Pediatric epilepsy

Five new things

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Summary

Epilepsy in children can be very different from epilepsy in adults, both in seizure type and epilepsy syndrome. The goal in treating children is seizure freedom, no treatment side effects, and function that is no different from the general population. In a significant percentage of patients, this goal remains unachievable, but many aspects of epilepsy are becoming clearer. This review will highlight 5 areas where progress is being made to achieve these goals in pediatric epilepsy. Specific research animal models are being developed to reflect the unique features of different pediatric epilepsies. As genetic syndromes are better identified, for some patients this has led to improved treatment. New advances in drug therapy have led to 3 new medications approved for children. More effective drug choices can now be recommended due to comparative drug trials and better overall care of children can be provided due to awareness of the comorbidities of epilepsy.

Epilepsy is one of the most common diagnoses seen by pediatric neurologists. One percent to two percent of the pediatric population has epilepsy. Seizure types in children can be very different than adults, for example, infantile spasms and epilepsy syndromes are often different in the pediatric population, such as Lennox-Gastaut syndrome, childhood absence epilepsy, and Dravet syndrome. The goal in treating these children is seizure freedom, no side effects, and function that is no different from the general population. In a significant percentage of patients, this goal remains unachievable, but many aspects of epilepsy are becoming clearer. Five areas were chosen to highlight in this review where prog-

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ress is being made to achieve these goals in pediatric epilepsy: research animal models, genetics, new advances in drug therapy, comparative drug trials, and comorbidities of epilepsy.

Animal models for pediatric epilepsy syndromes

Animal models have long played a crucial role in epilepsy research and are informative with regard to screening new anticonvulsant medications, understanding the mechanisms of epileptogenesis, and developing new treatment strategies. The challenge for pediatric epilepsy has been that the developing brain adds another layer of complexity such that pediatric syndromes have been difficult to faithfully reproduce in the laboratory. Recent efforts have been made to define necessary and sufficient criteria for developmental epilepsy models. Ideally, the model should approximate the age at onset of epilepsy, the etiology, seizure phenotype, and EEG characteristics, and long-term consequences.¹ In the case of infantile spasms, minimal criteria for a relevant model have been proposed to include age-dependent seizures during infancy that are ACTH responsive.² An ideal model would include spontaneous clusters of spasms, a characteristic EEG pattern which resembles hypsarrhythmia or electrodecrements, and neurodevelopmental sequelae.^{1–3} Differences in these criteria reflect complementary approaches used in the design of animal models—an intuitive model that attempts to closely replicate the human disease and a reductionist model which centers on specific components in order to facilitate research of specific hypotheses.¹

Unfortunately, in the case of infantile spasms, no model has been able to replicate all of these conditions, and lack of an adequate animal model has hindered ongoing research. Several recently refined hypotheses are offering new insights into this challenging and devastating disorder. Early studies focused on the role of ACTH and its effect on seizures in the developing brain using traditional kindling models.⁴ Expanding knowledge of the role of ACTH as a neuroendocrine molecule and participant in the stress response via its interaction with corticotropin releasing hormone (CRH) led to the implication of CRH in the pathophysiology of infantile spasms. Experimental injection of CRH into the ventricles causes limbic seizures in an age-dependent manner.^{5,6} The CRH excess hypothesis postulates that an insult to the developing brain causes an increase in CRH expression in the amygdala leading to seizures, neuronal injury, and long-term deficits.⁷ Shortcomings of this model include the lack of hypsarrhythmia, limbic seizures rather than spasms, and the lack of spontaneous seizures. However, it may provide insight into the role of glucocorticoids in brain development, the mechanisms underlying the multiple etiologies of infantile spasms, and the action of ACTH in this disorder.³

An alternative model undergoing continued research uses intraperitoneal injection of NMDA to induce seizures. Initial studies showed emergence of a seizure semiology similar to spasms (emprosthotonus) in infant rats as a response to injection and suppression of EEG activity.⁸ These animals also exhibit cognitive deficits as adults,⁹ another component of proposed models for infantile spasms. Because the initial model was not sensitive to ACTH, it was altered to include prenatal exposure to corticosteroids in order to alter the hypothalamic-pituitary-adrenal axis and simulate stress on the developing brain. This resulted in sensitization to the effects of NMDA and some treatment effect to acute ACTH administration.¹⁰ Although spontaneous seizures are not seen, the animals are sensitive to vigabatrin.^{3,10} This model also provides an avenue for research into cryptogenic infantile spasms perhaps also associated with developmental stressors.

Additional models include intrahippocampal infusion of tetrodotoxin,¹¹ multiple cortical and subcortical lesions designed to simulate symptomatic spasms,¹² and genetic knockout

mice.¹³ Although none of these models have yet yielded new treatments, significant strides have been made toward a better understanding of this multifactorial disorder that will hopefully result in targeted therapies and improved outcomes.

Epilepsy genetics

Epidemiologic data suggest a baseline risk for epilepsy of 1% in the general population.¹⁴ A number of studies have found a risk of 2%–4.6% for individuals with an affected first-degree relative.¹⁵ Although this represents a doubling of risk, over 75% of individuals with a positive family history have only one affected relative and few families follow Mendelian patterns of inheritance.¹⁶ This pattern implicates a complex form of inheritance where risk is imparted by the additive effects of multiple genes and environmental factors. Many discoveries to date have provided information about monogenetic epilepsies through the examination of multiply affected families with Mendelian patterns of inheritance and genetic mutations that impart a large increase in risk.¹⁷ Association studies often have more statistical power and offer a different approach to analysis, but validation has been problematic.¹⁸ Therefore, applicability of these discoveries to testing and treatment of the individual patient has been limited. However, there has been at least one success story which has provided clinically relevant information while opening additional avenues of research.

The story of Dravet syndrome, or severe myoclonic epilepsy of infancy (SMEI), has been a long but fruitful one. It began with the recognition of a distinct phenotype among children with catastrophic epilepsies. Initial cardinal features included the following: seizure onset in the first year of life, prolonged febrile hemiclonic convulsions, progression to additional seizure types between ages 1–4 with prominent myoclonic seizures, developmental regression after seizure onset, and refractory epilepsy.¹⁹ Because of a strong relationship between fever and seizures in addition to the prevalence of the generalized epilepsy with febrile seizures plus (GEFS+) phenotype in Dravet families, the *SCN1A* (voltage-gated neuronal sodium channel α -1 subunit) gene was investigated in connection with this disorder²⁰ and current estimates suggest that up to 70% of children with the classic phenotype will harbor a mutation in this gene.¹⁹ Subsequent studies have been directed at outlining genotype–phenotype correlations, understanding the mechanisms of epileptogenesis associated with altered gene function, creating animal models to study additional features of the disease, characterizing treatment response, and following long-term outcomes.

Formal recommendations regarding genetic testing in epilepsy have lagged behind the pace of discovery in this field and a full discussion is beyond the scope of this article. A recent report by the ILAE Genetics Commission outlines the testing available for a number of disorders in addition to providing a framework for how to analyze the clinical validity and utility of specific genetic tests. For *SCN1A* disorders, truncation mutations or deletions in the appropriate clinical context can provide confirmation of the diagnosis of Dravet syndrome and are more clinically useful than missense mutations, which can be associated with a broad range of phenotypes.²¹ *SCN1A* mutations have also been found in a subset of children with infantile epileptic encephalopathies²² and may therefore represent an important addition to the tiered diagnostic approach used in these disorders. A recent meta-analysis of the literature found 23 uncontrolled studies of standard antiepileptics in this population insufficient to make discrete recommendations regarding treatment; however, 2 small randomized controlled trials show benefit for stiripentol in this population.²³ The hope is that further study and earlier diagnosis may eventually lead to better outcomes and treatment strategies in addition to targets for intervention and translational research.

New advances in drug therapy

There are several new medications recently approved by the Food and Drug Administration (FDA) that are particularly helpful for pediatric epilepsy patients. These include clobazam, rufinamide, and vigabatrin. Some of the medications have been previously covered in another

Neurology[®] article on adult epilepsy.²⁴ Although also recently released, lacosamide is not discussed in detail as it is not FDA approved for use in children.

Clobazam was approved by the FDA in October 2010 and has been used in other countries for many years. It is a 1,5-benzodiazepine that enhances GABAergic neurotransmission by allosteric activation of GABA A receptor and downregulation of the GABA transporters 1 and 3 (GAT 1 and GAT 3). Unlike other benzodiazepines, clobazam has decreased affinity for the GABA A subunits that cause sedation and therefore there are reduced side effects such as sleepiness and tolerance. It has been studied in children with refractory epilepsy and found to be particularly effective at high dose for drop seizures in children with Lennox-Gastaut syndrome.²⁵

Rufinamide was released in November 2008 and was specifically studied in children with Lennox-Gastaut syndrome before the adult indication was obtained. The precise mechanism of action is not yet known, but it is thought to act on the sodium channel. In one study, drop seizures were improved by 42.5% in Lennox-Gastaut patients compared to an increase of 1.4% in the placebo group. Rufinamide may aid in myoclonic absence seizures as well.²⁶ In a study of Dravet patients with *SCN1A* mutations, rufinamide was less effective with a low responder rate (20% at 6 months, 5% at 34 months) and high dropout rate (30% due to aggravation of seizures).²⁷ Side effects described for rufinamide include fatigue, upset stomach, and allergic reaction in some patients.

Vigabatrin was first released in the United Kingdom in 1989 and was approved for use in the United States in 2009 for both infantile spasms and as adjunctive therapy for refractory complex partial seizures. This drug is an inhibitor of GABA transaminase which degrades GABA, the primary inhibitory neurotransmitter in the CNS. Vigabatrin is thus believed to work via increasing synaptic GABA levels. Vigabatrin is one of the primary treatments for infantile spasms and is especially helpful for children with tuberous sclerosis complex (TSC) and cortical dysplasia (CD). Low dose vigabatrin (18–36 mg/kg/day) was compared to high dose (100–148 mg/kg/day) in 221 children with infantile spasms; 15.9% of patients in the high dose group compared to 7% of the low dose group had cessation of seizures. During follow-up, 23% of patients relapsed with 72% retaining seizure freedom.²⁸ The most discussed side effect of vigabatrin involves peripheral vision defects (mainly bilateral nasal defects) with central vision sparing which is often mild to moderate. The incidence ranges between 14% and 92% of patients²⁹ and can be permanent. The FDA mandated that children have vision screening at baseline, every 3 months for 18 months, then every 6 months thereafter, while receiving treatment. If there is a field defect noted, then testing should continue every 3 months. Testing should end 6 months after vigabatrin stops. Irritability and sleepiness are common side effects. Reversible white matter signal abnormalities that are in the deep structures of the brain on DWI and T2 on MRI have been reported with vigabatrin, especially at high doses or in younger ages.^{28,30} These MRI changes were asymptomatic in patients on vigabatrin and there is no consensus as to whether screening neuroimaging should be performed and therapy terminated should MRI abnormalities appear. All the side effects must be weighed carefully in light of how devastating untreated infantile spasms can be to development. Many pediatric neurologists feel strongly that treatment benefits outweigh the potential of these risks, to which a young infant may be able to adapt.

Comparative effectiveness trials

There have been 2 comparative effectiveness trials performed that have changed the way pediatric neurologists prescribe treatments and counsel for certain seizure types. The UKISS study compared vigabatrin ($n = 52$) to prednisolone ($n = 30$) and ACTH ($n = 25$) in 107 children. The study concluded that steroids provided better seizure control at 2 weeks (73% both steroid treatments combined vs 54% vigabatrin) and improved development through testing with Vineland Adaptive Behavioral Scores (VABS) after 1 year in cryptogenic etiologies. But at follow-up at 4 years, there were no substantial differences in development between the 2 medications.³¹ Both vigabatrin and ACTH had similar rates of side effects (54% in

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vigabatrin and 55% in steroids). Based on these studies, steroids (ACTH or prednisolone) should be considered first-line treatment for patients with IS caused by a cryptogenic etiology.³² There was a follow-up study using the same UKISS patient population where VABS were performed at 4 years of age. The authors compared scores between children who had a long lead time to treatment and those with a short lead time from spasm onset to therapy. Lead time was categorized as follows: 7 days or less, 8–14 days, 15 days–1 month, 1–2 months, and greater than 2 months. They found that prompt diagnosis and treatment of infantile spasms resulted in better outcomes compared to a long lead time where each month delay in treatment was associated with a 3.1 decrease in VABS scores and each increase in lead time duration was associated with a 3.9 decrease. In addition, younger infants at the start of spasms were at more risk for poor developmental outcome than older infants.³³

Another multicenter comparative study evaluated the effectiveness of lamotrigine, ethosuximide, and valproic acid in childhood absence patients.³⁴ This was a double-blind, randomized controlled trial measuring the efficacy, tolerability, and neuropsychological effects of the 3 medications. In this study, ethosuximide and valproic acid were found to have better efficacy compared to lamotrigine (53% on ethosuximide, 58% on valproic acid, compared to 29% on lamotrigine). Ethosuximide had fewer side effects compared to valproic acid, with attention problems being more common (49% on ethosuximide vs 33% on valproic acid). Lamotrigine was believed to be better tolerated compared to the other two, although not as effective. However, ethosuximide may not treat generalized tonic-clonic seizures very effectively and this seizure type may be an issue with a subgroup of older absence patients. The results of this study have changed how pediatric neurologists counsel families on the efficacy of medication for childhood absence epilepsy, and which medication is prescribed as first-line therapy for this common pediatric epilepsy.

Epilepsy comorbidities

Pediatric neurologists have long recognized that caring for children with epilepsy requires attention to a host of other concerns beyond seizures, including behavior, education, and bone health. Children living with epilepsy are at increased risk of attention problems, nonattentional learning disabilities, aphasia, and mood disorders. There has also been clear demonstration that epileptiform discharges can cause an epileptic encephalopathy and epileptic aphasia. Some of these issues will respond to seizure medications and some will not. Recently, research has suggested that these concerns may persist despite adequate treatment of seizures. The Childhood Absence Epilepsy Study cited above followed neuropsychologic measures on treatment and demonstrated that attention deficits continue even with control of seizures.³⁴ A recent article followed patients with childhood epilepsy into adulthood and demonstrated that even those with well-controlled seizures and good educational achievement had difficulties with social and education outcomes.³⁵

While looking at the childhood epilepsy group as a whole, there are significant issues related to education, employment, marriage, and parenthood. Much of this effect appears to be related to cognitive issues. When education and employment were controlled compared to the general population, there were still issues related to establishing personal relationships.³⁵ Another population-based study of patients with idiopathic generalized epilepsy with generalized

tonic-clonic seizures demonstrated that with long-term follow-up, only 60% completed high school, 43% had mental health visits, and 37% lived either alone or with their parents.³⁶ A study of outcomes in juvenile myoclonic epilepsy demonstrated that 87% completed high school, 61% received a “mood altering medication,” and 30% lived alone. This group also had a large incidence of unplanned pregnancies.³⁷ Both studies indicate a significant rate of mental health needs and these should also not be ignored in the pediatric population. These studies emphasize that children living with epilepsy need educational and social support, beyond simple control of seizures, so they can become healthy, functioning adults.

There have been several advancements in recent years on the connection of bone health and seizures, especially on how this may affect children. Epilepsy patients have a 2 to 6 times greater risk of bone fractures³⁸ which may be due to the seizures themselves, lower vitamin D levels, or a lack of physical activity. Older antiepileptic medications such as valproic acid, phenytoin, primidone, and phenobarbital contribute to poor mineral deposition in bone. Although there are only a few studies with newer treatments such as the ketogenic diet and topiramate,³⁹ similar results have been found with these agents as well. The risk of osteoporosis appears associated with the cumulative dose of medication.⁴⁰ Some centers are testing for vitamin D deficiency and supplementing patients with cholecalciferol (vitamin D3).⁴¹ Bone density is especially troublesome in the pediatric population, as children with underlying neurologic problems may be at more risk due to the lower physical activity, poor nutrition, and reduced body mass. Decreased bone density can lead to issues with poor growth and frequent fractures that can impede mobility. In addition, epilepsy itself can impact growth in general.⁴² In a recent survey performed in the United Kingdom, many pediatric neurologists do not discuss bone health with children on anticonvulsants and do not give supplementation with vitamin D.⁴³ More research is needed to understand the complex relationship between bone health and children with epilepsy.

DISCUSSION

Animal models for pediatric epilepsy are now beginning to allow specific research to be done on seizure types that are unique to the pediatric population. As these models are refined, they will hopefully lead to a better understanding of pathophysiology and tailored treatment options. Genetic testing is beginning to result in earlier diagnosis and specific treatments for Dravet syndrome. It is hoped that this strategy can be replicated in other pediatric epilepsies. A future with new treatments, more comparative effectiveness trials, and a more specific diagnosis may lead to more effective treatment for children with epilepsy. Outcomes studies and endocrine studies emphasize that treating seizures alone is not adequate, and the child needs to be addressed as a whole person with treatment focusing on education, social interactions, bone health, and mental health, to allow children to mature into healthy adults. Treating epilepsy is more than simply stopping seizures.

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Pediatric epilepsy: Five new things

- New animal models of epilepsy are being developed that more closely represent pediatric epilepsy.
- Genetic testing may lead to more specific treatments in the future. Our knowledge in this area is growing.
- New medications have recently been approved specifically for use in children.
- Comparative effectiveness trials have begun to identify more effective treatments in absence epilepsy and infantile spasms. More of these types of collaborative trials are needed.
- Epilepsy comorbidities such as problems with education, social issues, and bone health need to be addressed along with seizure control to improve overall outcome.

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