Epileptic Encephalopathies in Childhood: The Role of Genetic Testing

Johannes R. Lemke, MD1  Steffen Syrbe, MD2

1Institute of Human Genetics, University of Leipzig, Leipzig, Germany
2Department of Women and Child Health, Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany


Abstract

The epileptic encephalopathies comprise a heterogeneous group of neurodevelopmental disorders characterized by marked epileptic activity associated with developmental regression. The genetic confirmation and classification of a clinical diagnosis in an individual may provide certainty in treatment decisions, prognosis, and evaluation of seizure recurrence risks and may also prevent unnecessary diagnostic investigations. Furthermore, without genetic testing it is challenging to classify the epileptic encephalopathies based on clinical and electroencephalogram features alone.

The significant gain of knowledge of the past few years associated with improvement in genetic analyses allows for precise diagnoses in an increasing number of patients. As a consequence, known encephalopathies have been associated with even broader phenotypic ranges and novel entities constantly expand the spectrum of these disorders. Accordingly, many entities of this heterogeneous spectrum escape a precise classification using current nomenclatures.

Epileptic encephalopathies comprise a spectrum of disorders manifesting epilepsy and consequent psychomotor delay. According to the International League Against Epilepsy (ILAE), the epileptic activity itself most likely contributes to the severe cognitive and behavioral impairments, above and beyond that expected from the underlying pathology alone.1 Many forms of epileptic encephalopathy worsen over time and are refractory to pharmacotherapy.

Here we provide an overview of the growing field of epileptic encephalopathies that have no detectable structural brain lesions or metabolic abnormalities during the neonatal period, infancy, and childhood. Furthermore, we discuss a classification based on the clinical phenotype and onset versus a classification based on the genetic background of this group of disorders.

The ILAE classification is based primarily on the age of seizure onset, and it differentiates epileptic encephalopathy entities that have a specific clinical appearance or a particular pattern on electroencephalogram (EEG):1

- Neonatal period
  - Early myoclonic encephalopathy
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders
- Childhood
  - Epilepsy with myoclonic atonic seizures
  - Lennox–Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave during sleep
  - Landau–Kleffner syndrome

Epileptic encephalopathies that have no recognizable EEG pattern, particular seizure semiology, or additional specific features are not covered by the current ILAE classification.
In contrast to the ILAE, Online Mendelian Inheritance in Man (OMIM; www.ncbi.nlm.nih.gov/omim) does not discriminate between clinical phenotypes, but classifies early-infantile epileptic encephalopathies exclusively according to the causative gene. This rapidly growing catalogue lists 30 such phenotypes (by May 2015). Some have so far only been

<table>
<thead>
<tr>
<th>OMIM entity</th>
<th>Gene</th>
<th>No. of published mutations in HGMD (as of May 6, 2015)</th>
<th>Allelic phenotypes (in addition to EIEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIEE1</td>
<td>ARX</td>
<td>69</td>
<td>Hydranencephaly with abnormal genitalia, X-linked lissencephaly 2, X-linked mental retardation 29, Partington syndrome, Proud syndrome</td>
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<td>EIEE2</td>
<td>CDKL5</td>
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<td>EIEE3</td>
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<td>SCN1A</td>
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<td>ARHGEF9</td>
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<td>SCN2A</td>
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<td>Benign familial infantile seizures 3</td>
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<td>EIEE13</td>
<td>SCN8A</td>
<td>27</td>
<td>Cognitive impairment with or without cerebellar ataxia</td>
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<td>KCNT1</td>
<td>15</td>
<td>Nocturnal frontal lobe epilepsy 3</td>
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<td>ST3GAL3</td>
<td>3</td>
<td>Autosomal recessive mental retardation 12</td>
</tr>
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<td>EIEE16</td>
<td>TBC1D24</td>
<td>21</td>
<td>DOOR syndrome, Autosomal recessive deafness 86 Familial infantile myoclonic epilepsy</td>
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<td>Idiopathic generalized epilepsy</td>
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<td>KCNB1</td>
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<td>GRIN2B</td>
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<td>Autism spectrum disorders</td>
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<td>EIEE28</td>
<td>WWOX</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>EIEE29</td>
<td>AARS</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>EIEE30</td>
<td>SIK1</td>
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reported as very rare and isolated cases, whereas others significantly overlap or form part of a continuum with different epileptic encephalopathies.

The allelic phenotypes include both incontrovertible monogenetic associations such as SCN1A and Dravet syndrome and as yet unproven risk alleles for complex phenotypes such as GABRA1 and juvenile myoclonic epilepsy.

The number of HGMD-listed mutations shows how often the disorder is diagnosed in the scientific literature. Due to allelic phenotypes, not all these mutations are associated with early infantile epileptic encephalopathy; for example, a minority of SCN1A mutations is associated with GEFS+ or hemiplegic migraine, and on the contrary, most KCNQ2 and SCN2A mutations cause benign familial epilepsy disorders—not early infantile epileptic encephalopathy (►Table 1).

Neonatal Period

Early Myoclonic Encephalopathy

Clinical Description

Early (or neonatal) myoclonic encephalopathy, together with Ohtahara syndrome, shows a characteristic burst-suppression pattern on EEG. Phenotypic similarities can make it difficult to distinguish these disorders, and some authors consider them as a fluid continuum.2 Aicardi and Goutières first described early myoclonic encephalopathy in 1978.1 It usually starts in the first days of life with predominantly myoclonic seizures. Recurrent familial cases have been attributed mainly to inherited disorders of metabolism, especially nonketotic hyperglycinemia, pyridoxine, and pyridoxal phosphate-dependent epilepsy, sulfite-oxidase deficiency, and Menkes disease, as well as brain malformations.4–6 The seizures are usually described as myoclonic or erratic myoclonus. Although shifting focal myoclonias that affect different parts of the body, including the face and eyelids, are regarded as nonepileptic, focal motor seizures occur in more than 80% of patients and can include autonomic ictal manifestations and apnea (►Figs. 1 and 2).7,8 A neonatal burst-suppression pattern may evolve into hypsarrhythmia within the first months of life. The prognosis is very poor, with severe global developmental delay and a mortality rate of up to 50% during the first 2 years of life. The prognosis is very poor, with severe global developmental delay and a mortality rate of up to 50% during the first 2 years of life.

Genetics

The genetic background of early myoclonic encephalopathy is unclear. There is a single report of a patient carrying a de novo reciprocal chromosomal translocation with consecutive disruption of the ERBB4 gene, being putatively involved in neuromigration.11 Another report associated mutations in PIGA with early myoclonic encephalopathy and other forms of epileptic encephalopathy.12

Ohtahara Syndrome or Early Infantile Epileptic Encephalopathy

Clinical Description

Ohtahara and colleagues first described early infantile epileptic encephalopathy in 1976 as a disorder starting during the first 3 months of infancy.13 It primarily differs from epileptic encephalopathy of infantile onset (e.g., West syndrome) because of dominating tonic spasms, the variable seizure types including focal motor seizures, and its specific EEG pattern (►Fig. 3).14 The cardinal EEG feature of Ohtahara

Fig. 1 Burst-suppression pattern in a patient with early myoclonic encephalopathy due to nonketotic hyperglycinemia. The patient showed shifting myoclonia, subtle seizures, and myoclonia including repetitive singultus. The burst-suppression pattern is more prominent during sleep.
Fig. 2 Burst-suppression pattern in a girl with early myoclonic encephalopathy of unclear etiology. She presented with near-constant myoclonus and increased muscle tone associated with multifocal myoclonia as well as frequent seizure-related apnea. Brain magnetic resonance imaging showed cerebellar hypoplasia and progressive global atrophy.

Fig. 3 Suppression period, followed by a burst of epileptic discharges that mark the onset of an ictal pattern in a 4-month-old girl with Ohtahara syndrome. Tonic seizures occurred at age 2 months, followed by multiple, predominantly focal seizure types. Brain magnetic resonance imaging showed severe brain atrophy during the first year of life. At 7 years old, she is severely impaired and has occasional seizures.
syndrome is a constant burst-suppression pattern during wakefulness and sleep.\textsuperscript{10} Trials with pyridoxine and pyridoxal-phosphate are recommended, and phenobarbital, vigabatrin, or adrenocorticotropic hormone are used among others, but the seizures are usually refractory to pharmacotherapy and most patients have severely impaired development. Many patients die within the first months of life; others may evolve into West and Lennox–Gastaut syndrome during the course.\textsuperscript{6,8,14,15} Metabolic causes appear to be rare. Some patients demonstrate structural brain anomalies on magnetic resonance imaging (MRI), such as lissencephaly, hemimegalencephaly, or agenesis of the corpus callosum.\textsuperscript{16}

**Genetics**

There are no published large-scale studies on the mutational spectrum of Ohtahara syndrome. Thus, our current knowledge is based upon small cohorts or isolated single case reports (\textsuperscript{\textendash}Table 2).

**Table 2** Ohtahara syndrome

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
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<tr>
<td>ARX</td>
<td>Male patients with additional malformations, such as hypospadias, agenesis of corpus callosum, lissencephaly,\textsuperscript{17} progressive microcephaly,\textsuperscript{16} or choreatic dystonia.\textsuperscript{18}</td>
</tr>
<tr>
<td>STXBPI</td>
<td>Patients without significant malformations or dysmorphism, but frequently with early-onset movement disorders. Seizure frequency may sometimes decrease during infancy. Patients with focal cortical dysplasia may benefit from epilepsy surgery.\textsuperscript{19} There were mutations in 2 out of 6 (33%) Ohtahara patients and 12 out of 266 (4.5%) of early infantile epileptic encephalopathy patients.\textsuperscript{19,20}</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>No significant malformations or dysmorphism. Seizure frequency may sometimes decrease during infancy. There were mutations in 19 out of 164 (11.6%) of EIEE patients.\textsuperscript{21,22} Majority of KCNQ2 mutation carriers do not develop early infantile epileptic encephalopathy, but develop benign neonatal seizures.</td>
</tr>
<tr>
<td>CASK</td>
<td>Male patients with microcephaly and pontocerebellar hypoplasia.\textsuperscript{23}</td>
</tr>
<tr>
<td>GNAO1</td>
<td>Patients may present with movement disorders including dystonia, chorea, and athetosis.\textsuperscript{24}</td>
</tr>
<tr>
<td>Copy number variations</td>
<td>Variable phenotypes; usually individual microdeletions</td>
</tr>
</tbody>
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Infantile (or epileptic) spasms (ISs) are flexor spasms with bilateral tonic contractions. They are classified as a distinct seizure type, defined as unknown if generalized or focal according to the 2010 classification of the ILAE.\textsuperscript{1} The term West syndrome describes the triad of ISs together with a hypsarrhythmia pattern on EEG and behavioral or mental regression (\textsuperscript{\textendash}Fig. 4).\textsuperscript{1,14} In West syndrome, ISs appear in clusters (with up to 150 spasms) up to 30 times per day, starting between 3 and 9 months of age, with an incidence of 3 to 5 per 10,000 live births.\textsuperscript{8,34} Hypsarrhythmia is the typical
interictal EEG pattern consisting of chaotic generalized asynchronous high-amplitude slow and sharp waves with interspersed multifocal irregular spikes and polyspikes. Given the co-occurrence of developmental regression, West syndrome is the prototypical epileptic encephalopathy, arguing for a causal relationship between epileptic activity and progressive psychomotor deterioration. Recent studies in tuberous sclerosis complex-related West syndrome provided evidence that prophylactic treatment of epileptic discharges in EEG before the onset of epilepsy can help both mental development and epilepsy outcome. Adrenocorticotropic hormone or vigabatrin are the drugs of choice in West syndrome, controlling seizures in about two-thirds of patients.

**Genetics**

The etiology of West syndrome and IS relate mainly to structural (e.g., due to tuberous sclerosis complex [TSC], hypoxic/ischemic encephalopathy, cortical dysgenesis) or metabolic abnormalities. Only 25% of cases are of unknown origin. In tuberous sclerosis complex—a multi-system organ disease often involving brain anomalies—West syndrome develops in 30% to 40% of patients; therefore, it is the single most prevalent genetic cause of West syndrome, accounting for around 7% of cases.

In the remainder of idiopathic cases, only a minority of genes have been repeatedly associated with West syndrome (Table 3). Additionally, several isolated cases have been associated with mutations in a plethora of genes: CDKL5, SLC25A22, SPTAN1, PLCB1, ST3GAL3, HDAC4, and others. By only regarding clinical aspects (IS) or EEG features (hypsarrhythmia), this spectrum of genes is even wider and will most likely increase in the near future.

**Dravet Syndrome and Severe Myoclonic Epilepsy of Infancy**

**Clinical Description**

Charlotte Dravet initially described Dravet syndrome (DS) as severe myoclonic epilepsy of infancy in 1978. Dravet syndrome manifests in otherwise normal infants aged 3 to

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>ARX</td>
<td>Often associated with brain malformations; see also Ohtahara syndrome</td>
</tr>
<tr>
<td>STXBP1</td>
<td>Patients without significant malformations or dysmorphic features. Mutations were found in 1 out of 65 (2%) of patients with West syndrome. Four out of 6 (67%) STXBP1 mutation carriers developed West syndrome.</td>
</tr>
<tr>
<td>DNM1</td>
<td>Severe psychomotor delay, no speech, muscular hypotonia. Mutations were found in 5 out of 356 epileptic encephalopathy patients (1.4%). All 5 patients had infantile spasms, 3 had hypsarrhythmia.</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>Severe psychomotor delay, no speech, muscular hypotonia</td>
</tr>
<tr>
<td>Copy number variations</td>
<td>Variable phenotypes; usually individual microdeletions</td>
</tr>
</tbody>
</table>

![Fig. 4 Interictal electroencephalogram (EEG) in a 5-month-old girl with infantile spasms in the context of Aicardi syndrome. The EEG shows hypsarrhythmia (high-amplitude slow waves with irregular interspersed spikes and polyspikes) with right hemispheric dominance.](Figure)
Childhood and School Age

Lennox–Gastaut Syndrome

Clinical Description

The description of a severe childhood epilepsy and its electroencephalographic features described by Lennox and Davis in 1950 and by Gastaut et al in 1966 led to the definition of Lennox–Gastaut syndrome as part of the epileptic encephalopathies in childhood.59,60 The diagnostic criteria of typical Lennox–Gastaut syndrome consist of:

1. Multiple epileptic seizures including axial tonic, atonic, and atypical absence seizures
2. Electroencephalogram abnormalities with frontally accentuated bursts of slow spike-waves during wakefulness and bursts of fast rhythmic activity during sleep
3. A slowness in intellectual growth and associated personality disorders58,61

The age at onset is 3 to 6 years. Lennox–Gastaut syndrome may be preceded by nonepileptic and/or epileptic encephalopathy, such as Ohtahara or West syndrome. Drop attacks from axial tonic or (myoclonic-) atonic seizures are among the predominating seizure types together with atypical absence seizures and nonconvulsive status epilepticus.8,61 Nearly all patients have severe intellectual disability and refractory epilepsy. In addition, there may be significant overlap with other epileptic encephalopathies, such as Dravet syndrome, epilepsy with myoclonic-ataxic seizures, Angelman syndrome, and others.

As pharmacoresistance is a predominant feature of Lennox–Gastaut syndrome, a combination of several antiepileptic drugs is usually inevitable with valproic acid, lamotrigine, topiramate, and benzodiazepines being of value, as well as rufinamide (and the cautiously used felbamate) are frequently prescribed drugs.61 The literature about pharmacotherapy in Lennox–Gastaut syndrome seems to reflect more the innovations of the antiepileptics than a formal therapeutic approach, and it is still debatable whether to reduce or increase the antiepileptic medications in affected individuals with refractory seizures.8

Genetics

The etiology of Lennox–Gastaut syndrome comprises a broad range of structural, metabolic, and primarily monogenetic pathologies, as well as tumor, infection, trauma, and intoxication. However, both structural malformations (e.g., cortical dysgenesis, neuronal migration disorders) and metabolic disorders (including mitochondrialopathies) may similarly have been caused by monogenetic defects.

Genes that have been repeatedly associated with Lennox–Gastaut syndrome comprise SCN1A, GABRB3, CHD2, and DNLM1.42,43,62 Single Lennox–Gastaut syndrome cases have also been reported to show mutations in MAPK10, ALG13, SCN2A, SCN8A, RYR3, and ST3GAL3. Some of those genes have been associated with West syndrome too, reflecting its transition into Lennox–Gastaut syndrome.
Epilepsy with Myoclonic–Atonic Seizures (Doose Syndrome, MAE)

Clinical Description
Epilepsy with myoclonic–atonic seizures is a generalized epilepsy and belongs to the myoclonic epilepsies of childhood. It was first described by Kruse (1968) and Doose (1970) and occurs with an explosive onset in otherwise healthy children with a male predominance. Myoclonic seizures that can be subtle and difficult to recognize followed by an atonic, postmyoclonic phase are the hallmark of the syndrome, leading to typical drop attacks or head-nodding attacks. Patients also display generalized tonic–clonic, tonic, and atypical absence seizures (Fig. 5). The onset is usually around age 1 to 5 years. The seizures are often difficult to treat, and besides valproic acid and ethosuximide, ketogenic diet has shown to help in epilepsy with myoclonic–atonic seizures. The seizure outcome is very good, with 90% of patients becoming seizure free within 3 years. The cognitive outcome is highly variable, with up to 40% developing mild to severe intellectual disability.

Genetics
Little is known on the etiology of epilepsy with myoclonic–atonic seizures. Fourteen to 32% of affected children have a family history of idiopathic epilepsy. A few children resembling epilepsy with myoclonic–atonic seizures belong to large GEFS+ families carrying SCN1B missense mutations. Other cases may carry mutations in SLC2A1. A recent study identified six individuals carrying de novo mutations in SLC6A1 among 160 MAE patients (4%). Additionally, one out of 39 MAE patients (2.5%) was found to carry a de novo mutation in KCNA2.

Epileptic Encephalopathy with Continuous Spike-and-Wave during Sleep and Landau–Kleffner Syndrome

Clinical Description
This is a disorder with intellectual disability and language deficits associated with a subclinical EEG pattern during sleep, first described by Patry et al in 1971, and referred to "epileptic encephalopathy with continuous spike-and-wave during sleep" by Tassinari et al in 1977. Together with the acquired epileptic aphasia / Landau–Kleffner syndrome, continuous spike-and-wave during sleep is recognized as an electroclinical syndrome by the ILAE. Both syndromes share the main features of marked sleep activation of mainly focal epileptic discharges into a continuous or near-continuous spike-and-wave pattern together with a regression in different aspects of development. The degree of bioelectrical status during sleep remains a controversial topic. The diagnosis is considered in patients with (1) spike-and-wave pattern occupying more than 85% of nonrapid eye-movement sleep for more than a month, or (2) a significant increase of...
EEG abnormalities during sleep associated with intellectual and behavioral impairment, as well as language deficits and transient motor impairment (►Fig. 6).8,72,73 Continuous spike-and-wave during sleep and Landau–Kleffner syndrome belong to the spectrum of genetic focal epilepsies of childhood with overlap to benign epilepsy with centrotemporal (rolandic) spikes.74 One-third to one-half of children with continuous spike-and-wave during sleep have neurologic abnormalities before disease onset, with mainly pre- or perinatally acquired brain lesions.8,72,73 In the other half, genetic factors most likely contribute to the phenotype. Landau–Kleffner syndrome occurs in previously healthy children aged 2 to 8 years. Half of affected children develop seizures as the first symptom of disease; the other half show exclusively progressive linguistic disturbances that commonly start with an inability to understand spoken words that evolves into sensory and expressive aphasia (►Fig. 7).

Seizures are infrequent in continuous spike-and-wave during sleep and Landau–Kleffner syndrome. This is particularly so in continuous spike-and-wave during sleep, where they can occur before and after diagnosis with mainly nocturnal focal seizures but also generalized tonic-clonic and absence seizures. Treatment options include all classical antiepileptic medications; however, most authors suggest trying sulthiame, benzodiazepines alone, or combined with valproic acid and corticosteroids.73 The continuous spike-and-wave during sleep pattern and seizures usually remit in puberty. Simultaneously, neuropsychological function may improve; residual impairment correlates with the length of continuous spike-and-wave during sleep and early age at diagnosis.8,72

Fig. 6 Electrocencephalogram during wakefulness (A) and sleep in a 7-year-old boy, initially referred for attention-deficit-hyperactivity disorder. Multifocal singular sharp waves (A) are markedly activated during sleep into a pattern of continuous spike-and-wave activity (B). Despite several treatment trials including sulthiame, levetiracetam, oxcarbazepine, and methylprednisolone, the continuous spike-and-wave during sleep pattern remained. His learning disabilities became apparent and school performance declined significantly. The genetic diagnosis remains unclear.
Genetics

Individuals with idiopathic focal epilepsy may also have relatives with epilepsy. However, the severity and clinical presentation may vary considerably between affected individuals, even within the same family. Mutations in GRIN2A, a gene encoding the NMDA receptor subunit GluN2A has recently been identified to account for up to 20% of cases with continuous spike-and-wave during sleep and Landau–Kleffner syndrome.\(^{75–77}\) Mutation detection rates were higher in familial compared with isolated cases. In 5 to 10% of cases with milder epilepsies of the same spectrum, such as atypical partial epilepsy and benign epilepsy with centro-temporal spikes, the individual disorder has similarly been assigned to mutations in GRIN2A.\(^{75}\)

Discussion

The ILAE classification is a pragmatic grouping of the heterogeneous spectrum of epileptic encephalopathies defined by clinical and electroclinical characteristics that are “reliably identified,” but do not reflect the specific etiology.\(^1\) There is no differentiation of channelopathies, synaptopathies, or epileptic encephalopathies due to structural anomalies, though this could have significant implications for prognosis and therapeutic decisions. As an example, seizures in Ohtahara syndrome due to STXBP1 or KCNQ2 mutations may reduce in frequency during infancy, and they may require other therapeutic strategies when compared with ARX-related burst-suppression epilepsy associated with abnormal gyration. Likewise, the transition from Ohtahara into West syndrome and from West into Lennox–Gastaut syndrome has been well described in numerous cases. Thus, a patient with Lennox–Gastaut syndrome may previously have had Ohtahara and West syndrome, and may therefore be etiologically very different from other Lennox–Gastaut syndrome patients without such history. Hence, without genetic classification of an epileptic encephalopathy, the prognosis on the individual course and treatment outcome of the disorder remains empirical. Furthermore, physicians are often confronted with patients suffering from less distinct epileptic encephalopathy phenotypes that can barely be assimilated into the current ILAE schemes.

The phenotypic series of early infantile epileptic encephalopathy according to OMIM represents a quite different way to group epileptic encephalopathies. In contrast to Ohtahara et al, OMIM uses the term early infantile epileptic encephalopathy not only for neonatal epilepsy with a specific EEG pattern and marked developmental delay,\(^{13}\) but for a far broader spectrum of disorders with onset within the first year of life (–Table 1). Within this phenotypic series, epilepsy aspects are barely considered, allowing for a more comprehensive delineation of the phenotype (beyond epilepsy) attributed to a specific gene. As an example, early infantile epileptic encephalopathy-4 (EIEE4) is caused by mutations in STXBP1 and may result in (1) Ohtahara syndrome, (2) West syndrome, (3) Dravet syndrome, (4) severe epilepsy without distinct EEG features, (5) nonsyndromal intellectual disability without seizures, and (6) autism spectrum disorders and others.\(^{20,54,78}\) The OMIM phenotypic series does not include epileptic encephalopathy phenotypes with onset beyond the
first year of life. Therefore, both the ILAE and the OMIM classification only depict a narrow spectrum out of the broad group of epileptic encephalopathies.

An alternative to established classifications might be a system primarily focusing on genetic aspects and only secondarily, on phenotypic features. Onset, phenotypic appearance, and severity would have less importance compared with pathophysiology and its implications on possible therapeutic aspects as well as prognostic assertions. Overlap and transition of different phenotypes within one genetic entity would also be better acknowledged by a classification primarily considering genetic etiology. Moreover, emphasis on pathophysiology reflects the increasing importance of personalized therapy in patients with epileptic encephalopathy. Several therapies can help by specifically targeting individual genetic defects, such as quinidine in KCNT1 encephalopathy,79,80 retigabine in KCNQ2 encephalopathy,81 memantine in GRIN2A encephalopathy,82 and the ketogenic diet in SLC2A1-related epilepsy. Thus, genetic testing can significantly influence clinics and therapy of epileptic encephalopathy; it can be expected that this development will increasingly gain importance in the years to come.

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Epileptic Encephalopathies in Childhood: The Role of Genetic Testing

Lemke, Sybre

321

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