Catastrophic epilepsies of infancy: From bedside to the bench and back

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Abstract

Catastrophic epilepsies are age-related epileptic syndromes characterized by a variety of behavioral seizure manifestations, malignant EEG patterns, and dismal outcomes including mental retardation. Most of these syndromes occur early in life and can be either cryptogenic or symptomatic in origin. There are also genetic syndromes. Most syndromes of catastrophic epilepsy are refractory to conventional antiepileptic drugs although infantile spasms may respond to steroids. Because catastrophic epilepsies are associated with devastating outcomes, it is important to develop innovative, effective and non-toxic treatments to probably stop the seizures and their regression that may be independent of the underlying condition. This will require the identification of model systems to be used to identify new treatments and screen for their efficacy in clinical studies. Understanding the pathophysiology of the catastrophic epilepsies in the models will lead to the identification of new therapeutic regimens that can be translated to clinical practice.

Epilepsy is one of the most common neurological disorders diagnosed in children and although some childhood seizures have a benign prognosis; Early infantile epileptic encephalopathy (EIEE), early myoclonic encephalopathy (EME), infantile spasms (IS), severe myoclonic epilepsy of infancy, Lennox Gastaut and Doose syndromes and the progressive myoclonic epilepsies have been categorized as “catastrophic epilepsies” because these conditions are known to have devastating long term consequences with regards to the subsequent development of intractable epilepsy, mental retardation or even death. Here we discuss advances in our understanding of the pathophysiological mechanisms underlying seizure expression in EIEE, EME and IS. We will also highlight recent progress in the development of new animal models of IS.

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY and EARLY MYOCLONIC ENCEPHALOPATHY

EIEE and EME are devastating seizure disorders that are related and may form a continuum. In EIEE the characteristic features are frequent tonic seizures associated with ictal burst-suppression discharges on the EEG. In EME, the initial predominant seizure type is erratic or fragmentary myoclonus, however tonic seizures may supersede myoclonic seizures as the condition worsens. In EIEE, diffuse brain pathology, involving cortical, subcortical including brainstem structures, is the most common etiologic finding. Damage to the brainstem is thought to occur progressively. This could explain the later appearance of tonic seizures in some patients with EME compared to EIEE. Tonic seizures in EME may result from “kindling” of the brainstem subsequent to the occurrence of frequent repetitive seizures or may be due to release of the brainstem from cortical influences as the disease progresses. Abnormalities in the metabolism of glutamate have also been implicated in EME. An autosomal recessive form of EME has been mapped to chromosome 11p15.5 where a missense mutation in the gene encoding a mitochondrial glutamate/H+ ‘symporter’ GC1 has been identified. This co-transporter is expressed in an age-specific manner in many areas of the brain including the brainstem and may provide a novel target for therapeutic intervention.

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INFANTILE SPASM

IS, are an age-related epileptic disorder characterized by brief spasms, specific EEG patterns (hypsarrhythmia and electrodecremental response), with frequent subsequent cognitive deterioration. The spasms can be of the flexion, extension or mixed (flexion/extension) types. They are often difficult to control but may respond to treatment with ACTH or vigabatrin. Because IS are associated with such a dismal prognosis there is a pressing need to develop better treatments. This will require an appropriate model system to be used to study pathogenic mechanisms, identify new drugs and screen for efficacy in preclinical studies. There have been several attempts to create an animal (rodent) model using different approaches, which include intracerebroventricular injections of corticotrophin releasing hormone (CRH), N-methyl-D-aspartate (NMDA) administered systemically in rats with prenatal brain impairment, intracerebral infusions of tetrodotoxin (TTX), and a multiple hit model.

CRH-induced seizures

This model of IS involves intracerebroventricular administration of CRH to neonatal rats. This approach was taken because of 1) the peculiar response of IS to ACTH; 2) the perinatal stress caused by the etiologies associated with IS may increase endogenous CRH levels in seizure-prone areas of the developing brain; 3) CSF ACTH levels are low in some patients with IS; and 4) vigabatrin (effective in some forms of IS) has been found to downregulate CRH levels in the hypothalamus. However, CRH injections have not adequately reproduced the features of IS in humans. In fact, the seizure phenotype is primarily “limbic”, the seizures are not spontaneous or recurrent nor do the EEG abnormalities mimic the features of the human syndrome. Moreover, ACTH is ineffective in controlling the seizures even though it reduces CRH gene expression in certain neuronal populations.

NMDA-induced flexion spasms

Another model IS involves an intraperitoneal injection of NMDA in infant rats. This agent causes an age-specific clinical seizure described as ‘emprosthotonus’, consisting of whole-body tonic flexion with back-arching. These seizures are accompanied by a diffuse attenuation of the EEG amplitude or sometimes by epileptiform discharges. Hippocampal learning and memory deficits and decreased seizure thresholds are seen in adult rats following NMDA induced seizures at postnatal (P) day 15; there are no structural lesions. In this model, pretreatment with ACTH is ineffective and pretreatment with hydrocortisone may even exacerbate this seizure type. Recently NMDA spasms were induced in P15 rat pups, prenatally exposed to betamethasone, which offsets hypothalamo-pituitary-adrenal brain control systems. Consequently, in betamethasone-exposed rats, ACTH increases the latency to the onset of the ‘emprosthotonic’ seizures. NMDA spasms generated in infant rats prenatally exposed to betamethasone have been proposed as a model of idiopathic IS, since no gross brain abnormalities have been found.

TTX-induced seizures

Lee et al have recently reported that infusions of TTX into the brains of rat pups, for several weeks starting from the 10th day of life, lead to the development of spontaneous recurrent seizures that were characterized by frequent myoclonic jerks involving the whole body. The ictal EEG often showed a slow wave followed by generalized voltage attenuation that resembled a electrodecremental response and interictally some rats with seizures also have diffuse EEG multifocal discharges resembling hypsarrhythmia. It is noteworthy that in this model, the seizures occur in adulthood, not in infancy.

Multiple hit model

Lado and Moshé, have recently proposed that structural or functional abnormalities that lead to hypereactivity in either or both the cortex and brainstem, along with abnormal communication between these two regions (such as may result with white matter injury), may be necessary to produce IS. Consequently, Scantlebury and Moshé proposed a rodent model of symptomatic IS that was induced by producing in rat pups damage to the cortex, brainstem and white matter in a short space of time. In order to damage these structures pups were injected with doxorubicin and lipopolysaccharide intracerebrally at P3 followed by an intraperitoneal injection of p-chlorophenylalanine at P5. Pups receiving the three agents developed recurrent seizures between the ages of P7 and P12 that resembled human flexion or extension spasms. The EEG recorded during the spasms depicted ictal discharges that were similar to the electrodecremental response.
also observed in IS. Moreover, developmental behavioral abnormalities were identified in injected pups and similar to the clinics some pups with spasms went on to develop partial seizures once the spasms have stopped. Work is ongoing to determine the effectiveness of ACTH and vigabatrin in controlling the spasms in this model.

CONCLUSION

The clinical data obtained in patients with EIEE, EME and IS has been pivotal in guiding the experimental approach to understanding the basic mechanisms underlying the catastrophic epilepsies. Because there are no animal models for EIEE and EME advances in our understanding have been slow. However, there are several new models of IS of different etiologies paralleling the human syndrome. These models may provide important insights into the pathophysiology of IS and may lead to new treatments beyond the currently available ones that have limitations due to toxicity.

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