
OXC	oxcarbazepine
PER	perampanel
PB	phenobarbital
PCW	postconceptional weeks
PHT	phenytoin
RTG	retigabine
SBP	suppression-burst patterns
SDs	segmental duplication
SLC25A22	solute carrier family 25, member 22 gene
SMEN	severe myoclonic epilepsy in infancy
STN	subthalamic nucleus
SPZ	subplate zone
STP	stiripentol
S- XLMR	syndromic X-linked mental retardation
TARPs	transmembrane AMPA regulatory proteins
TGB	tiagabine
TPM	topiramate
VPA	sodium valproate
VGB	vigabatrin
WM	white matter
WS	West syndrome
XLMR	X-linked mental retardation
ZNS	zonisamide

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