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Pediatric Epileptic Encephalopathies: Pathophysiology and Animal Models

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Epileptic encephalopathies are syndromes in which seizures or interictal epileptiform activity contribute to or exacerbate brain function, beyond that caused by the underlying pathology. These severe epilepsies begin early in life, are associated with poor lifelong outcome, and are resistant to most treatments. Therefore, they represent an immense challenge for families and the medical care system. Furthermore, the pathogenic mechanisms underlying the epileptic encephalopathies are poorly understood, hampering attempts to devise novel treatments. This article reviews animal models of the three classic epileptic encephalopathies—West syndrome (infantile spasms), Lennox-Gastaut syndrome, and continuous spike waves during sleep or Landau-Kleffner syndrome—with discussion of how animal models are revealing underlying pathophysiological mechanisms that might be amenable to targeted therapy.
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Introduction

Epileptic encephalopathies represent one of the most daunting challenges in pediatric neurology.[1,2] As they arise early in life and cause lifelong disability, these epilepsies take an immense toll on the lives of patients and families and have a considerable impact on the health care system, both medically and financially. Yet, our understanding of the basic mechanisms, clinical consequences, and therapeutic options of the epileptic encephalopathies is woefully incomplete. The goals of this paper are to discuss the current understanding of the pathophysiology of epileptic encephalopathies, with the assumption that greater knowledge about underlying mechanisms would aid the development of improved therapies. The central importance of animal models in this endeavor is highlighted, updating several reviews of this topic that have already been published.[3-7]

The most recent International League Against Epilepsy Commission report defines an epileptic encephalopathy as a syndrome in which seizures or interictal epileptiform activity contribute to or exacerbate underlying brain dysfunction, above and beyond what might be expected from the underlying pathology alone; furthermore, the associated neurocognitive impairments can progress and worsen over time.[8] This definition has several important corollaries—(A) epileptic encephalopathies can be either static or progressive, (B) seizures or electroencephalographic (EEG) abnormalities such as interictal discharges can directly worsen cognition or behavior, and (C) treatment of the seizures or EEG abnormalities would be expected to improve the cognitive or behavioral deficits as well as the seizures.[9] This definition implies that treatment of the seizures or interictal discharges should allay the encephalopathy and improve cognitive function. In reality, failure of treatment to improve either seizures or encephalopathy is commonplace, and epileptic encephalopathies are extremely difficult to treat.[10] Furthermore, while the term epileptic encephalopathy implies a contribution of seizures or EEG abnormalities to the encephalopathy, the underlying etiology undoubtedly also plays a role in prognosis (Fig. 1). The term epileptic encephalopathy would be best used when seizures or interictal discharges directly alter cognition, a process, rather than using this term to describe a category that includes any severe epilepsy with intellectual dysfunction.[11,12] Owing to their detrimental effect on neurodevelopment and behavior, plus their notorious treatment refractoriness, the term "catastrophic" has also been applied to the epileptic encephalopathies.[13]

Historically, epileptic encephalopathies have included Ohtahara syndrome (early infantile epileptic encephalopathy), infantile spasms (West syndrome [WS]), Lennox-Gastaut

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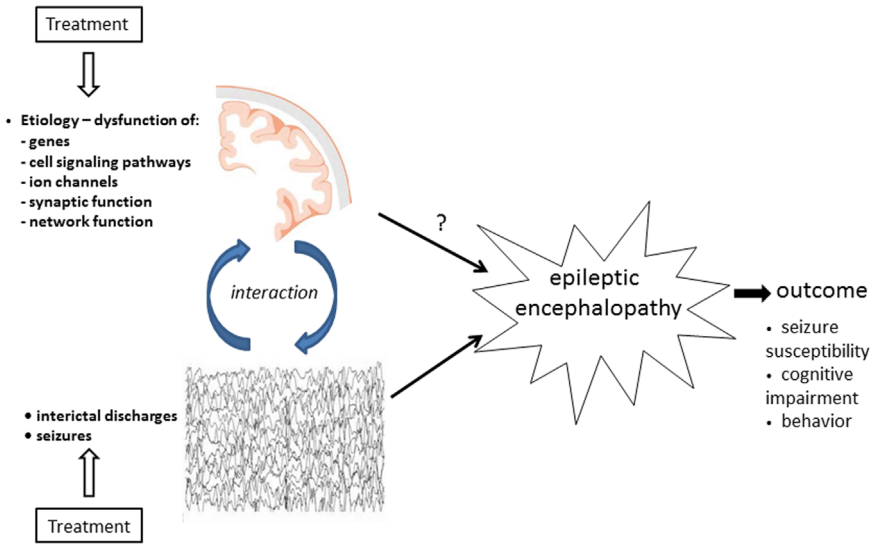

Figure 1 Schematic representation of epileptic encephalopathies, defined as conditions in which epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology.[8] The definition would include only disorders in which interictal discharges or seizures lead to encephalopathic changes consisting of cognitive impairment and increased seizure susceptibility. Numerous disorders with epilepsy and intellectual disability, especially those with a known genetic mutation, would not necessarily fit this definition (question mark). Implicit in the definition is that treatment of the epileptiform abnormalities (or possibly the etiology) could portend a less severe encephalopathic outcome. The etiology and epileptiform abnormalities likely interact in leading to the epileptic encephalopathy. Mechanisms underlying each component of this diagram need to be elucidated. (Color version of figure is available online.)

syndrome (LGS), Dravet syndrome (severe myoclonic epilepsy of infancy), and the spectrum of continuous spike waves during sleep (CSWS) or electrical status epilepticus in sleep (ESES) or Landau-Kleffner syndrome (LKS). In this article, we focus on 3 epileptic encephalopathies—WS, LGS, and CSWS. In the current literature, numerous other syndromes are included under the rubric of epileptic encephalopathy, particularly those associated with novel genetic mutations, structural lesions, and autoimmune dysfunction. However, unless the disorder specifically entails neurocognitive compromise as a consequence of seizures or interictal discharges (rather than a consequence of the etiology itself), it would not conform to the International League Against Epilepsy definition. That is, the co-occurrence of severe epilepsy and intellectual disability does not always denote an epileptic encephalopathy unless a causal relationship exists (Fig. 1). For example, in the earliest stages of Dravet syndrome, seizures are relatively mild and infrequent and cognitive decline is more prominent (ie, this stage would not be considered an epileptic encephalopathy); however, later in childhood, seizures predominate and likely exacerbate cognitive deficits. The cognitive deficits early in Dravet syndrome would therefore be more attributable to the underlying etiology (sodium-channel mutation), whereas later stages would constitute an epileptic encephalopathy.[12] Supporting this notion is a Dravet syndrome model in which mice are genetically engineered with down-regulation of the sodium-channel NaV1.1 only in basal forebrain, a network involved in learning and memory. In this model, mice have cognitive deficits but no spontaneous seizures, leading to the conclusion that the genetic etiology (NaV1.1 mutation) not seizures is most responsible for the cognitive impairment.[14] Another apropos example is mutations in dynamin 1 (*DNM1*), a gene that has been implicated in both WS and LGS. *DNM1* encodes a GTPase necessary for synaptic vesicle endocytosis. In *Dnm1* mutant mice, seizure activity has been shown to be independent of developmental and behavioral deficits, which progress even when seizures are controlled.[15] Therefore, *DNM1* mutations would not be defined as a classical epileptic encephalopathy. Severe childhood epilepsies associated with intellectual disability that are caused by a specific gene mutation might better be termed "genetic encephalopathy with epilepsy."[7]

Why Has it Been so Difficult to Establish an Animal Model of Epileptic Encephalopathy and Why Bother Creating One?

Epileptic encephalopathies are among the most complex epilepsies known. The question arises as to whether an animal model can be created in complex epilepsies, or whether the epileptic encephalopathies are unique to the human brain.[16] Clearly, brain development in experimental animals differs from humans, but at a fundamental level, the nervous system of each species works similarly, that is, the function of ion channels, synapses, and neural networks are shared.[17] Ultimately, epilepsy is a circuit disease involving aberrant neuronal networks, though its underpinnings are obviously determined at cellular, subcellular, and molecular levels. Therefore,