Article

Infantile Spasms and Lennox-Gastaut Syndrome

Edwin Trevathan, MD, MPH

ABSTRACT

Infantile spasms and Lennox-Gastaut syndrome are rare but are important to child neurologists because of the intractable nature of the seizures and the serious neurologic comorbidities. New antiepileptic drugs offer more alternatives for treating both infantile spasms and Lennox-Gastaut syndrome. Selected children with infantile spasms are candidates for epilepsy surgery. Vagus nerve stimulation, corpus callosotomy, and the ketogenic diet are all options for selected children with Lennox-Gastaut syndrome. The epidemiology, clinical manifestations of the seizures, electroencephalographic characteristics, prognosis, and treatment options are reviewed for infantile spasms and Lennox-Gastaut syndrome. Additional therapies are needed for both infantile spasms and Lennox-Gastaut syndrome as many children fail to achieve adequate seizure control in spite of newer treatments. (*J Child Neurol* 2002;17:2S9–2S22).

Of the childhood epilepsy syndromes, infantile spasms and Lennox-Gastaut syndrome are among the most rare. However, because of the intractable nature of the seizures and the serious comorbidities, infantile spasms and Lennox-Gastaut syndrome are among the most important syndromes faced by neurologists caring for children. Infantile spasms and Lennox-Gastaut syndrome share common therapies. Because up to 50% of children with infantile spasms develop Lennox-Gastaut syndrome, and because the ictal electrodecremental electroencephalographic (EEG) pattern of the spasm is virtually the same ictal EEG manifestation of atonic seizures among children with Lennox-Gastaut syndrome, several investigators have hypothesized that these epilepsy syndromes may have similar pathogenic mechanisms.[1,2] This article reviews the current knowledge of the epidemiology, clinical manifestations, therapeutic options, and prognosis of these important epilepsy syndromes.

INFANTILE SPASMS

Infantile Spasm Terminology and Classification

Infantile spasms are a unique seizure type as well as an epilepsy syndrome. Although the infantile spasm seizure type is an essential component of the infantile spasms syndrome, patients with the syndrome of infantile spasms may have other seizure types in addition to spasms. Conversely, partial seizures, gastroesophageal reflux, movement abnormalities in spastic infants and other nonepileptic disorders may mimic infantile spasms and require video-EEG monitoring for proper diagnosis.[1,3]

Individual spasms are typically characterized by brief (1–5 seconds) symmetric, salaam-like contractions of the trunk, with extension and elevation of the arms, and tonic extension of the legs, with clusters of 3 to 20 spasms typically occurring several times per day in untreated patients. When defined as an epilepsy syndrome, infantile spasms are often referred to as West's syndrome. West's syndrome classically consists of the clinical-EEG triad of spasms (the seizure type), hypsarrhythmia (the classic EEG signature), and mental deficiency (although mental retardation may be absent). Alternatively, some infants may have epileptic spasms and psychomotor delay in the absence of documented hypsarrhythmia. These patients who lack hypsarrhythmia are also considered to have an age-specific epileptic encephalopathy or an epileptic syndrome with infantile spasms but do not have West's syndrome.

In 1991, the International League Against Epilepsy (ILAE) modified previous infantile spasms classification schemes[4–6] and suggested that infantile spasms be considered a specific seizure type as well as an epilepsy syndrome.[7] Spasms or epileptic spasms currently refer to the seizure type, and infantile spasms and West's syndromes are age-related epilepsy syndromes.[8] West's syndrome and infantile spasms are used interchangeably by some authors; the author and others prefer that West's syndrome be reserved

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Address correspondence to Dr Edwin Trevathan, Director, Pediatric Epilepsy Center, Suite 12E47, St. Louis Children's Hospital, St. Louis, MO 63110-1093. Tel: 314-454-4089; fax: 314-454-4225; e-mail: trevathan_e@kids.wustl.edu.

for patients with documented hypsarrhythmia in combination with epileptic spasms and that infantile spasms be used as a general term for age-related epilepsy syndromes that include spasms.

The etiology of infantile spasms has been divided into symptomatic and cryptogenic, and, most recently, an idiopathic classification has been designated. In most earlier studies, the symptomatic group included patients with known etiologies, as well as developmental delay at onset without an identified etiology, leaving the cryptogenic group to include those patients with normal development and no known etiology. An idiopathic category previously was either not recognized or was synonymous with the cryptogenic group. More recent classification schemes of epileptic syndromes presume that cryptogenic disorders are actually symptomatic, but the specific etiology is unknown, whereas idiopathic epilepsies are typically attributed to a known or presumed genetic predisposition with generally favorable prognoses. In spite of the category of idiopathic infantile spasms designated by the International League Against Epilepsy, there is not a single gene mutation or genetic syndrome known that causes only infantile spasms and no other neurologic abnormality. Therefore, most pediatric neurologists classify children with infantile spasms, normal development at onset, normal examination and neuroimaging, and hypsarrhythmia on EEG without focal epileptiform abnormalities as having cryptogenic infantile spasms.[7]

Epidemiology of Infantile Spasms

The cumulative incidence of infantile spasms ranges from approximately 2 to 5 per 10,000 live births and is similar throughout the world.[9–14] The lifetime prevalence of infantile spasms at age 10 years has been estimated at 1.5 to 2.0 per 10,000 children.[10,13] The consistently lower prevalence rates of infantile spasms among children compared to incidence are likely attributable to the high mortality associated with infantile spasms, the evolution of spasms into other seizure types, and incomplete ascertainment in population-based studies of older children.

Approximately 90% of patients with infantile spasms present during the first year of life, with peak age of onset occurring between 4 and 6 months.[10] Although the age of onset of West's syndrome has been reported to range from 1 day to more than 6 years,[15] infantile spasms rarely present at less than 2 weeks or after 18 months of age.[10] Most population-based studies report either no sex difference[13,14] or a moderate male predominance.[9,12]

Clinical Manifestations of Infantile Spasms

Initial manifestations of spasms may initially be unrecognized and are typically characterized by subtle head drops with slight elevation and extension of the arms. Spasms then evolve to have variable features but generally consist of brief muscle contractions involving the neck, the trunk, and the extremities in a symmetric bilateral fashion and that typically occur in clusters on transition from waking to sleep and on arousal. Spasms have been categorized into three subtypes (flexor, extensor, and mixed flexor-extensor) based on postural manifestations and patterns of muscle involvement during the seizure.[16–18] Asymmetric spasms are typically seen in association with focal brain lesions.

Almost one half of patients with epileptic spasms have partial, myoclonic, tonic, and/or tonic-clonic seizures preceding or accompanying the onset of the spasms.[19–22] Spasms usually cease spontaneously by age 5 years and are often replaced by other seizure types but rarely persist into young adulthood. Mental retardation and cerebral palsy occur in about 75% and 50%, respectively, of children with infantile spasms.[13–15,20–23]

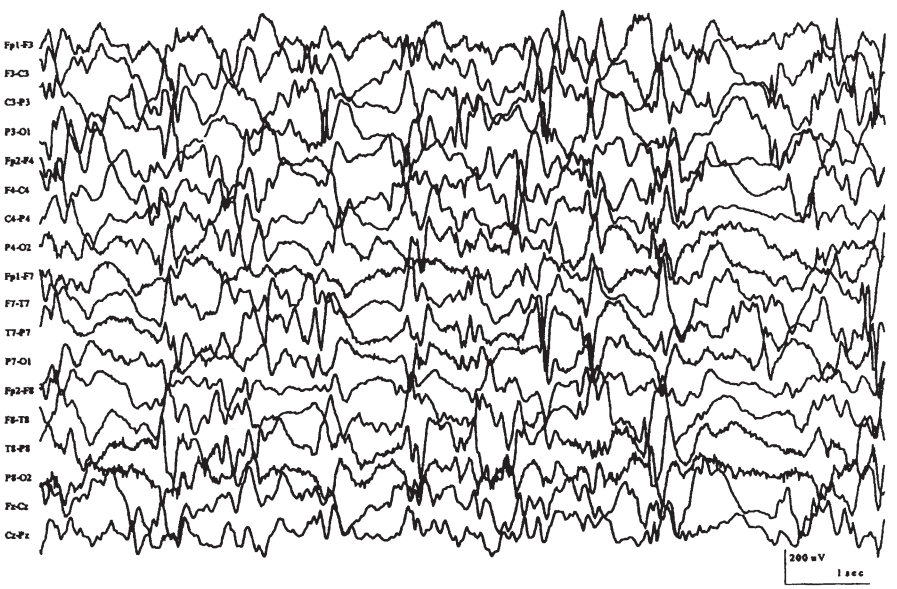


Figure 1. Hypsarrhythmia in a 4-month-old girl with cryptogenic infantile spasms. (Adapted with permission from Wong and Trevathan.[1])

Electroencephalographic Features of Infantile Spasms

The classic interictal EEG pattern of patients with epileptic spasms is hypsarrhythmia (Figure 1), a completely chaotic and disorganized background pattern consisting of high-amplitude, asynchronous, nonrhythmic slow waves and spikes.[24, 25] Because most studies of infantile spasms include hypsarrhythmia as a diagnostic criterion, there are few data on the proportion of patients with clinical spasms without hypsarrhythmia. Epileptic spasms have also been reported to occur in patients with other epilepsy syndromes that do not feature hypsarrhythmia.[26] Conversely, hypsarrhythmia is not specific for infantile spasms as it may also be seen in other disorders.[27]

Hypsarrhythmia usually develops during early infancy and disappears by early childhood. Through serial EEGs in the same patients, hypsarrhythmia has been shown to evolve from and to other abnormal EEG patterns, such as the slow spike-wave of Lennox-Gastaut syndrome.[28,29] Variations on the prototypical pattern of hypsarrhythmia[30,31] appear to impart limited additional prognostic information,[32] and the International League Against Epilepsy workshop on infantile spasms concluded that the term "modified hypsarrhythmia" should be discarded and atypical features simply specified when applicable.[7]

The ictal EEG correlates of epileptic spasms have been studied in detail using video-EEG monitoring[16–18] (Figure 2). Electrodecremental discharges represent the most common ictal feature, occurring in over 70% of recorded spasms, and may also occur without clinical manifestations.

Etiology and Pathophysiology of Infantile Spasms

In the early 1980s, most studies identified symptomatic etiologies in approximately 45 to 60% of cases.[15,19,21] More recent studies have consistently classified 70 to 80% of patients into the symptomatic group.[12,14,22] This trend can be attributed mostly to the improved sensitivity of diagnostic testing, especially neuroimaging studies.[33,34] Prenatal causes, accounting for almost 50% of symptomatic cases, include a variety of intrauterine insults and infections, malformations of cortical development, neurocutaneous syndromes, metabolic disorders, and other genetic or chromosomal defects.[15,19] The perinatal group consists primarily of hypoxic-ischemic encephalopathy, obstetric trauma, and other labor complications.[35] Postnatal etiologies include infection, trauma, hypoxic-ischemic insults, and tumors. History and physical examination alone identify the majority of symptomatic etiologies, and brain magnetic resonance imaging (MRI) increases the etiologic yield by 20%, but other testing, such as cerebrospinal fluid analysis and comprehensive metabolic studies, rarely reveals additional etiologies.[36]

Given the diverse etiologies of infantile spasms, a popular but unproven idea is that infantile spasms represent a nonspecific age-dependent reaction of the immature brain to injury. Many pathophysiologic models for infantile spasms have focused on subcortical structures, especially the brain stem, as the primary central mechanism for generating clinical spasms and hypsarrhythmia. In turn, abnormal brainstem function could influence the cerebral hemispheres diffusely through widespread cortical projections.[37–39]

The role of other subcortical structures in infantile spasms has also been considered. Given the dramatic effects of ACTH and glucocorticoids on spasms, the hypothalamus and the associated pituitary-adrenal axis have been implicated in the pathogenesis of infantile spasms, with a variety of stressors being hypothesized to result in excessive release of ACTH-releasing hormone, a known convulsant.[40] The involvement of the lenticular nucleus has also been suggested as hypermetabolism in that the nucleus was the most prominent and consistent finding in positron emission tomography (PET) studies of patients with infantile spasms.[41] Despite the abundance of hypotheses, no comprehensive or unifying mechanism for the pathophysiology of infantile spasms has been established.

Medical Treatment of Infantile Spasms

The subtle nature of epileptic spasms and the occasional occurrence of spontaneous remission make uncontrolled clinical reports of spasm frequency unreliable. In spite of the vast literature on infantile spasms therapy, few well-designed clinical trials have been reported.

ACTH was first reported in the 1950s to have dramatic, rapid effects on spasms.[42] Although ACTH and prednisone quickly became established as primary treatment for infantile spasms, studies detailing the therapeutic properties of these compounds have been fraught with uncertainty and controversy. No placebo-controlled trials of ACTH or corticosteroids have been performed, but in most open-label studies, ACTH or prednisone was associated with a reduction or complete cessation of spasms, as well as an improvement in the EEG, in approximately 50 to 75% of patients.[15,19,23,43–46] Whereas some studies report similar efficacy of ACTH and prednisone,[19,45] others indicate that ACTH is more effective.[46] Some patients who do not initially respond to ACTH may respond to prednisone and vice versa.[45] A large variety of doses of ACTH have been used, but there is no evidence that larger doses (150 U/m^2/day) are more effective than lower doses (20–30 U/day).[23,47] Longer treatment periods usually do not improve remission rates.[47] A second course of ACTH is often effective in about one third to one half of patients who relapse.[45]

A variety of findings are reported to predict responsiveness to ACTH or corticosteroids. A shorter time lag between diagnosis and treatment improves spasm remission rates in some studies[48] but not others.[45] Age at onset of the spasms has occasionally been correlated with treatment efficacy, with later onset (>8 months) having a better seizure control.[48] Whether the etiology of the infantile spasms impacts responsiveness to treatment is also controversial, as some studies report equal efficacy in symptomatic and cryptogenic groups,[45] but others find a better response in the cryptogenic group.[22,23,46] Whereas some studies report an association between initial responsiveness to ACTH and improved long-term intellectual development,[19,22,23,49] others

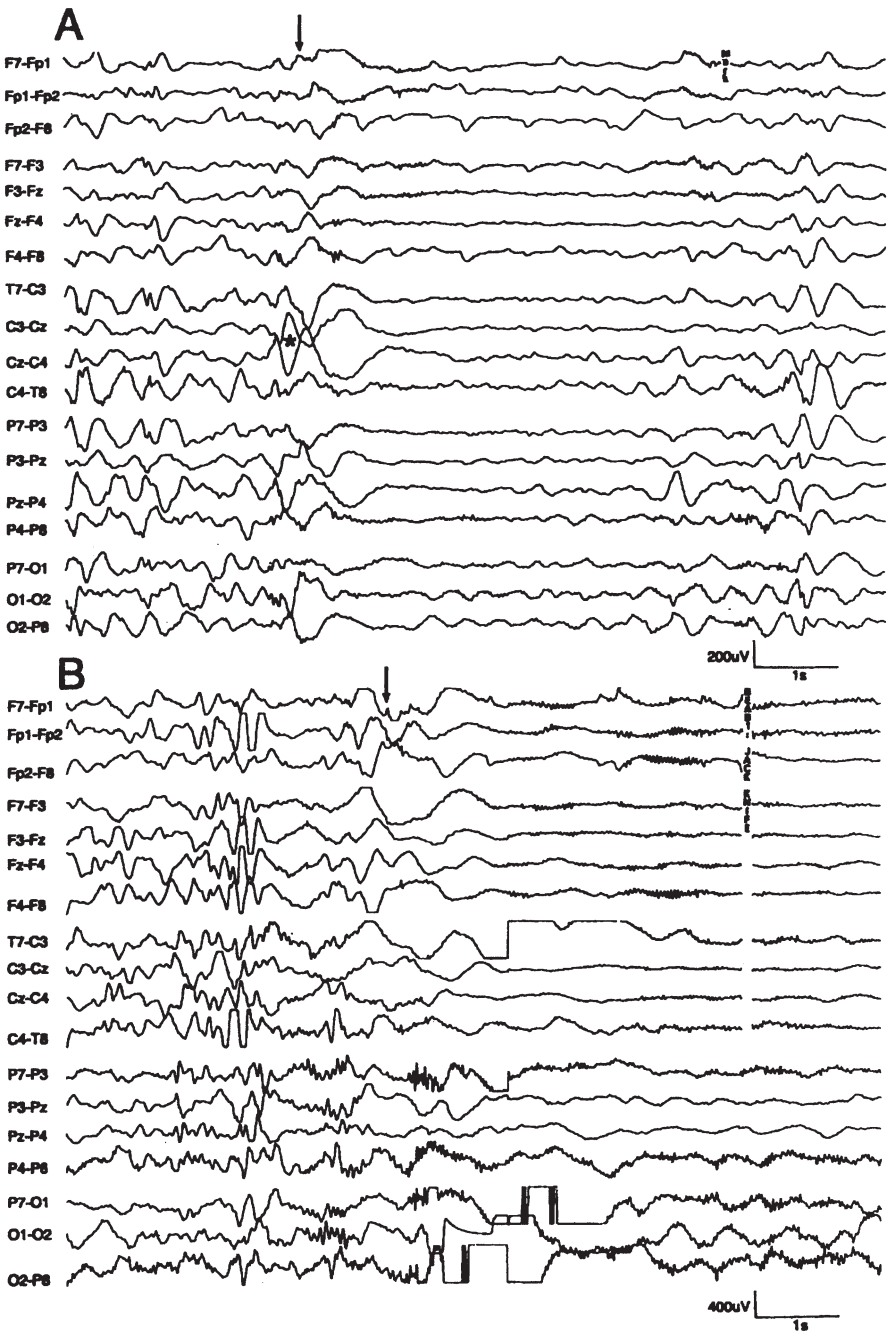


Figure 2. Ictal EEG patterns during epileptic spasms. *A,* Ictal EEG from a 10-month-old girl with infantile spasms and Down syndrome. *Arrow* denotes the onset of the clinical seizure that involved bilateral flexor spasms of the trunk and extremities. The electrographic seizure starts with a positive vertex wave, marked by the *asterisk,* followed by a generalized electrodecremental response. *B,* Ictal EEG from a 4-month-old girl with cryptogenic infantile spasms. *Arrow* denotes the onset of the clinical seizure that involved bilateral flexor spasms of the trunk and extremities. The electrographic seizure is characterized by a generalized electrodecremental response and fast beta activity, but no definite vertex positive wave is present. (Adapted with permission from Wong and Trevathan.[1])

found no significant difference in prognosis between initial responders and nonresponders to hormonal therapy.[15,21,50]

Hormonal therapy with ACTH or corticosteroids may have significant, potentially fatal, side effects.[51] Because of the serious morbidity of hormonal therapy, a number of other therapies have received attention for infantile spasms, including valproate, nitrazepam, pyridoxine, vigabatrin, felbamate, lamotrigine, topiramate, and zonisamide.[52–76]

The emergence of vigabatrin as a potential first-line therapy comparable to ACTH has been the most significant recent development in the treatment of infantile spasms. Vigabatrin has been repeatedly documented to be effective therapy for infantile spasms.[59–67] Studies directly comparing vigabatrin and ACTH have found either similar efficacy between the two drugs[61] or the superiority of ACTH.[62] Vigabatrin is superior to hydrocortisone among children with infantile spasms and tuberous sclerosis.[65,67] Vigabatrin may be especially effective for infantile spasms in patients with tuberous sclerosis, with some series reporting complete control occurring in about 95% of patients.[60,66,67] All studies report that vigabatrin is better tolerated, with fewer side effects than ACTH.[61,62]

ACTH is frequently used in the United States,[68] and vigabatrin has become a first-line therapy in many European countries.[69] Unfortunately, recent reports of visual field constriction associated with vigabatrin therapy may not

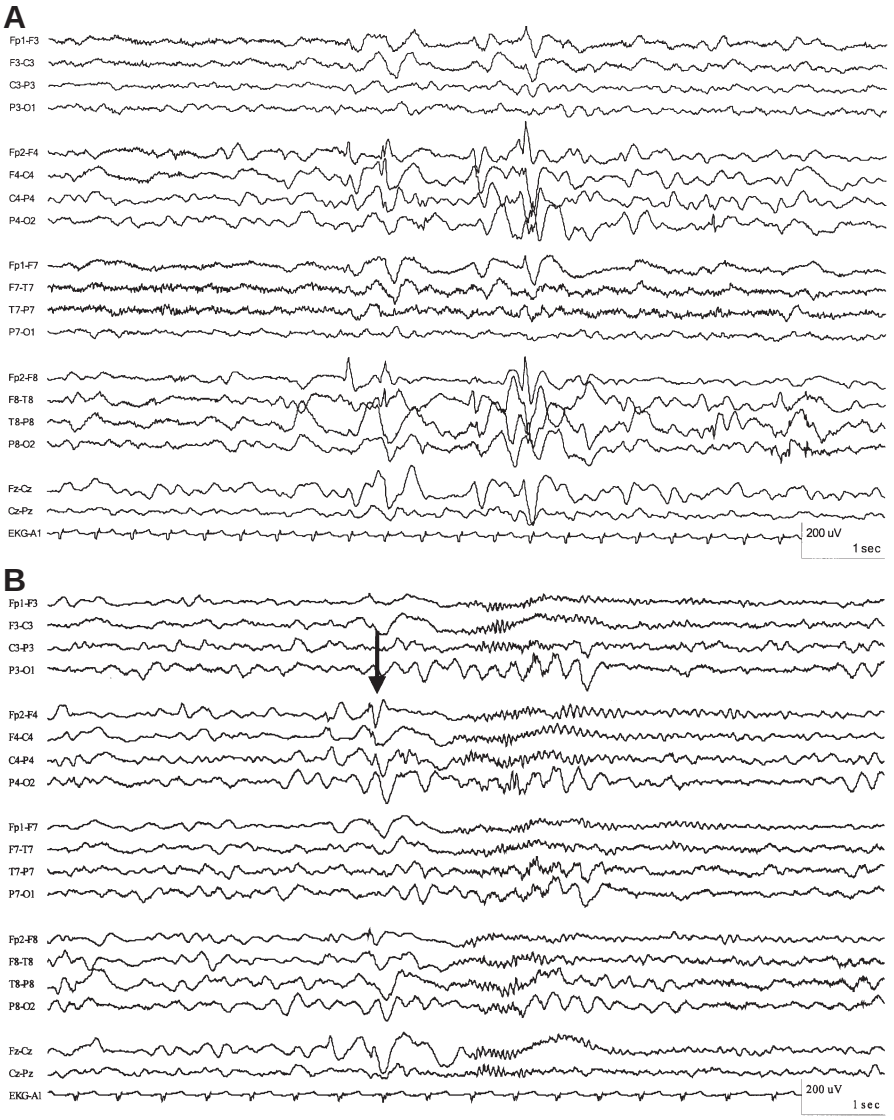


Figure 3. Surgical treatment of infantile spasms. This 10-month-old boy presented with a progressive left hemiparesis, left arm clonic seizures that progressed to left arm and leg hemispasms, and finally generalized spasms occurring multiple times per day and resistant to all antiepileptic drugs. The MRI showed very subtle findings consistent with delayed myelination within the right hemisphere. An interictal fluorodeoxyglucose PET scan demonstrated diffuse hypometabolism throughout the right hemisphere. Following a right hemispherotomy, the child became seizure free without significant change in baseline deficit. *A,* Interical spikes seen over the right hemisphere. Typical hypsarrhythmia was not seen. *B,* This child's typical ictal pattern with electrodecremental responses associated with either hemispasms of the left arm, trunk, and left leg or classic-appearing infantile spasms. Note the right frontoparietal sharp wave (↓) that was consistently time-locked just prior to the clinical spasm and the generalized electrodecremental response.

only prevent vigabatrin from becoming an approved treatment in the United States but may also limit its utility in other countries.[70,71] Ophthalmologic evaluation is recommended prior to starting vigabatrin and about every 3 months while on the drug. Only patients who have a clear response to vigabatrin should be considered for long-term vigabatrin treatment. Open-label studies have already provided preliminary evidence for the efficacy of felbamate, lamotrigine, topiramate, and zonisamide in infantile spasms.[72–76]

Only valproate, ACTH, prednisone, vigabatrin, and nitrazepam have been shown to be effective in controlled clinical trials of infantile spasms.[52–56,62,64–66] Pyridoxine has also been used successfully in some patients.[57,58] Nitrazepam and vigabatrin are not available in the United States. Few studies have directly compared mainstream antiepileptic drugs with hormonal therapy, making conclusions about relative efficacy difficult. Some experienced pediatric neurologists believe that rapid effective therapy, usually with corticosteroids, improves developmental outcome.[1,19] There are no published data that prove that treatment of spasms improves developmental outcome. The anecdotal reports of improved development with specific therapies may be confounded by spontaneous remission of spasms in some reports.

Surgical Treatment of Infantile Spasms

Surgical treatment of patients with infantile spasms has become more common as focal lesions associated with infantile spasms have been identified with newer imaging techniques. Cessation of spasms after surgical treatment of obvious cerebral lesions, such as brain tumors or cysts, has been reported,[77–79] and after localization of more subtle focal epileptogenic zones identified by video-EEG and PET (Figure 3).[80,81] Partial seizures prior to onset of clinical spasms, focal epileptiform abnormalities on EEG, suspected focal cortical dysplasia on MRI of the brain, evolution of a hemiparesis, and/or incomplete response of the spasms to routine therapy should prompt a referral to a major pediatric epilepsy center for a presurgical evaluation. Among children with infantile spasms without a resectable epileptogenic

zone, corpus callosotomy may reduce the frequency of spasms and other seizure types, such as drop attacks.[82]

Management Strategies for Infantile Spasms

Because of the risk of hormonal therapy and the almost certain poor developmental outcome in symptomatic infantile spasms, the author finds the risk-benefit ratio of corticosteroids as first-line therapy for symptomatic infantile spasms too high. The author reserves the initial use of ACTH for cryptogenic cases. Although the author would prefer more published clinical trials and more choices for therapy, open-label studies and the author's experience with drugs such as topiramate and zonisamide make these drugs reasonable initial options for children with symptomatic infantile spasms.

Recently, we have recommended that all children with cryptogenic infantile spasms receive a trial of pyridoxine. We typically use 20 mg/kg/day of pyridoxine given over a 2-week trial, although higher doses have been reported by other investigators.[57] Note that treatment of infantile spasms with pyridoxine is simply using pyridoxine as an antiepileptic drug; those children whose spasms appear to respond to pyridoxine are often weaned off the pyridoxine after a period of seizure freedom and do not have pyridoxine-dependent seizures. Children with pyridoxine-dependent seizures have a lifelong dependence on supplemental pyridoxine and typically do not present with infantile spasms.[83]

Prognosis of Infantile Spasms

Epileptic spasms remit spontaneously in the majority of patients with or without treatment by mid-childhood.[20,23,84] In spite of remission spasms in most, other seizure types arise in 50 to 70% of patients.[21,22] Chronic intractable epilepsy occurs in approximately 50% of patients with a history of infantile spasms.[15,21–23] Infantile spasms and Lennox-Gastaut syndrome share clinical and electrographic features, such as intractable seizures, strong association with mental retardation, and characteristic interictal EEG abnormalities.[13,24,85] Twenty to 50% of patients with infantile spasms evolve into Lennox-Gastaut syndrome,[13,14,19,85] and a similar percentage of patients with Lennox-Gastaut syndrome have a history of infantile spasms.[80,86]

Mental retardation occurs in 70 to 90% of patients with infantile spasms,[12,13,15,20–23] and most of those with infantile spasms and mental retardation have severe to profound retardation.[13] Other neurologic deficits, such as cerebral palsy, may be seen in about 30 to 50% of patients.[13,22,23] Etiology is the most important factor in predicting neurologic prognosis, including developmental outcome and long-term epilepsy. Thirty to 50% of children with cryptogenic infantile spasms have mental retardation, whereas 80 to 95% of children with a symptomatic etiology have mental retardation.[12,14,22,23] Although cases of symptomatic infantile spasms generally have a poor prognosis, neurofibromatosis and Down syndrome are notable exceptions, both with a relatively benign course associated with infantile spasms.[87,88] Other factors that have been associated with a good prognosis include a normal neurologic examination and development at onset, absence of other seizure types at onset, older age of onset, short duration of spasms, and early effective treatment of spasms (reported with ACTH).

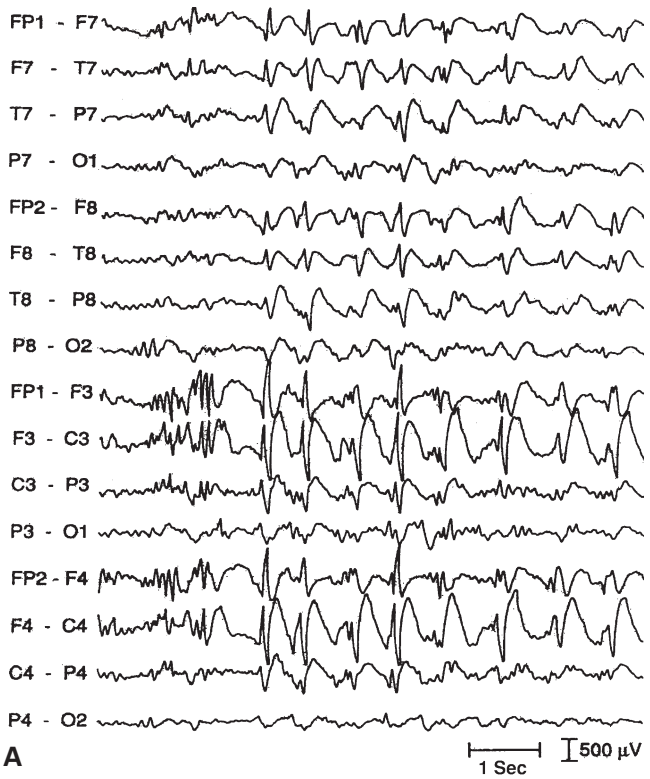
The case fatality rate associated with infantile spasms is 5 to 30% and varies with the factors mentioned above that also impact morbidity.[13,49,50] Although the higher mortality figures understandably come from a study that followed patients into adulthood,[49] about one third of the deceased patients from that study died before age 3 years, and more than 50% died before age 10 years. The most common cause of death was infection, followed by complications related to the underlying disease process.[49]

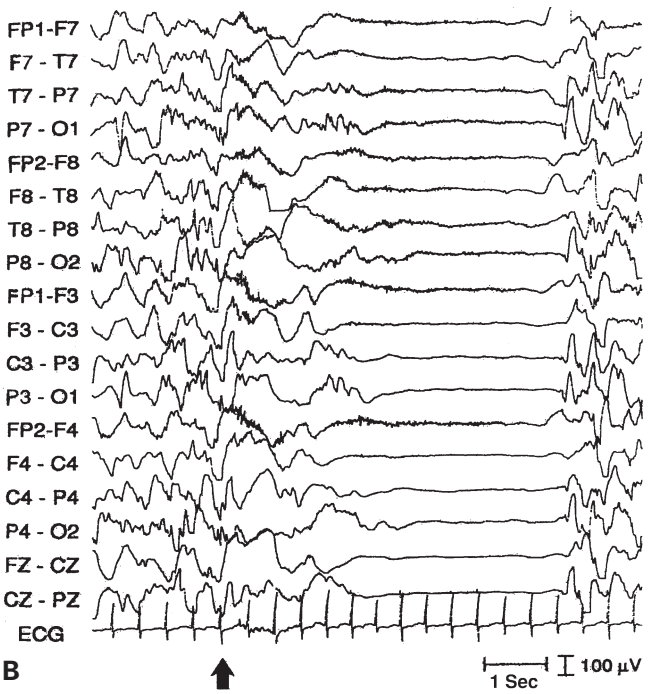
LENNOX-GASTAUT SYNDROME

In the early 1930s William Lennox described the clinical features of "epileptic encephalopathy," an entity that included those with multiple seizure types and mental deficiency. In the late 1930s, Lennox and Gibbs described "slow spike and wave," which was thought to be a variant of the spike and wave they had previously described in petit mal epilepsy.[89] Lennox in 1945[90] and Lennox and Davis in 1950[91] published the symptomatic triad of (1) slow spike and wave on EEG, (2) "mental deficiency," and (3) three seizure types (that we now refer to as atypical absence seizures, myoclonic seizures, and head drop attacks evolving to axial spasms and falls). In 1966, Gastaut expanded on the original observations of Lennox and Davis.[92] Gastaut's contribution, largely derived from the thesis of Charlotte Dravet, incorporated more clinical details, verified the EEG findings reported by Lennox, and documented the poor cognitive outcome.[92] Based on the contributions of Lennox and others at Boston Children's Hospital and Gastaut, Dravet, and colleagues of the Marseilles school, the term "Lennox-Gastaut syndrome" was adopted.[93]

Clinical investigators have refined the diagnostic criteria of Lennox-Gastaut syndrome over the last 30 years, but the essential elements of the syndrome have remained unchanged since Lennox and Davis's publication in 1950.[85,93–103] The syndrome is currently defined by several criteria: (1) multiple seizure types including atypical absence and seizures resulting in falls (axial tonic, massive myoclonic, and atonic seizures); (2) EEG demonstrating slow spike and wave (< 2.5 Hz) and bursts of fast rhythms at 10 to 12 Hz during sleep; and (3) static encephalopathy and learning disabilities, most often associated with profound mental retardation (Figure 4). Other seizure types usually are present, including generalized tonic-clonic and partial seizures.[104]

Distinguishing Lennox-Gastaut syndrome from other epilepsy syndromes may be particularly challenging; comparing the diagnostic criteria used for Lennox-Gastaut syndrome between different clinical series and clinical trials is somewhat frustrating, as it is often unclear as to whether consistent application of the terms is used between authors. Some authors have considered that there is a continuum between the more severe generalized epileptic encephalopathies with multiple





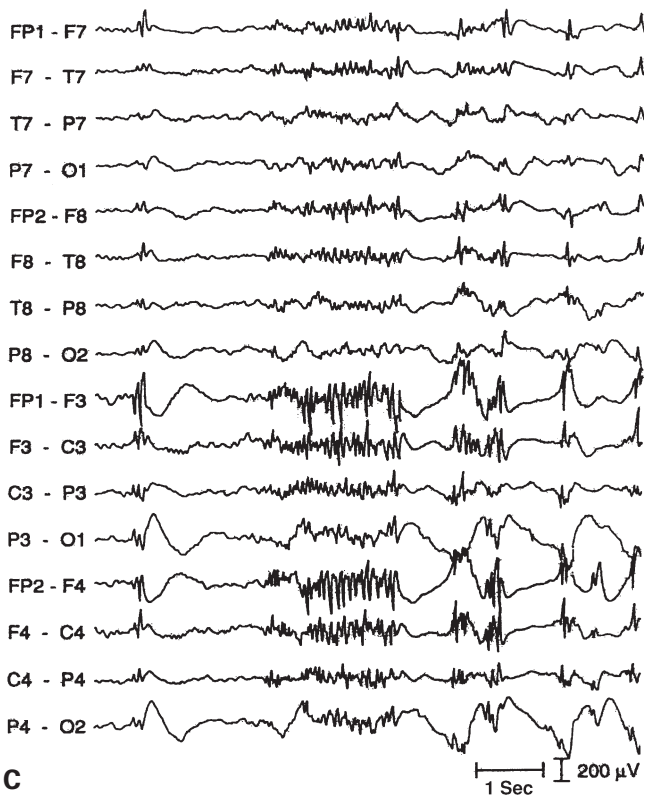


Figure 4. Electroencephalographic patterns associated with Lennox-Gastaut syndrome. *A,* Slow spike-wave. *B,* An electrodecremental response. *C,* Fast recruitment rhythms.

seizure types (eg, Lennox-Gastaut syndrome) and cases of myoclonic astatic epilepsy that typically enjoy a much better prognosis. Other authors have considered Lennox-Gastaut syndrome to be a symptomatic epilepsy and myoclonic astatic epilepsy to be genetically determined.[105]

Epidemiology and Prognosis of Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome represents about 5% of childhood epilepsy, with a prevalence of about 2.6 per 10,000 children at 10 years of age.[86] The presence of slow spike-wave on EEG among children with multiple seizure types

predicts the coexistence of profound mental retardation. Children with Lennox-Gastaut syndrome are also more likely to have cerebral palsy than children with multiple seizure types but without slow spike-wave on EEG and multiple seizure types.[86] Oguni and colleagues documented the progressive decline in IQ and progressive gait disturbances with age that were associated with worsening of the epileptic encephalopathy of Lennox-Gastaut syndrome.[106] In an analysis of 101 patients with Lennox-Gastaut syndrome, Hoffmann-Riem and colleagues reported that nonconvulsive status epilepticus significantly increased the odds of severe mental retardation.[107] The risk of serious injuries from falls associated with seizures is high. Up to 10% of children with Lennox-Gastaut syndrome die prior to age 11 years.[108–110]

Medical Therapy for Lennox-Gastaut Syndrome

Before the introduction of valproic acid in the 1970s, a variety of antiepileptic drugs were used in the treatment of seizures associated with Lennox-Gastaut syndrome. Phenytoin is probably helpful for the axial spasms but may exacerbate the frequency of absence seizures. Barbiturates have some apparent efficacy but are associated with sedation and anecdotal reports of exacerbation of seizures in some patients. Likewise, benzodiazepines have long been used to treat seizures associated with Lennox-Gastaut syndrome, especially clusters of seizures that often accompany even the most minor febrile illness or minor physical stress. Rare anecdotes suggesting an increased risk for development of tonic status epilepticus among children with Lennox-Gastaut syndrome have limited the use of benzodiazepines by some epileptologists.[111] Clobazam[112] and nitrazepam,[113] each available in Canada and Europe but not marketed in the United States, have reduced the frequency of seizures among children with Lennox-Gastaut syndrome in an open-label study. Some authors have reported that clobazam is better tolerated than other benzodiazepines such as clonazepam or nitrazepam, but comparative studies have not been published.

Succinimides, especially methsuximide (Celontin), may have an adjunctive role in the treatment of atypical absence, tonic, and myoclonic seizures associated with Lennox-Gastaut syndrome.[114] Ethosuximide may reduce the frequency of atypical absence seizures in some patients. Trimethadione (Tridione) is a rarely used drug with considerable efficacy in absence seizures and possible efficacy in the myoclonic and atonic seizures of Lennox-Gastaut syndrome.[90] There have been no controlled trials of methsuximide or of trimethadione in Lennox-Gastaut syndrome. Unfortunately, trimethadione is only available now via a compassionate-use protocol. Bromides have not been shown to be effective in Lennox-Gastaut syndrome,[115,116] yet on a few occasions, the author has found bromides to be apparently effective in open-label treatment of refractory clonic seizures associated with Lennox-Gastaut syndrome.

Acetazolamide (Diamox) is typically well tolerated and has been shown to have efficacy against multiple types of seizures.[117–119] The role of acetazolamide among patients with Lennox-Gastaut syndrome may deserve further study, especially since another carbonic anhydrase inhibitor (topiramate) has recently been proven to reduce atonic seizures in children with Lennox-Gastaut syndrome.[120]

ACTH has been reported to benefit patients with Lennox-Gastaut syndrome,[121] but side effects and a lack of objective data regarding benefit have limited interest in ACTH. Roger and colleagues have suggested that if corticosteroids are given early in the course of Lennox-Gastaut syndrome, long-term benefit may be achieved,[122] but controlled data are not available.

Valproic acid was approved for use in the 1970s. Although randomized clinical trials have never been conducted to prove the efficacy of valproate in Lennox-Gastaut syndrome, most epileptologists have viewed valproate as a first-line drug for Lennox-Gastaut syndrome since the early 1980s because of (1) valproate's efficacy against partial seizures and generalized seizures (including absence), (2) a lack of exacerbation of any of the seizure types associated with Lennox-Gastaut syndrome, and (3) a relative lack of sedative side effects compared to barbiturates. The major risks of valproate are increased risk of neural tube defects in the offspring of mothers taking valproate during the first trimester of pregnancy, idiosyncratic hepatic failure, and pancreatitis.[123] All females of child-bearing age with Lennox-Gastaut syndrome should receive adequate birth control and folate supplementation.[124]

In the early 1980s, anecdotal reports of the possible efficacy of cinromide in the treatment of Lennox-Gastaut syndrome[125] led to the first major multicenter clinical trial of treatment for Lennox-Gastaut syndrome.[126] Seventy-three patients entered the double-blind, placebo-controlled trial that was terminated prematurely because of no efficacy. The cinromide study was important for two reasons. First, the cinromide study documented the "enormous commitment by investigators and their staff, by consultants, by the sponsor, and most notably by the patients' parents" in terms of time, documentation, and patient recruitment and retention in controlled trials of this complex patient population.[126] Defining and recruiting a homogeneous population of patients with Lennox-Gastaut syndrome was difficult, requiring multiple centers. Identifying and quantifying seizure activity in Lennox-Gastaut syndrome is very difficult; many of these patients have seizures that are difficult to classify, and their frequent seizures (especially myoclonic and atypical absence) are often difficult to quantify. Second, the cinromide study demonstrated an unexpectedly large placebo response,[126] much like all subsequent clinical trials of Lennox-Gastaut syndrome,[120,127–130] emphasizing the importance of viewing open-label studies with a degree of skepticism and making clinical decisions when possible based on the results of well-designed controlled clinical trials.

The efficacy of felbamate among children and adults with Lennox-Gastaut syndrome was documented in a double-blind, placebo-controlled trial.[128] Seizure frequency was

assessed by guardian report and by serial 4-hour video-EEG monitoring sessions during the course of the study. Felbamate significantly reduced the number of atonic seizures compared to placebo in both the treatment and the maintenance phases of the study, and there was a significant reduction of all seizure types among felbamate-treated patients. A dose-response relationship was demonstrated for reduction of atonic seizures, with a linear reduction in the number of atonic seizures per day with increasing plasma felbamate levels; 5 patients had no atonic seizures during the maintenance phase. In an open-label follow-up felbamate study, patients who converted from placebo to felbamate had the same degree of improvement on felbamate as those who received felbamate during the trial.[129] At the end of the double-blind trial, only 2 of the 22 subjects randomized to placebo had experienced a > 50% reduction in atonic seizure. However, during the first month that these patients from the placebo group were treated with felbamate, 12 of the 22 subjects (55%) had a > 50% reduction in atonic seizures.

In a study of the efficacy of felbamate as add-on therapy to valproate in Lennox-Gastaut syndrome, valproate was found to significantly reduce the frequency of drop attacks after controlling for the effect of felbamate. The authors concluded that the therapeutic effect of felbamate on drop attacks is attributable in part to increased valproate levels but that a synergistic effect of the two drugs likely resulted in a reduction in overall seizure frequency.[130]

No pattern of serious adverse events caused by felbamate was apparent at the time of US Food and Drug Administration approval in 1993. By the summer of 1994, 120,000 patients had been exposed to felbamate, and reports of both aplastic anemia and hepatic failure had been reported to Wallace Laboratories and the Food and Drug Administration. After letters had been sent to over 200,000 physicians in the United States informing them of these new risks, most patients were withdrawn from felbamate. Recent analyses have led to better estimates of the risk of felbamate. Kaufman et al reviewed all case reports of aplastic anemia among patients treated with felbamate. The incidence of aplastic anemia among those treated with felbamate was estimated to have a lower limit of 1 per 37,037 patients and an upper limit of 1 per 4784 patients, with a "most probable" incidence of 1 per 7874 patients treated.[131] Pellock and Brodie estimated the incidence of hepatotoxicity to be about 1 per 26,000 to 34,000 patients treated with felbamate[132]—similar to the recently reported risk of hepatotoxicity for valproate.[133] At the time of this writing, no children under the age of 13 years have been reported to have felbamate-related aplastic anemia. Female sex, history of immune disorders (eg, systemic lupus erythematosus), a history of prior blood dyscrasias, and allergic reactions to medications are probably associated with increased risk for felbamate-associated aplastic anemia. These factors may prove helpful in selecting patients for felbamate therapy.

The apparent efficacy of lamotrigine in open-label studies[134,135] led to clinical trials among children with Lennox-Gastaut syndrome. A large double-blind, placebo-controlled trial of lamotrigine and Lennox-Gastaut syndrome with collaborators from 40 different epilepsy centers in the United States and Europe documented lamotrigine's efficacy in Lennox-Gastaut syndrome.[127] Following a single-blind baseline study in which all patients received placebo, 169 patients (ages 3–25 years) were randomized to placebo or lamotrigine added to their baseline antiepileptic drugs for 16 weeks. Thirty-three percent of the lamotrigine group and 16% of the placebo group experienced a > 50% reduction in the frequency of all major seizures (generalized tonic-clonic, tonic, atonic, and major myoclonic seizures). Thirty-seven percent of those treated with lamotrigine and 22% of those who received placebo had a > 50% reduction in the frequency of drop attacks (atonic, tonic, and/or major myoclonic seizures that resulted in falls). Forty-three percent of lamotrigine-treated patients and 20% of placebo-treated patients had a 50% or greater reduction in the frequency of generalized tonic-clonic seizures. The only clinically significant adverse event was serious rash in two patients, both of whom were not only receiving valproate but also had lamotrigine dose-escalation rates that were faster than current recommendations. Global evaluations of patient's functioning in terms of speech, language, and attention were significantly improved in the lamotrigine group.[136]

Eriksson and colleagues published a randomized, double-blind, crossover study of lamotrigine as add-on therapy in 30 children with severe generalized epilepsy, 20 of whom had Lennox-Gastaut syndrome.[137] Lamotrigine was more effective than placebo during the double-blind crossover phase in reducing the frequency of tonic, tonic-clonic, and atonic seizures ($P < .0001$). Thirteen of the 20 children with Lennox-Gastaut syndrome improved in the open phase of the study and entered the double-blind phase; 7 of the 20 children (35%) responded to lamotrigine treatment with a > 50% seizure frequency reduction. Two children with Lennox-Gastaut syndrome became seizure free on lamotrigine. No apparent relationship between lamotrigine blood level and response was noted; none of the children improved on placebo, and none developed a rash.

Lamotrigine's efficacy against typical absence seizures has been documented in a placebo-controlled trial,[138] but no randomized clinical trials of any drug have been reported for atypical absence seizures. Video-EEG monitoring is required to quantify atypical absence seizures in children with Lennox-Gastaut syndrome.[139]

The efficacy of topiramate has been reported for tonic-clonic seizures, tonic seizures, and drop attacks associated with Lennox-Gastaut syndrome.[121] In the Lennox-Gastaut syndrome study, topiramate was associated with only a 14% reduction in the frequency of drop attacks compared with baseline, but this reduction was significantly better statistically than the placebo group.[120] This reduction in drop attacks was maintained in an open-label follow-up study after completion of the placebo-controlled trial.[140] As with the felbamate and lamotrigine trials, the topiramate trial was not designed to appropriately determine whether topiramate is

effective in atypical absence seizures. However, unlike lamotrigine, there are no published data that document the efficacy of topiramate in simple absence or atypical absence seizures.

Topiramate has been associated with impairment of cognitive processing, especially language processing.[141,142] Just as a slow dose titration is required with lamotrigine to reduce the risk of rash, a slow dose-titration schedule is also required with topiramate to avoid problems with cognition, especially expressive language processing. Recent reports of glaucoma associated with topiramate use[143] are of uncertain significance, but eye pain or eye erythema among patients on topiramate warrants immediate referral to an ophthalmologist for evaluation.

Comparative trials of topiramate, lamotrigine, and felbamate have not been published. Currently available safety data suggest that topiramate may have safety that is comparable to or better than lamotrigine, with the primary risks of topiramate being problems with language processing and a risk of renal stones. However, there is still significantly less postmarketing surveillance experience with topiramate than with lamotrigine. Therefore, the recent reports of glaucoma and liver failure associated with topiramate will require further investigation.[143,144] Preliminary reports and the author's experience suggest that topiramate may be useful in combination with lamotrigine.[145]

Zonisamide, approved for treatment of partial seizures in adults in the United States, has been shown to have efficacy among children with multiple seizure types and myoclonic seizures. Although controlled trials of zonisamide among children with Lennox-Gastaut syndrome have not been reported, zonisamide is likely helpful and has been considered by most epileptologists as a treatment option for patients with Lennox-Gastaut syndrome.[146]

Ketogenic Diet

The ketogenic diet has been used in children with refractory seizures of multiple types since the late 1920s.[147] Over the last decade, there has been a resurgence of interest in the ketogenic diet as more open-label data have become available on the "classic diet" that appears to offer better results with fewer side effects than the medium-chain triglycerides oil diet introduced in the 1970s.[148,149] Recently, a multicenter open-label study of the ketogenic diet has reproduced the good results previously reported by the Johns Hopkins Hospital group.[150] Fifty-one children (ages 1–8 years) with multiple seizure types and generalized epileptiform abnormalities on EEG who had failed to respond to at least two antiepileptic drugs were placed on the classic ketogenic diet. Fifty-four percent of children on the diet at 3 months had a greater than 50% decrease in seizure frequency.[151] If the placebo-controlled trial of the ketogenic diet (in progress at Johns Hopkins Hospital) confirms efficacy demonstrated in the open-label studies, the place of the diet in the armamentarium of the child neurologist may depend on the frequency of adverse events.[151,152]

Vagus Nerve Stimulation and Corpus Callosotomy

Vagus nerve stimulation has been approved for treatment of intractable partial seizures in the United States.[153] Reduction in seizure frequency among children with Lennox-Gastaut syndrome treated with vagus nerve stimulation in open-label, nonrandomized studies has recently been reported.[154] As expected, sedative side effects are less severe with vagus nerve stimulation than with antiepileptic drugs in children, but other significant adverse events have been reported.[155]

Patients with intractable atonic or tonic seizures that result in falls may benefit from a corpus callosotomy. Various epilepsy centers have used slightly different approaches to selecting patients for this procedure. However, as long as seizures resulting in severe falls with associated injuries are targeted, a significant number of patients can achieve palliative improvement and a reduction in drop attacks.[156] Some authors have suggested that vagus nerve stimulation should be performed prior to corpus callosotomy,[123] primarily because the perceived morbidity risk is less with vagus nerve stimulation. However, our experience has been that patients who are properly selected for corpus callosotomy tend to have a more dramatic reduction in drop attacks than those with Lennox-Gastaut syndrome who are implanted with a vagus nerve stimulator. Therefore, the decision of whether to place a vagus nerve stimulator or perform a corpus callosotomy in a child or young adult with Lennox-Gastaut syndrome should consider the following issues: (1) whether the seizures that result in falls are clearly primarily generalized (by careful video-EEG monitoring), in which case the corpus callosotomy may be more effective in reducing or eliminating the drop attacks; (2) the general medical condition and size of the child, which influence anesthesia and operative risks; and (3) other factors that influence the perceived benefit of each procedure. Decisions regarding whether to perform a corpus callosotomy or place a vagus nerve stimulator first will be made based on subjective data until and unless a comparative trial is performed.

Management Strategies for Lennox-Gastaut Syndrome

In the absence of head-on comparative studies, the choice of initial therapy is debatable. The author's approach is to use as primary antiepileptic drugs those that have been shown effective against multiple seizure types and/or Lennox-Gastaut syndrome in clinical trials (lamotrigine, topiramate, and felbamate) as well as valproate, with the hope of limiting the number of primary drugs to no more than two to three. Whether topiramate, lamotrigine, or valproate is used first or second depends on individual patient characteristics and risk-benefit ratios. The author usually does not use felbamate unless these initial drugs fail but tends to use felbamate prior to considering surgical procedures such as vagus nerve stimulation or corpus callosotomy. (The estimated risk of general anesthesia with a surgical procedure is probably greater than the risk

of felbamate in most children.) We do not use the vagus nerve stimulator or recommend corpus callosum section unless children have failed therapy with the major antiepileptic drugs and usually have also failed the ketogenic diet treatment.

We tend to use the ketogenic diet early in the treatment of the seizures associated with Lennox-Gastaut syndrome. Yet we carefully select patients for the ketogenic diet based on our impression of whether they and their families are able to comply with the rigors of the ketogenic diet. We are convinced that the use of a well-organized ketogenic diet treatment team that includes an experienced pediatric dietitian, combined with intensive parent education, improves ketogenic diet outcomes. We discourage the casual use of the ketogenic diet without the personal involvement of a pediatric dietitian with experience in ketogenic diet management.

Children with Lennox-Gastaut syndrome almost always have exacerbation of seizure frequency when they have viral illnesses or experience some other type of physical stress. The author uses short-term benzodiazepines to bridge these periods of seizure frequency and duration exacerbation rather than add another primary drug. Clinicians with access to clobazam should consider the use of this drug, given the impression of several experienced clinicians that clobazam may produce fewer adverse events than other benzodiazepines. The use of benzodiazepines only on a short-term basis, and minimizing the use of barbiturates, may enhance the effect of benzodiazepines used for the treatment of prolonged seizures or clusters of seizures to prevent status epilepticus, a common complication of Lennox-Gastaut syndrome and a possible contributor to cognitive decline.[107]

Children with Lennox-Gastaut syndrome often have coexisting behavioral problems and depression. Although there are limited published data on the impact of our therapies on behavior among children with Lennox-Gastaut syndrome, clinicians should carefully listen to caregivers who report potential behavioral side effects of therapy. In the author's experience, the emotional impact of drop attacks among even the most profoundly mentally retarded children with Lennox-Gastaut syndrome can be significant and only truly apparent in retrospect after improved seizure control with the return of more confident ambulation.

The therapeutic options for treatment of Lennox-Gastaut syndrome and infantile spasms have expanded during the last decade. Yet we need more options for the treatment of these devastating childhood epilepsy syndromes. There have been too few controlled clinical trials of newer antiepileptic drugs among children with infantile spasms. Antiepileptic drug development directed specifically at these generalized childhood epilepsy syndromes is needed.[157,158]

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