The Generalized Epilepsies: Description, Pathophysiology, Treatment, and Prognosis

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Abstract Over the years, our understanding of the generalized epilepsies has changed drastically. Researchers and clinicians have come to appreciate the differences among generalized seizure disorders and design better protocols for treating and following affected patients. During the 68th Annual Meeting of the American Epilepsy Society, an expert panel delved into the current terminology of generalized epilepsies and covered their origin, pathophysiology, clinical and electroencephalographic features, treatment options, and prognosis.

A symposium held during the 68th Annual Meeting of the American Epilepsy Society in Seattle, Washington, experts focused on our current understanding of generalized epilepsies, including idiopathic, symptomatic, and progressive conditions. Topics including their pathophysiology, clinical and electroencephalographic (EEG) manifestations, current treatment options, and prognosis were covered. The symposium was chaired by Michael R. Sperling, MD, Professor of Neurology and Director of the Jefferson Comprehensive Epilepsy Center and Clinical Neurophysiology Laboratory, Thomas Jefferson University, Philadelphia, Pennsylvania.

REVISED TERMINOLOGY AND CLASSIFICATION

In 2010, the International League Against Epilepsy (ILAE) issued a report revising the terminology of seizures and epilepsies.1 Generalized seizures were defined as “originating at some point within, and rapidly engaging, bilaterally distributed networks.” Figure 1 illustrates a conceptual diagram of such a network superimposed on a functional magnetic resonance imaging (MRI) scan of generalized spike-wave activity.

Generalized seizures can be classified as tonic-clonic, absence, clonic, tonic, atonic, or myoclonic (Figure 2).2 Absence seizures can be further subdivided into typical, atypical, and absence with special features (myoclonic absence seizures or eyelid myoclonia).

Traditionally, epilepsy etiologies were considered to be idiopathic (no underlying cause other than a possible hereditary predisposition), symptomatic (due to a known or presumed cause), and cryptogenic (presumed symptomatic). However, the revised ILAE classification modifies these concepts, replacing them with the categories genetic (caused by a genetic defect that directly contributes to the epilepsy, with seizures being the core symptom of the disorder), structural-metabolic (caused by a structural or metabolic disorder of the brain), and unknown (caused possibly by a genetic, structural, or metabolic defect).1

PATHOPHYSIOLOGY OF THE GENERALIZED EPILEPSIES

Based on a presentation by Solomon L. Moshé, MD, Charles Frost Chair in Neurosurgery and Neurology; Professor and Vice Chairman of Neurology; and Director of Child Neurology and Clinical Neurophysiology, Neuroscience, and Pediatrics; Albert Einstein College of Medicine, Bronx, New York.

Generalized Genetic Epilepsies

Examples of generalized genetic epilepsies include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalized tonic-clonic seizures alone, and familial adult myoclonic epilepsy. Some syndromes may mimic generalized epilepsies, including glucose transporter disorders such as glucose transporter-1 (GLUT1) deficiency, West syndrome, Lennox-Gastaut syndrome, and progressive myoclonic epilepsies.

Several genes have been associated with the development of generalized genetic epilepsies. Many can be found on the Online Mendelian Inheritance in Man website (http://omim.org/). Table 1 includes a number of genes with various functions that can cause different types of generalized seizures.

Generalized Seizure Models

Several animal models are helpful in understanding the pathophysiology of epilepsy, including its causes, ictogenesis, epileptogenesis, and response to treatment.2 Several models (eg, electroshock, use of pentylenetetrazole) refer to specific induced seizure types, including
Absence, tonic-clonic, and myoclonic seizures. Genetic animal models of specific seizure types or syndromes, including absence or tonic-clonic seizures, Dravet syndrome, and genetic epilepsy with febrile seizures plus, have an important place in the study of epilepsy. Some models of absence epilepsy are spontaneous models, whereas others involve transgenic mice obtained with gene-targeting strategies (e.g., knock in, knock out, or conditional knock out).3

Benign Familial Neonatal Seizures

This rare, autosomal-dominant epilepsy is characterized by seizures that typically begin in newborns on the second or third day of life and remit by 6 weeks. The seizures are tonic and clonic, but they sometimes have focal components. They recur later in life in about 10% of patients.4 Mutations found in KCNQ2 and KCNQ3 lead to changes in the slowly inactivating and nonactivating M-channel current.5

Benign Myoclonic Epilepsy in Infancy

This rare form of epilepsy occurs twice as often in boys than in girls. The onset of seizures usually occurs between 5 months and 5 years of age, and about 40% of patients have a family history of epilepsy or febrile seizures. Affected children present with head drops, upward eye deviation, and arm jerks that rarely cause falls. Interictal EEG findings in this type of epilepsy usually are normal and rarely show focal abnormalities or generalized spike-wave complexes. During the jerks, fast generalized spike- or polyspike-wave complexes may be seen. Typically, patients with benign myoclonic epilepsy in infancy have a good prognosis, but some may exhibit moderate cognitive impairment.6

Pyridoxine-Dependent Epilepsy

This epilepsy results from an abnormality in the lysine degradation pathway due to a mutation in ALDH7A1. Elevated pyroglutaric acid levels in cerebrospinal fluid are noted.7 Seizures typically begin during the first 24–48 hours of life, but they sometimes occur in children 2 to 3 years of age. Seizures may be preceded by encephalopathy, abdominal distention, or vomiting and consist of multifocal myoclonus, spasms, or grimacing. The EEG shows multifocal spikes or a suppression-burst pattern.
When this type of epilepsy is suspected, intravenous injection of 100 mg of pyridoxine, ideally during EEG monitoring, typically elicits a prompt response. If there is no response, 30–50 mg/kg of pyridoxal-5-phosphate is given daily.

**Genetic Epilepsy with Febrile Seizures Plus (GEFS+)**

GEFS+ is a spectrum of disorders, beginning with febrile seizures, then switching to both febrile and afebrile seizures, and then afebrile seizures only. Examples include typical febrile seizures, fever-related seizures occurring after 5 years of age, myoclonic-astatic epilepsy (Doose syndrome), and severe myoclonic epilepsy in infancy (Dravet syndrome). The “G” in GEFS+ once stood for “generalized” but now stands for “genetic.” Mutations in SCN1A and GABRG2 have been implicated in GEFS+.

**Dravet syndrome**. Seizures typically begin at 6–15 months of age and often are triggered by fever, illness, or immunization. Several seizure types (e.g., generalized or hemiclonic convulsions; myoclonic, atonic, or focal dyscognitive seizures; and nonconvulsive status epilepticus) may be involved. Initially, the EEG can be normal or show focal spikes, but it eventually demonstrates multifocal or generalized spikes and spike-wave-complexes. Imaging can be normal or show nonspecific atrophy.

The child’s development initially is normal but then slows when seizures start; ongoing seizures may lead to an unfavorable outcome. The course typically stabilizes after 5 years of age. Mutations of the voltage-gated sodium channel gene SCN1A have been found in 70%–80% of affected individuals. Typically, they are de novo mutations. Girls who are SCN1A-negative may have mutations involving the protocadherin-19 gene (PCDH19).

This condition may be associated with the sodium channel. Therefore, it is advised that patients not be given drugs that modify the sodium channel, such as carbamazepine, oxcarbazepine, phenytoin, or lamotrigine.

**Doose syndrome** accounts for at least 1%–2% of childhood epilepsies, making its first appearance between 7 months and 6 years of age. Children with Doose syndrome develop normally before seizures begin. The EEG background initially is normal, but it slows upon initiation of symptoms and then normalizes once the seizures resolve. The interictal EEG typically shows brief bursts of generalized 2- to 4-Hz spike waves or polyspikes.

Clinically, children have symmetric myoclonic jerks with frequent head nods and falls. About one third of patients have episodes of myoclonic status that last from hours to days. Absence and tonic seizures also may occur.

One third of patients have a family history of seizures, including GEFS+. Prognosis varies, with at least half of affected individuals having normal or mildly delayed cognition. The ketogenic diet is effective in treating Doose syndrome and often is used with antiepileptic drugs (AEDs).

**Absence Epilepsies**

Absence epilepsy occurs in about 8% of children with seizure disorders, making it second only to benign epilepsy with centrotemporal spikes in this patient population. About one third of children with this disorder have a positive family history, and 10% of siblings also develop seizures. In monozygotic twins, 75% had absence seizures, and 85% had the spike-wave trait. About 10% of patients experienced febrile convulsions before the absence seizures began.

Associated epilepsies include childhood absence epilepsy, early-onset absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy. Absences also occur in the setting of structural brain lesions, chromosomal disorders, and Angelman syndrome. Some syndromes also feature atypical absences, typically with a spike-wave complex pattern slower than 2.5 Hz.

**Typical absence seizures** consist of brief episodes of behavioral arrest with staring and unresponsiveness, often occurring many times per day. The degree of unconsciousness varies and is most pronounced at seizure onset. The duration is typically < 10 seconds; recovery is quick and without postictal confusion. Hyperventilation, a possible provoking factor, often is used in the office or during routine EEG examinations to elicit an absence seizure. Longer absence seizures can have automatisms, and there may be clonic, tonic, or atonic features.

The EEG typically shows generalized 3-Hz spike-wave discharges. Interictal spike-wave complexes are identical to ictal discharges, which last > 3 seconds. Spike-wave complexes in children < 5 years of age may be maximal in the occipital area.

**Childhood absence epilepsy** typically first occurs in children 4–8 years of age. About 10% of patients may have prior febrile convulsions, and absence status occurs in 10%–15% of affected individuals. Distinct myoclonic seizures typically are not seen, but they may have clonic or myoclonic twitching as part of their
absences. Tonic-clonic seizures occur in 40%, usually as they approach puberty, but these occurrences typically are infrequent and easily controlled.

Seizures in childhood absence epilepsy are controlled in most patients with the use of valproic acid, ethosuximide, or lamotrigine. Wirrell et al\(^1\) showed that 60% of 75 patients with childhood absence epilepsy and 11 with juvenile absence epilepsy were successfully treated with the initial AED tried (77% responded to valproic acid, and 55% benefited from ethosuximide). The success rate was lower among patients with generalized tonic-clonic or myoclonic seizures. Terminal remission was less likely if the initial AED failed; these patients were more likely to develop juvenile myoclonic epilepsy. Refractory absence epilepsy is seen in 5%–20% of patients.

About one third of patients have poor social adaptation, attention deficit with hyperactivity disorder (ADHD), or academic difficulties. Remission occurs during mid-adolescence in about 60% (range, 21%–89%) of patients.

Markers of poorer outcome include onset after age 8 years, associated generalized tonic-clonic seizures, positive family history, subnormal intelligence, abnormal neurologic examination, and presence of polyspikes on the EEG.

**Early-onset absence epilepsy** initially occurs before 2 years of age. Most patients exhibit control readily with medications. About 10% of patients have an \( S L C 2 A 1 \) mutation causing GLUT1 deficiency. These children have refractory seizures and also may have ataxia, intellectual disability, movement disorders, and microcephaly. If the child has GLUT1 deficiency, the ketogenic diet is the treatment of choice.\(^1\)\(^2\)\(^3\)

**Atypical absence seizures** occur without an abrupt clinical onset or offset and typically are not precipitated by hyperventilation. They usually last > 10 seconds. Patients often have other seizure types; for example, children with Lennox-Gastaut syndrome can experience absence seizures. Unlike children with childhood absence epilepsy, children with atypical absence seizures often have an abnormal neurologic exam. The EEG also shows a slower spike-wave pattern < 2.5 Hz. These seizures typically are more difficult to control.

**Juvenile Myoclonic Epilepsy**

This disorder accounts for about 10% of all epilepsies and typically starts at 12–18 years of age. Patients exhibit myoclonic jerks (often, in the morning), which may be the only manifestation or may precede generalized tonic-clonic seizures that often start upon awakening. About one third of juvenile myoclonic epilepsy patients also have absence seizures.

Precipitating factors for the seizures include lack of sleep, stress, flickering lights, alcohol, and menstrual periods. Seizures are usually controlled with medication; most patients require lifelong treatment. The mode of inheritance has not been fully elucidated, although many models have been proposed.

Patients with juvenile myoclonic epilepsy can have focal semiology or EEG features that can be mistaken for focal epilepsy. Clinical findings may be asymmetric, including focal myoclonus version or “figure four” sign. The EEG also may show focal spikes or slowing. Ictal EEG patterns can have asymmetric evolution, but onset is always generalized.\(^4\)\(^5\)\(^6\)

Focality on the EEG often confers a worse prognosis for seizure control, suggesting a diagnosis of an atypical generalized epilepsy.\(^6\)\(^7\) Other factors associated with a worse prognosis for seizure control include presence of all three seizure types, epileptiform discharges on the baseline EEG, younger age at presentation, and longer duration of epilepsy.\(^8\)

Table 2 summarizes the characteristics of idiopathic generalized epilepsy syndromes in children and adolescents.

### PROGNOSIS AND COGNITIVE OUTCOMES OF THE GENERALIZED EPILEPSIES

Based on a presentation by Katherine C. Nickels, MD, Assistant Professor of Neurology, Mayo Clinic, Rochester, Minnesota.

**Childhood Absence Epilepsy**

**Prognosis.** Wirrell and colleagues\(^1\)\(^9\) evaluated 72 children diagnosed with childhood absence epilepsy for a mean of 14.1 years to an average age of 20.4 years. By 12 years of age, on average, 65% were seizure free and had discontinued treatment. Overall, 15% of the total cohort (44% of those who did not remit) met the criteria for juvenile myoclonic epilepsy. Predictors against remission included myoclonic or generalized tonic-clonic seizures while on AEDs, absence status epilepticus before or during AED treatment, family history of generalized seizures, and abnormal background on initial EEG.

Callenbach and others\(^1\)\(^0\) followed 47 children with childhood absence epilepsy for 12–17 years, finding that poor seizure control during the first 6 months of AED therapy predicted longer duration of epilepsy and older age at remission.

**Cognitive outcomes.** Traditionally, clinicians believed that social and cognitive outcomes in absence epilepsies were favorable. However, mounting evidence shows that this may not be the case.

Caplan et al\(^1\)\(^1\) evaluated 69 children with childhood absence epilepsy and 103 controls, finding that 25% of the affected children had subtle cognitive deficits, 43% had linguistic difficulties, and 61% had a psychiatric diagnosis (typically ADHD or anxiety).

Vega and others\(^2\)\(^2\) compared attention problems in childhood absence epilepsy and controls using a standardized questionnaire and showed that children with childhood absence epilepsy had greater hyperactivity and inattention. In both studies, predictors of problems included longer duration of illness and higher seizure frequency.

Masur and others\(^2\)\(^3\) conducted a larger study of 446 children with childhood absence epilepsy, finding that the full-scale intelligence quotient (IQ) of these patients was normal, but 35% had clinically significant attention problems that persisted after successful treatment.

Finally, Vega and coworkers\(^2\)\(^4\) compared psychiatric outcomes between 45 patients with childhood absence epilepsy with 41 controls. Patients with childhood absence epilepsy had more anxiety and depression: 11% of the patients with childhood absence epilepsy had clinically significant anxiety scores compared with
2% of the controls, and 24% of childhood absence epilepsy patients had clinically significant depression scores compared with 2% of the controls. There was no correlation between risk of anxiety/depression and disease duration, intractability, or medication effects.

Social outcomes. Wirrell and colleagues25 compared social outcomes of young adults with absence epilepsy diagnosed in childhood to young adults with juvenile rheumatoid arthritis. Young adults with childhood absence epilepsy were more likely to be in remission than those with juvenile rheumatoid arthritis (57% vs 28%). Despite the increased remission percentage, those with childhood absence epilepsy—including those whose epilepsy was in remission—had poorer social outcomes than patients with juvenile rheumatoid arthritis. Of the childhood absence epilepsy/juvenile absence epilepsy patients, 36% failed to graduate, 48% repeated a grade, 39% had a history of heavy alcohol use, 54% had current or past psychiatric or emotional problems, and 34% had an unplanned pregnancy.

Epilepsy with Generalized Tonic-Clonic Seizures Alone

Camfield and Camfield26 followed 36 patients with idiopathic generalized epilepsy with only generalized tonic-clonic seizures (mean age of onset, 6.7 years) for an average of 22.2 years. In all, 58% had fewer than 11 seizures altogether. All patients had a normal IQ; 92% were seizure-free long enough to attempt AED withdrawal, and 75% were in complete terminal remission. However, of 30 patients who were > 21 years of age by the end of the study, 70% exhibited below-average academic achievement, with only 60% of these patients graduating from high school. Furthermore, 27% had a psychiatric diagnosis, 33% were unemployed, and 38% had a pregnancy outside of a stable relationship.

Juvenile Absence Epilepsy

Trinka and others27 followed 163 patients with either childhood absence epilepsy, juvenile absence epilepsy, or an overlap for a mean of 25.8 years (range, 3–69 years) and found a remission rate of 56%, 62%, and 54% for these groups, respectively. Interestingly, 19% of juvenile absence epilepsy patients and 3% of childhood absence epilepsy patients eventually developed juvenile myoclonic epilepsy. Tovia et al28 studied 17 patients with juvenile absence epilepsy for a mean of 6.05 years, reporting that 44% were seizure-free at their last follow-up. In both studies, patients with absence seizures only had better outcomes than did those who also had generalized tonic-clonic seizures.

Juvenile Myoclonic Epilepsy

Prognosis. Baykan et al29 followed 48 patients for a mean of 19.6 years, reporting that 66.6% had a benign course; 16.7% were resistant to drug treatment; and 16.7% were pseudoresistant due to lifestyle issues, lack of medication adherence, or inappropriate medication. However, only 8.3% were able to stop using AEDs and remain seizure-free.

Camfield and Camfield30 followed 23 patients for a mean of 25.8 years; 18 patients (78.3%) became seizure-free, and AED withdrawal was attempted. Of these patients, six patients became seizure-free off AEDs, and five stayed off AEDs but continued to have ongoing seizures, including three who had occasional myoclonic seizures only.

Geithner and others31 reported that predictors against remission in juvenile myoclonic epilepsy include generalized tonic-clonic seizures preceded by bilateral myoclonic seizures, longer duration of epilepsy with unsuccessful treatment, and AED polytherapy.

Social outcomes. In a study of 23 patients with juvenile myoclonic epilepsy, Camfield and Camfield30 found that 87% graduated from high school, 70% had some college or higher education, and 69% were fully employed. However, 61% of these patients were using a mood-altering medication, and 80% of their pregnancies were unplanned and conceived outside of a stable relationship. No clear relationship between seizure and social outcomes was noted.

After following 33 patients for a mean of 37.8 years, Schneider-von Podewils and colleagues32 observed that 88% had more than one major unfavorable social outcome. Worse outcomes were noted among patients who were not free from seizure activity.

TREATMENT OF THE IDIOPATHIC (GENETIC) GENERALIZED EPILEPSIES

Adapted, with permission, from a presentation by Katherine C. Nickels, MD, at the 68th Annual Meeting of the American Epilepsy Society.

### TABLE 2

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at onset</th>
<th>Seizure type(s)</th>
<th>Electroencephalographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy</td>
<td>Early to mid-childhood</td>
<td>Absence seizures (typically 20–50 times daily)</td>
<td>3-Hz generalized spike-and-wave discharges, activated by hyperventilation</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>Young to mid-adolescence</td>
<td>Absence seizures (fewer 1–2 times daily and GTCS (in 80% of patients)</td>
<td>3- to 4-Hz generalized spike-and-wave discharges</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Adolescence through young adulthood</td>
<td>GTCS and myoclonus (rarely, absence seizures)</td>
<td>3.5- to 6-Hz generalized spike-and-polyspike (40% incidence) wave discharges</td>
</tr>
<tr>
<td>Idiopathic generalized epilepsy</td>
<td>Childhood through young adulthood</td>
<td>GTCS</td>
<td>Generalized spike-and-wave discharges</td>
</tr>
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GTCS = generalized tonic-clonic seizures
Medical Therapy

According to the 2013 ILAE evidence review, treatment of generalized epilepsy exists only for use of valproate or ethosuximide in children with absence seizures. In a large, randomized, controlled trial, Glauser and others analyzed data on 453 children with childhood absence epilepsy who were randomized to receive ethosuximide, valproate, or lamotrigine. Use of ethosuximide or valproate was more effective than lamotrigine administration after 16–20 weeks of therapy. However, more patients had attentional difficulties with use of valproate than with administration of ethosuximide or lamotrigine (49%, 33%, and 24%, respectively).

A follow-up study with 12-month outcomes showed that the effectiveness of valproate and ethosuximide compared with lamotrigine persisted, but patients on valproate had a higher rate of adverse events that led to discontinuation of therapy. Thus, the authors concluded that ethosuximide was the optimal initial monotherapy for childhood absence epilepsy.

An interesting study by von Podewils and others evaluated the natural course of 15 patients with genetic generalized epilepsy (5 patients each with absence seizures, generalized tonic-clonic seizures, or both) who had refused AED therapy. These patients were followed for a mean of 15.3 years (range, 7–27 years), and 53.3% eventually remitted (mean seizure freedom, 13.1 years).

Dietary Treatment

The efficacy of dietary treatment with either the ketogenic diet or modified Atkins diet has been evaluated in patients with childhood absence, juvenile absence, and juvenile myoclonic epilepsy. Groomes et al studied 21 patients with childhood absence and juvenile absence epilepsy on a ketogenic diet and 13 patients who followed a modified Atkins diet. At 3 months, 18 patients (86%) had a > 50% seizure reduction, and 4 (19%) were seizure-free. Only two patients (9.5%) had no change in seizure frequency.

Kossoff et al evaluated eight patients with juvenile myoclonic epilepsy who followed a modified Atkins diet. Of them, two (25%) were seizure-free, and four (50%) had a > 50% seizure reduction. Two patients (25%) had no change in seizure frequency, but one did not achieve urinary ketosis.

Early dietary treatment of GLUT1 deficiency syndrome improves outcomes. Shiohama et al reported on a child with GLUT1 deficiency syndrome who developed white-matter lesions on serial MRI while following a ketogenic diet. The lesions disappeared on subsequent imaging, so it is not entirely clear whether they resulted from dietary therapy.

Surgery

Jenssen et al evaluated corpus callosotomy with an anterior 2/3 callosotomy to treat nine adult patients with refractory generalized tonic-clonic seizures (some also had absence and/or myoclonic seizures). Over a mean follow-up of 5.4 years (range, 0.6–10.3 years), eight patients (89%) had a > 50% seizure reduction, and four (44%) had a > 80% reduction in general tonic-clonic seizures.

Arya et al studied vagal-nerve stimulation for medically refractory absence epilepsy in nine patients (seven with childhood absence epilepsy, two with juvenile absence epilepsy). After a mean follow-up of 33.9 months (± 25.5 months, minimum 4 months), they noted a mean reduction in daily seizure frequency of 53.5% ± 60.3%, with a 50% responder rate of 55.6%.

Infantile Spasms

Infantile spasms typically begin at 4–7 months of age and always commence before 1 year of age. West syndrome comprises a triad of infantile spasms, arrest of psychomotor development, and hypersarrhythmia on EEG. Prognosis depends upon etiology, with infants having no prior brain damage and a good response to therapy often having an excellent prognosis, normal development, and no seizure recurrences. By contrast, infants with a symptomatic etiology and incomplete treatment response often do poorly and have intellectual disability and persistent seizures.

The Children’s Healthcare of Atlanta 2014 Treatment Guideline for Infantile Spasms is illustrated in Figure 3. Infants who present with spasms undergo a routine EEG, brain MRI, and metabolic workup. If treatment is indicated, patients typically receive either the ketogenic diet or steroid therapy for 2 weeks. Patients who respond to the ketogenic diet continue on it for 6 months. Patients who do not respond to the diet are switched to oral prednisolone or adrenocorticotropic hormonal therapy. Steroid therapy is tapered over 2 weeks for responsive patients; those who do not respond receive a trial of an increased steroid dose.

Dravet Syndrome

Overall outcome of patients with Dravet syndrome typically is poor and features intellectual disability and ongo-
ing seizures. Many drugs and the ketogenic diet can be used to treat seizures in Dravet syndrome. However, as discussed previously, the use of sodium-channel drugs (eg, carbamazepine, phenytoin, lamotrigine) may worsen seizures and must be avoided.

**GLUT1 Deficiency Syndrome**

Patients with this syndrome tend to be refractory to standard AEDs. As reviewed before, the main treatment for GLUT1 deficiency syndrome is the ketogenic diet. Use of GLUT1 transporter inhibitors (eg, barbiturates, valproate, theophyllines, methylxanthines) must be avoided, because it may further inhibit any remaining transporter activity and result in increased seizure frequency.

**Doose Syndrome**

As with Dravet syndrome, the ketogenic diet and use of multiple AEDs are effective treatments.

**Lennox-Gastaut Syndrome**

Seizures often are very difficult to control. Multiple pharmacologic treatments, the ketogenic diet, vagal-nerve stimulation, and corpus callosotomy have been tried. Frost and others studied 50 children with medically refractory Lennox-Gastaut syndrome who underwent implantation with a vagal-nerve stimulator. Median seizure reduction was 42% at 1 month and 57.9% by 6 months.

**CONCLUSION**

Multiple generalized epilepsy syndromes exist. Each type has its own characteristic symptoms and diagnostic findings. The treatment of each patient is an individualized endeavor. As with any medical condition, the goal of therapy for generalized seizures is to relieve patients of seizure activity and allow them to develop to their full potential and enjoy an optimal quality of life. Continued research...
into the genetic etiologies as well as the medical, dietary, and surgical treatments for the generalized epilepsies reveals ever-increasing information about the pathophysiology of these phenomena and the best treatment options for their resolution.

REFERENCES


