What’s New, What’s Hot: The 2015 AES Hot Topics Symposium

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Abstract Prompt diagnosis and treatment of epilepsy usually result in the best outcomes, but many other issues face physicians considering management options for their patients. During a symposium held at the 69th Annual Meeting of the American Epilepsy Society, experts described cutting-edge research into this challenging disease. Among the topics covered were when to send a patient with a seizure disorder for genetic testing and how to interpret the results, ways to diagnose and treat autoimmune epilepsy, the safety of valproate in women of childbearing age, and the potential role of cannabis and cannabinoids in the management of epilepsy.

Research into the medical and surgical management of seizure disorders continues to provide new avenues for diagnosis and treatment. In many cases, however, clinicians need to carefully analyze the results to understand how the findings can best be applied to treat this difficult disease. At a symposium held during the 69th Annual Meeting of the American Epilepsy Society, speakers discussed four current “hot button” issues in the management of epilepsy: genetic testing, autoimmune epilepsy, the teratogenicity of valproate, and the potential of cannabis and cannabinoid derivatives.

The symposium was chaired by Michael R. Sperling, MD, Professor of Neurology, Sidney Kimmel Medical College, Thomas Jefferson University; Director of the Jefferson Comprehensive Epilepsy Center; and Director of the Clinical Neurophysiology Laboratory, Jefferson University Hospitals, Philadelphia, Pennsylvania.

Genetic Testing and Epilepsy

Based on a presentation by Annapurna Poduri, MD, MPH, Associate Professor of Neurology, Harvard Medical School, and Director of the Epilepsy Genetics Program, Boston Children’s Hospital, Boston, Massachusetts.

When should a patient with epilepsy be sent for genetic testing? Short answer: When a genetic diagnosis would impact clinical care and practice. The benefits of genetic tests include diagnostic certainty, information about the patient’s prognosis, and possible changes in the management of epilepsy. The drawback is their cost.

Status of Epilepsy Genetics in 2016

A growing body of evidence is emerging for the importance of genetics in epilepsy. Results of twin studies have shown that monozygotic twins have a higher rate of concordance than do dizygotic twins. Family studies have shown that the risk of generalized epilepsy is 10% in siblings of a patient with the same condition, and the risk of focal epilepsy is 5% in siblings of patients with focal epilepsy. Phenotypic studies have identified families with inherited epilepsy syndromes, such as generalized epilepsy with febrile seizures plus (GEFS+). Genetic studies of these families using copy-number variants, linkage analysis, and positional cloning have produced discoveries of associated genes.

Discoveries related to epilepsy genetics have increased exponentially over the past few years (Figure 1). Before 2001, the “channelopathy era” saw the discovery of specific channel mutations (e.g., CHRNA4, SCN1B, SCN1A, and GABRB2). From 2001 to 2009, the “dark ages” of epilepsy genetics, more than 100 association studies yielded negative or unreproducible results. Since 2009, the study of microdeletions, microduplications, and next-generation sequencing has led to an exponential increase in epilepsy genetics. At Children’s Hospital in Boston, Massachusetts, for example, a recent study of 805 children with epilepsy and chromosomal microarray analysis found that 40 patients (5%) had microdeletions or microduplications that explained the patient’s epilepsy phenotype.

Genetic Findings Related to Epilepsy

Patterns of genetic epilepsy include inherited genes, de novo mutations, and de novo postzygotic mutations. Inherited genes can be autosomal dominant or autosomal recessive. For example, the heterozygous LGI1 mutation causes autosomal-dominant epilepsy with auditory features and channelopathies. De novo mutations can also include channelopathies. In genome-wide association studies of patients with infantile spasms or Lennox-Gastaut syndrome (LGS) and their parents, de novo causative mutations can be identified; increasing the size of these studies allows better identification of enriched de novo mutations in patients...
with epileptic encephalopathy when compared with the general population.\textsuperscript{5,6}

Identification of a specific mutation can provide prognostic information for clinicians and parents, since many mutations carry a uniformly poor prognosis. For example, the \textit{DNM1} mutation on chromosome 9 is associated with profound hypotonia and intellectual disability. Postzygotic de novo mutations cause phenotypes that include hemimegalencephaly, polymicrogyria, and/or hydrocephalus.

**Which Patients Should Have Genetic Testing?**

Genetic testing should be undertaken when diagnostic certainty and prognosis are important. Identifying genetic causes of epilepsy can help to improve patient care by leading to clinically relevant models, preclinical trials, and precise treatment. A 6-month-old boy with new-onset infantile spasms and hypsarrhythmia (with negative MRI findings) who has a specific mutation in a gene associated with epilepsy or infantile spasms could forgo further workup (eg, metabolic testing, lumbar puncture). Likewise, a teenage patient with a history of juvenile myoclonic epilepsy and a family history of generalized seizures can be reassured that the disease is benign and nonprogressive after genetic test results are gathered.

Another reason to perform genetic testing is when information on specific genes can guide specific treatments to pursue or avoid. Genetic diagnoses that influence treatment decisions include mutations in the following genes: \textit{SCN1A}, in which lamotrigine and phenytoin therapy may be helpful; \textit{SLC2A1}, in which the ketogenic diet may be useful; \textit{ALDH7A1}, in which response to pyridoxine may be expected; and \textit{PNPO}, in which patients may respond to pyridoxal-5-phosphate. Other mutations may be related to promising off-label use of specific treatments, although more information is needed. They include mutations of \textit{KCNQ2}, in which ezogabine therapy could be considered; \textit{KCNQ1}, in which quinidine use could be helpful; and \textit{GRIN2A}, in which memantine could be prescribed.\textsuperscript{6} Further, in tuberous sclerosis, therapy with everolimus could be prescribed.

In the future, pharmacogenomics testing to guide treatment based on human leukocyte antigen type may provide even more precise treatment guidance.

Patients with “epilepsy plus” syndromes—the combination of epilepsy with dysmorphic features, intellectual disability, infantile spasms, or autism—also should undergo genetic testing. The clinical picture may suggest a classic syndrome associated with a single gene. For example, Down syndrome suggests trisomy 21 (verified with a karyotype), Dravet syndrome suggests a \textit{SCN1A} mutation (tested with \textit{SCN1A} sequencing for deletion or duplication), and Rett syndrome suggests a \textit{MECP2} mutation (which can be sequenced for deletion or duplication).

Patients with refractory epilepsy that affects treatment should also be tested, particularly if surgery is considered. Examples are those with early-onset epileptic encephalopathy, patients < 4 years of age with early-onset absence seizures, and individuals with familial focal epilepsy. In refractory cases, an identifiable genetic cause may influence the consideration of surgical treatment.

**Specific Approaches to Genetic Testing in Epilepsy**

Available options for genetic testing include chromosomal microarray analysis; single-gene testing (sequencing, duplication, deletion testing); panel testing, including an “epilepsy panel” or “autism panel” (all panels have the option for sequencing, but only some have the option for deletion or duplication testing); and whole-exome sequencing.

When a phenotype highly suggests the diagnosis of a specific syndrome, testing for that syndrome should be performed. For example, when a response to pyridoxine may be expected, testing for a mutation in \textit{ALDH7A1} should be done. A patient with a history and examination suggesting Angelman syndrome should undergo chromosomal microarray analysis. If the results of \textit{UBE3A} sequencing are negative, an epilepsy panel for Angelman-like genes should be considered. If all results are negative, whole-exome sequencing should be performed, since the syndrome is highly likely to be genetic. For early-onset absence seizures that occur before the age of 4 years, the \textit{SLC2A1} gene should be tested, and determination of glucose levels in the cerebrospinal fluid (CSF) can be considered. For patients with “epilepsy plus” or early-onset refractory epilepsy, a

**FIGURE 1** Evolution/explosion of epilepsy genetics since 1995—discoveries and advances. NGS = next-generation sequencing. Adapted, with permission, from a presentation by Annapurna Poduri, MD, MPH, at the 69th Annual Meeting of the American Epilepsy Society in Philadelphia, PA.
AUTOANTIBODY TESTING AND EPILEPSY

Based on a presentation by Prof. Dr. med. Christian G. Bien, Clinical Director, Krankenhaus Mara, Epilepsy Center Bethel, Bielefeld, Germany.

Autoimmune epilepsy is related to “evidence of autoimmune-mediated CNS (central nervous system) inflammation,” according to the International League Against Epilepsy's Revised Terminology for Organization of Seizures and Epilepsies. Examples of immune-mediated epilepsy include anti-LGI1 encephalitis and anti-NMDA receptor encephalitis. Similarly, “autoimmune epilepsy” is “autoimmune encephalitis” with a predominant epileptic phenotype. Approximately 80% of people with autoimmune encephalitis have epilepsy or seizures, and some 2% of all epilepsies have an autoimmune etiology. Antibodies causing autoimmune epilepsy are immunoglobulin-G (IgG) complexes directed against extracellular or intracellular CNS antigens. Extracellular antigens include AChR (GlyR), NMDAR, LG11, and CASPR2; intracellular antibodies include GAD65 and VGKC. Rates of association with systemic malignancies vary, depending on the autoantibody.

In a study of 300 consecutive patients tested for autoantibodies, epilepsy was the second most common cause of testing (22%) after encephalitis/encephalopathy (42%). Autoantibodies were less commonly tested in patients presenting with cognitive/psychiatric disorders (9%) or peripheral neurologic disorders (4%). The frequency of positive antibodies identified in that laboratory was 4.7% (out of 6,893 patients tested from 2012–2014). The most commonly detected antibody was GAD65, which was found in 338 (27.9%) patients; the next most common were NMDAR (23.4%) and LG11 (18.1%).

When Should Autoimmune Epilepsy Be Suspected?

Specific syndromes, including limbic encephalitis, faciobrachial dystonic seizures, and encephalopathy, raise the possibility of autoimmune epilepsy. Particular features of the patient and the patient’s medical history also are highly suggestive. Young women and patients with other autoimmune conditions are at increased risk of autoimmune epilepsy.

Seizure types and patterns that raise the possibility of autoimmune epilepsy include unexplained new-onset epilepsy in adult life, new-onset epilepsy with status epilepticus or with very high seizure frequency, and pilomotor seizures. Among supportive diagnostic findings are an “extreme delta brush” on electroencephalography (which has been associated with NMDAR encephalitis), an elevated cell count in the CSF, and unmatched oligoclonal bands in the CSF but not in the serum. Likewise, encephalitic lesions on MRI, especially in the mediotemporal areas, or histopathology showing “chronic encephalitis” is highly suggestive.

The incidence of antibody-confirmed autoimmune epilepsy may be surprisingly high. In one study of 19 women (age, 15–45 years) with new-onset epilepsy and no obvious preceding cause or syndrome, 5 (26%) had NMDAR antibodies. Of those five women, four (80%) had prominent psychiatric symptoms. In a series of 13 patients with new-onset status epilepticus, 8 had NMDAR antibodies; 9 had oligoclonal bands in the CSF; and additional patients had GAD65, Ri, and neuropil antibodies. The remaining two patients had no specific detectable antibody.

Faciobrachial dystonic seizures, a clinically distinctive seizure type consisting of shoulder and arm elevation with facial grimacing (unilateral or bilateral), are mediated by antibodies against the VGKC complex/LGI1. This seizure type should always prompt antibody testing.

Which Antibody Tests Should Be Ordered?

Should antibody testing be done on serum or CSF or both? CSF-only antibodies are found in < 25% of cases. However, CSF testing is more sensitive than serum testing for NMDAR antibodies. In a study of 250 patients with confirmed NMDAR encephalitis, CSF antibodies were detected in all patients, but serum antibodies were detected in only 214 patients on both immunohistochemical and cell-based assays. Serum-only antibodies are common for LGI1 and amphiophysin antibodies. In general, paired CSF and serum specimens should be sent to the laboratory whenever possible.

Positive test results must be compared to the clinical response of patients. The specificity of some tests is not confirmed (e.g., the significance of NMDAR antibodies in serum only; CASPR2 at < 1:200; VGKC complex antibodies other than those directed to LGI1/CASPR2). Positive findings on nonspecific tests should be treated with caution. Non-IgG antibodies have no proven clinical significance.

How Should Autoimmune Epilepsy Be Treated?

If the presence of autoantibodies is confirmed by testing, a suggested treatment approach using several drugs off-label (Figure 2) may be tried. Start with 1 g/d of methylprednisolone IV for
5 days, followed by 80 mg/d of oral prednisolone for 4 weeks (with or without 10 cycles of plasma exchange). After 2 weeks, re-evaluate the patient for autoantibodies and assess the clinical picture. If there is a reduction in antibody titer and clinical improvement, taper the prednisolone dosage by 10 mg/d once a week, monitoring the patient for signs of deterioration that would indicate a need to increase the corticosteroid dosage. If there is no improvement after initial high-dose prednisolone treatment, try 375 mg/m² of rituximab weekly for 4 weeks and/or 750 mg/m² of cyclophosphamide once a month.

If the antibody test is not confirmatory (“gray cases”), 80 mg/d of prednisolone for 4 weeks can be tried, followed by tapering the dosage by 10 mg/d each week. After 3 months and while the patient is on 10 mg/d of prednisolone, re-evaluate the clinical picture. If no improvement is noted, prednisolone should be discontinued. If the patient shows partial improvement, escalate immunotherapy by increasing the dosage of prednisolone or switching to cyclophosphamide and/or rituximab. If the patient has had a clinical remission, continue giving prednisolone at a daily dose of 5 mg for 6 months.¹⁸

Treatment responses to immunotherapy can be high. One study of 30 patients with autoimmune epilepsy (69% with daily seizures) treated with monthly methylprednisolone or intravenous immunoglobulin found that 62% had a ≥ 50% reduction in seizure frequency, including 10 patients (33%) who were seizure-free.²⁰

**FIGURE 2** Suggested approach to managing patients with autoantibodies and epilepsy. All medications are used off-label. Adapted, with permission, from Bien and Bien.¹⁸

Dr. Tomson addressed questions about valproate’s teratogenicity in girls and women of childbearing age or who are pregnant.

**Concerns Regarding Valproate and Pregnancy**

The European Medicines Agency released a guideline in 2014 that strengthened the warning on valproate use in girls and women: “Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant, or in girls unless other treatments are ineffective or not tolerated.”²¹

Similarly, the US Food and Drug Administration (FDA) released a drug safety announcement in 2013, stating that “valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable…. All non-pregnant women of childbearing age taking valproate products should use effective birth control.”²²

However, many providers in the epilepsy community are concerned that the alternatives to valproate in treating generalized idiopathic/genetic epilepsies may not be as effective.²³ The risk of uncontrolled seizures is not considered, and women may be encouraged to rapidly discontinue valproate during pregnancy, with potentially serious consequences. In a recent study, epilepsy-related deaths, mainly sudden unexplained death in epilepsy patients (SUDEP), accounted for 4%–7% of maternal deaths—10-fold higher than expected—in the United Kingdom.²⁴

**Risks of Valproate Use in Pregnancy**

Data from pregnancy registries show that the risk of major congenital malformations (MCMs) is higher with valproate than with other antiepileptic drugs (AEDs).²⁵,²⁶ This is a dose-dependent effect, with the highest risks occurring at doses exceeding 700 mg/d (Figure 3).²⁵,²⁷

Valproate accounts for the high rate of MCMs observed with polytherapy; adding other AEDs to valproate has no major impact on the frequency of MCMs.²⁸

When compared with the use of car-
Valproate

- ≥ 1,500 mg/d (n = 99)
- 700–1,499 mg/d (n = 480)
- < 700 mg/d (n = 431)

Carbamazepine

- ≥ 1,000 mg/d (n = 207)
- 400–999 mg/d (n = 1,047)
- < 400 mg/d (n = 148)

Phenobarbital

- ≥ 150 mg/d (n = 51)
- < 150 mg/d (n = 166)

Lamotrigine

- ≥ 300 mg/d (n = 444)
- < 300 mg/d (n = 836)

FIGURE 3  Dose-dependent teratogenic effects of antiepileptic drugs. Adapted, with permission, from Tomson and Battino.32

bamazepine, lamotrigine, and phenytoin, valproate therapy has negatively affected neurodevelopmental/cognitive outcomes and the intelligence quotient of children exposed to valproate in utero when measured at 3 and 6 years of age.29–31 These cognitive findings are also most significant when high doses of valproate (> 800 mg/d) are used. In addition, there is an increased absolute risk of autism spectrum disorder after valproate exposure.32

Task Force Recommendations

The ILAE Commission on European Affairs and the European Academy of Neurology formed a task force to examine the issue. In 2015, the task force recommended that “whenever possible, valproate should be avoided in the treatment of girls and women of childbearing potential.”33 The task force used the guiding principle of “the informed patient’s right to express a preference and the principle of shared decision between physician and patient.”33 The task force recommended that women with epilepsy be informed about the teratogenic risks of valproate, and the drug should not be used to treat focal epilepsy. If valproate is used in women of childbearing potential, it should be given at the lowest effective dose, and women not planning pregnancy should use effective birth control.

Specific Cases

Teratogenic risks need to be weighed against efficacy. Whenever possible, valproate therapy should be avoided in women of childbearing potential. The continued need for valproate should be reassessed prior to conception. The task force addressed four specific scenarios: women with newly diagnosed epilepsy, women on valproate not planning pregnancy, women on valproate who are planning pregnancy, and women who discover they are pregnant while already taking valproate.

In cases of newly diagnosed generalized epilepsies, the risks and benefits of valproate versus those of alternative therapies should be carefully weighed. Valproate is a reasonable choice provided that the woman is fully informed about its risks and benefits and is not planning pregnancy. Valproate is also appropriate therapy for girls with epilepsy when there is a high likelihood of seizure remission and AED discontinuation before puberty. Valproate treatment also may be considered in patients with severe or disabling epilepsies for whom the likelihood of pregnancy is extremely low.33

For women already taking valproate who are not planning pregnancy, use of a different AED should be considered if seizure control is suboptimal. If seizures are controlled, valproate withdrawal or a change in therapy should be considered if the risk of relapse is acceptable to the patient. In patients with generalized genetic epilepsies, patients and clinicians together may agree that continuing valproate is reasonable after carefully weighing the risks and benefits. For patients with seizures that did not respond to other AEDs before valproate therapy was started, continuation of valproate is also reasonable. When possible, total daily doses should be reduced to below 600 mg.33

Women who are taking valproate and are considering pregnancy should undergo a careful reassessment of their treatment. A switch or withdrawal from valproate should always be considered in patients with focal epilepsies, as well as those who are willing to take the risk of relapse. When possible, the lowest effective dose of valproate should be established before conception. If seizures are well controlled on low doses of valproate (< 600 mg/d), and if the patient considers the risk of withdrawal or switch unacceptable, continued low-dose valproate therapy may be considered.33

Women already on valproate who become pregnant should have their dose reduced if the risk is acceptable to the patient (usually when the history suggests that the patient does not need a high dose for seizure control). These patients may consider withdrawing from valproate therapy if they agree that they do not need the drug for seizure control. In general, the task force recommended continuing treatment in patients who discover they are pregnant while on valproate, even though such a change generally is not recommended for patients with good seizure control.33

CURRENT STATUS OF CANNABINOIDS

Based on a presentation by Kelly Knupp, MD, Associate Professor of Pediatrics and Neurology, University of Colorado School of Medicine, and Co-Director, Pediatric Epilepsy Program, Children’s Hospital Colorado, Aurora, Colorado.
Endocannabinoid receptors are abundant G-protein–coupled receptors in the brain. CB1R is found in the hippocampus, association cortices, basal ganglia, cerebellum, dorsal root ganglion, and peripheral nerves. CB2R is found in lymph tissues, pancreas, intestine, retina, and (in low concentrations) the CNS.

Endocannabinoids undergo rapid synthesis, activation, and degradation, suggesting a role for them as neuromodulators. These proteins undergo synthesis on demand by neurons, travel in retrograde fashion to the synaptic cleft, and bind to CB1 receptors in the presynaptic neuron. Activation leads to the opening of potassium channels, closing of calcium channels, inhibition of adenyl cyclase, stimulation of kinases, and inhibition of some neurotransmitter release.

Not all cannabinoids act on the endocannabinoid system. Of 100 plant-based cannabinoids, the only 3 that bind CB1R and CB2R are tetrahydrocannabinol (THC), a partial CB1R and CB2R agonist and the principal psychoactive component; cannabidiol (CBN), a CB1R and CB2R agonist; and tetrahydrocannabinol (THCV), a neutral CB1R antagonist and partial CB2R agonist.

**Preclinical Studies**

Preclinical evidence shows mixed effects on seizures. THC had anticonvulsant effects in a majority of preclinical studies and proconvulsive effects in a minority of those studies. Cannabidiol (CBD), in comparison, had anticonvulsant effects in the majority of studies and no proconvulsant effects. CBD has multiple molecular targets, including ion channels and enzymes; many of these targets have been demonstrated only in vitro.

Recent animal studies have shown promise. In mice, the CB1R agonist ACEA was shown to protect against cocaine-induced seizures and cell death in the hippocampus. In rats, enhancing endocannabinoids led to protection against kainic acid–induced seizures.

**Clinical Data**

Legalization of medical cannabis products has led to the accumulation of initial clinical data on the therapeutic and side effects of the drug. In a survey of families with children taking CBD for infantile spasms, Lennox-Gastaut syndrome (LGS), and severe myoclonic epilepsy of infancy (Dravet syndrome), a majority of families reported a decrease in seizures (Figure 4). In a retrospective study of 75 patients (mean age, 7 years) in Colorado, one third of the families reported at least a 50% decrease in seizures, and two families (2.6%) reported seizure freedom in their children. Families that had children with LGS reported the highest decrease in seizures. Eleven families (15%) discontinued CBD, mostly due to inefficacy. Although 44% of families reported adverse effects of CBD, such as increased seizures, fatigue, and gastrointestinal symptoms, 33% of families reported seeing improved alertness or behavior, and 11% saw improvements in motor and language skills. Families who moved to Colorado from other states were twice as likely to report an improvement in seizures, and their children had spent a significantly longer length of time on CBD before discontinuing it.

CBD alters the metabolism of other medications. In a study of 13 patients taking both clobazam and CBD, clobazam serum levels increased an average of 60%, while serum levels of the active metabolite norclobazam rose 500%, requiring most patients to decrease their dosage of clobazam to avoid precipitating side effects.

Efficacy and safety data from 261 patients treated for 3 months in the CBD expanded-access program showed a mean decrease in seizure frequency of 45%, while patients with Dravet syndrome experienced a decrease of 62.7% in seizure frequency and those with LGS, a drop of 71.1%. Seizure freedom was achieved by 9% of the patients. Somnolence and diarrhea were the most common side effects (23%), Serious side effects occurred in 106 patients, including death in seven gravely ill patients. Additional clinical studies of CBD are ongoing.

**REFERENCES**


