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The Expanding Clinical Spectrum of Genetic Pediatric Epileptic Encephalopathies

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Pediatric epileptic encephalopathies represent a clinically challenging and often devastating group of disorders that affect children at different stages of infancy and childhood. With the advances in genetic testing and neuroimaging, the etiologies of these epileptic syndromes are now better defined. The various encephalopathies that are reviewed in this article include the following: early infantile epileptic encephalopathy or Ohtahara syndrome, early myoclonic encephalopathy, epilepsy of infancy with migrating focal seizures, West syndrome, severe myoclonic epilepsy in infancy (Dravet syndrome), Landau-Kleffner syndrome, Lennox-Gastaut syndrome, and epileptic encephalopathy with continuous spike-and-wave during sleep. Their clinical features, prognosis as well as underlying genetic etiologies are presented and updated.
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Introduction

With the advent of modern genetic methods including microarray techniques allowing genome-wide detection of microdeletions and duplications, as well as targeted gene sequencing and whole exome sequencing, there has been a much better understanding and improved identification of the etiologies of specific epileptic encephalopathies (EEs). The International League Against Epilepsy defines EEs as conditions "in which the epileptiform abnormalities are believed to contribute to progressive disturbance in cerebral function."[1] In this article, the various encephalopathies that are reviewed are presented according to age of onset of symptoms starting with the infantile EEs, and followed by the childhood EEs. As will be evident in our following review, currently, workup of such encephalopathies includes ruling out structural and metabolic disorders as well as often epilepsy gene sequencing panels and even whole exome sequencing.[2]

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Infancy Onset EEs

EIEE or Ohtahara Syndrome

Early Infantile EE (EIEE) or Ohtahara syndrome (OS) is a severe early epileptic encephalopathy. It presents within the first 3 months of life, and may occur as early as the first hour after delivery, or even in utero. The most common seizures in this syndrome are tonic, but other types can also occur, including focal and myoclonic seizures. It is a rare disorder.[3] OS may evolve into West syndrome and, later, into Lennox-Gastaut syndrome (LGS). The prognosis is poor, with severe psychomotor retardation being the rule. Death often occurs during infancy. The electroencephalogram (EEG) (Fig. 1) is characterized by burst suppression during both wakefulness and sleep.[4]

The etiologies of OS are variable, including specific genetic mutations, cortical brain malformations, and less commonly mitochondrial (mt) disorders, nonketotic hyperglycinemia, and severe perinatal hypoxic-ischemic injury; in some cases the cause is unknown.[5] Specific genetic abnormalities associated with OS are presented in Table 1, the most frequently of which are as follows:

(1) *ARX* (aristaless-related homeobox) gene mutations at Xp22.13 (EIEE-1),[6,7]
(2) *CLDK5* (cyclin dependant kinase like-5) (STK9) gene at Xp22 (EIEE-2),[4]
(3) *SLC25A22* (solute carrier family 25 [mt carrier, glutamate carrier-1/GC-1] member 22) gene at 11p15.5 (EIEE-3),[4]

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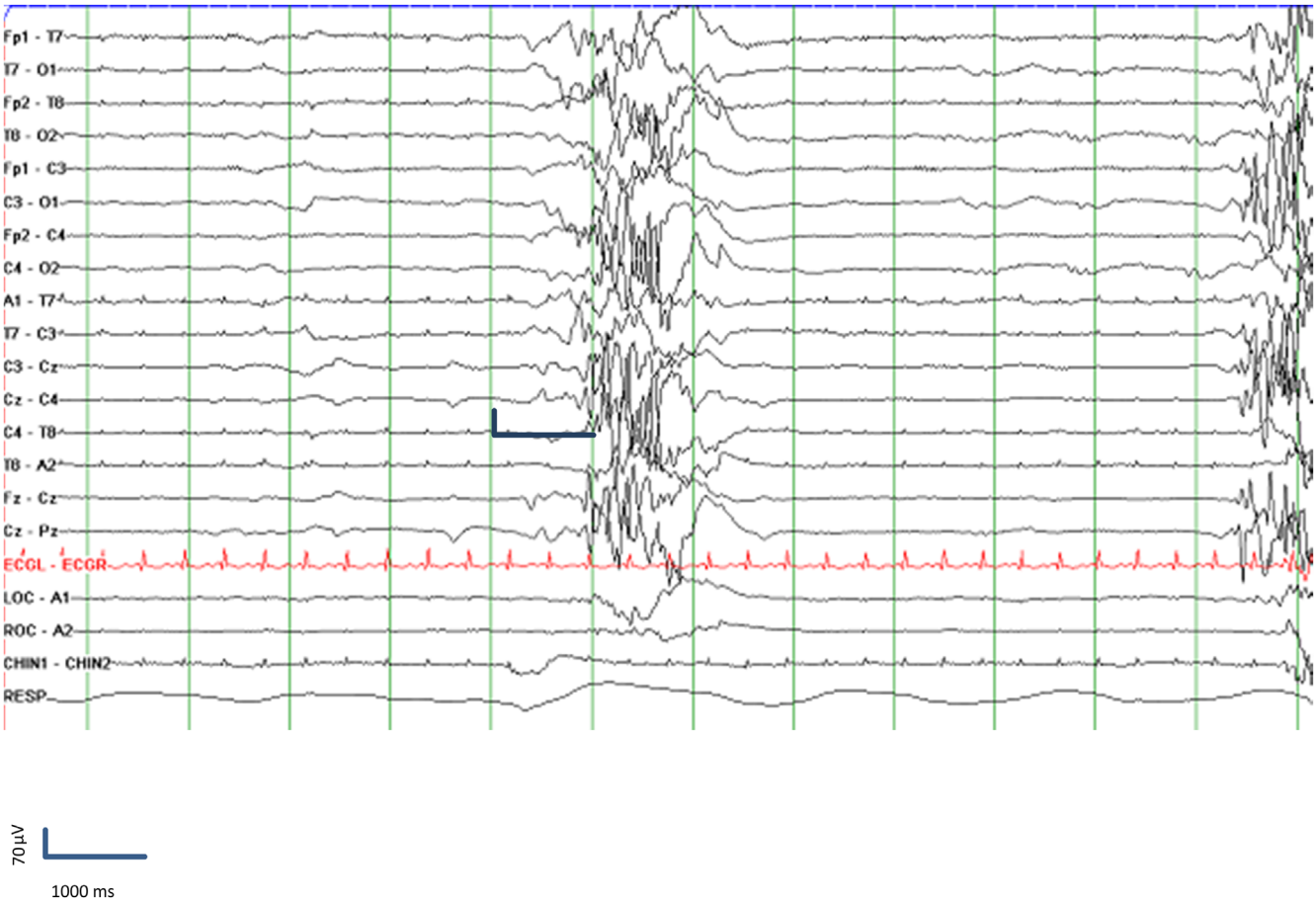

Figure 1 Electroencephalogram in Ohtahara syndrome: burst-suppression pattern. (Color version of figure is available online.)

(4) *STXBP1* (*MUNC18-1*) gene microdeletion at 9q33.3–q34.11 (EIEE-4),[8]
(5) *KCNQ2* gene mutations (EIEE-7),[6]
(6) *SCN2A* gene mutations (EIEE-11), and[9]
(7) *GABRA1* gene mutations (EIEE-19).[10]

Also, in this and other EEs vitamin responsive disorders need to be ruled out as a potential underlying etiology (Table 2).

Early Myoclonic Encephalopathy

Early myoclonic encephalopathy (EME) is an epileptic syndrome that starts in the early neonatal period or in the first few months of life. It is characterized by erratic myoclonus, refractory partial seizures, and abnormal neurologic status. A burst-suppression pattern is typically present on EEG, usually during sleep, especially deep sleep.[11] Affected patients have severe delays in psychomotor development, with hypotonia, and encephalopathy. Peripheral neuropathy may also be present. This syndrome is associated with inherited metabolic disorders, including nonketotic hyperglycinemia, organic acidemias, Zellweger syndrome, and molybdenum cofactor deficiency.[4] Seizures are typically refractory to treatment, and the prognosis is poor.

A genetic cause was suggested by Cohen et al[12] who reported in 2014, a rare missense mutation in the gene *SLC25A22* (EIEE2) in 2 siblings with early myoclonic encephalopathy, born to consanguineous parents of Arab Muslim origin. Therefore, a potential mutation of *SLC25A22* should be considered in the differential diagnosis in infants presenting with clinical symptoms compatible with EME, severe microcephaly and autosomal recessive inheritance with negative metabolic workup. Of note is that many of the genes presented in Table 1 may manifest as phenotypes that overlap not only with OS and EME but also with other EEs such as West syndrome or other syndromes reviewed in this article.

Epilepsy of Infancy With Migrating Focal Seizures

This is a severe form of epilepsy that begins before the age of 6 months and commonly starts within a few weeks of birth.[13] The seizures are focal, and emanate from multiple foci in the brain. Seizure activity may migrate from one region to another during an episode[14] and is refractory to treatment.[13] Persistent seizures affect growth of the brain and lead to microcephaly, developmental regression and intellectual disability.[15] Most children with this condition do not develop language skills and many do not survive past infancy or early childhood.