Effect of Seizures on the Developing Brain and Cognition
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Epilepsy is a complex disorder, which involves much more than seizures, encompassing a range of associated comorbid health conditions that can have significant health and quality-of-life implications. Of these comorbidities, cognitive impairment is one of the most common and distressing aspects of epilepsy. Clinical studies have demonstrated that refractory seizures, resistant to antiepileptic drugs, and occurring early in life have significant adverse effects on cognitive function. Much of what has been learned about the neurobiological underpinnings of cognitive impairment following early-life seizures has come from animal models. Although early-life seizures in rodents do not result in cell loss, seizures cause changes in neurogenesis and synaptogenesis and alteration of excitatory or inhibitory balance, network connectivity and temporal coding. These morphological and physiological changes are accompanied by parallel impairment in cognitive skills. This increased understanding of the pathophysiological basis of seizure-induced cognitive deficits should allow investigators to develop novel targets for therapeutic interventions.

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Introduction

Although seizures are the most striking clinical manifestation of childhood epilepsy, children with epilepsy are at risk not only for seizures, but also for a myriad of comorbid health problems that occur at a higher rate than would be expected by chance. Among the comorbidities associated with epilepsy in children, cognitive abnormalities are among the most common and troublesome. The distribution of intelligence quotient (IQ) scores of children with epilepsy is skewed toward lower values and the number of children with epilepsy experiencing difficulties in school because of learning disabilities is greater than children without epilepsy.

Although most children with epilepsy maintain stable IQ scores, there is now strong evidence that some of them slow, or even regress, in their mental development. In a community-based cohort study, Berg et al assessed and prospectively followed 198 children (aged < 8 years) with new-onset epilepsy for 8-9 years. In this cohort refractoriness to antiepileptic drugs (AEDs) was associated with an 11.4 point lower full scale IQ. There was substantial age-resistance to treatment interactions for IQ, indicating a lessening impact of recurrent seizures with increasing age. The authors appropriately concluded that uncontrolled seizures impair cognitive function with effects being most severe in infancy. Cognition is of particular concern in children with an epileptic encephalopathy, a condition characterized by the slowing or regression of development due to seizures, abnormal interictal cortical and subcortical EEG activity, or both, rather than to the underlying etiology of the epilepsy.

Much of the cognitive impairment that occurs in people with epilepsy is related to its underlying etiology. Both acquired disorders such as trauma, hypoxic-ischemic insults, and mesial temporal sclerosis secondary to prolonged febrile seizures and genetic disorders, including tuberous sclerosis, fragile X, Rett, and Dravet syndromes, can lead to significant cognitive impairment in addition to causing epilepsy. Although etiology of the epilepsy clearly plays a major role in cognitive development, there are indications that early-life seizures (ELS) independent of etiology can lead to cognitive impairment. For example, in a study of neuropsychological function in children with focal cortical dysplasia by Korman et al. It was found that age of onset of epilepsy and extent of the dysplasia each contributed independently to cognitive dysfunction indicating that early onset of epilepsy
disrupted critical periods of development leading to poor cognitive outcomes.

To prevent, limit, and reverse cognitive comorbidities, it is essential to understand the neurobiological basis of cognitive dysfunction of seizures in children. While studies have indicated that children with ELS, particularly when frequent and resistant to therapy, are at highest risk for cognitive deficits, it is difficult to ascertain the neurobiological disturbances that lead to cognitive impairment. In the clinic it is difficult to differentiate the effects of the number, duration and seizure type, EEG abnormalities and AED therapy from the etiology of the epilepsy (Fig. 1). For this reason, many of the advances in our understanding of the long-term effects of ELS come from rodent studies in which the investigator has control over the etiology and treatment of the seizures.

**Genetic Models**

Animal models of ELS include genetic and acquired models. The discovery of multiple genetic mutations associated with human epileptic encephalopathies and advances in genetic techniques have resulted in the generation of multiple models in animals carrying the human equivalent of these genes. Mutations in the gene coding for the type-1 alpha subunit of the Nav 1.1 sodium channel in neurons, SCN1A, has been linked to the epileptic encephalopathies, especially Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS+). Models of Dravet syndrome have thermally-induced and spontaneous seizures that develop during the animal’s maturation.20-23 Likewise, models of generalized epilepsy + (GEFS+) mimic the clinical features of the condition with increased susceptibility to thermally-induced seizures and generalized tonic-clonic seizures.24,27

There is some evidence that the current Dravet syndrome models have social and spatial cognitive impairment when compared with control animals. Some of them have performed poorly in a social recognition and social novelty task compared with controls.28-30 Others, however, have shown similar performance to control animals.31 Regarding animal models’ ability to mimic the cognitive decline seen in this disorder, few examples of behavioral testing specific for spatial memory have been reported. However, those that have had such testing have shown significant impairments. This includes Ohmori et al.’s work31 showing impaired performance of mice on a Barnes maze, a cognitive task assessing spatial learning in rodents. Similar results have been repeated in at least one other animal model specific for the SCN1A mutations thought to underlie Dravet syndrome.30 Additional assessments of cognition have shown deficits in the memory requiring components of context-dependent fear conditioning.30,31 Behavioral tests in the GEFS+ model have been similar to those seen in the Dravet models, including hyperactivity, impaired social performance, and deficits in spatial memory.32 In addition, deficits in cued fear conditioning and risk assessment have also been reported in this model.32

Discerning if the cognitive impairments associated with genetic models of ELS are a result of the seizures seen in the other models, or a result of the mutated protein itself and resultant physiologic changes is important. Bender et al33 caused a similar decrease in the expression of Nav 1.1 protein seen in the genetic models of Dravet syndrome featuring SCN1A mutations, but through injection of specific small interfering RNA (siRNA) into the medial septum and diagonal band of Broca, a brain region important for spatial cognition through its regulation of theta oscillations in the hippocampus, of adult Sprague-Dawley rats. This allowed for an evaluation of the effect of less SCN1A expression on cognition without affecting development of the rats or inducing the spontaneous seizures seen in the Dravet syndrome models. Rats with siRNA-induced firing of interneurons had spatial memory impairment compared with controls indicated by a comparative behavioral lack of response to a change in object location during a reaction-to-novelty task. This specific finding would suggest that the mechanistic changes underlying Dravet syndrome may also play a role in the cognitive impairment seen in the disorder that could be compounded by the effect of the associated developmental seizures.

In general, there has been limited work on the cognitive effects of seizures in the genetic disorders. In addition, the genetic models currently used only affect 1 specific gene or protein, when multiple genetic changes likely underlie the pathophysiology of many of the epileptic encephalopathies. Finally, while many advances have been made regarding the generation of models of specific syndromes such as West syndrome, Dravet syndrome or GEFS+, there remain few models that exhibit most qualities of the other encephalopathies, like Ohtahara syndrome, beyond the early repetitive seizure models. There are also no animal models that consistently exhibit the characteristics that match some of the syndromes like Lennox-Gastaut syndrome, indicating that further work must be done in order to fully understand the processes behind such disorders.
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