

# Infantile Spasms

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**Infantile spasms constitute both a distinctive seizure type and an age-specific epilepsy syndrome that have been extensively described for over a century. Standardization of the classification of infantile spasms has evolved, culminating in recent recommendations for separately recognizing and distinguishing the seizure type (spasms or epileptic spasms) and the epilepsy syndrome of infantile spasms (West syndrome). More-detailed descriptions of the clinical and electrographic features of epileptic spasms and hypsarrhythmia have emerged. Advances in neuroimaging techniques have revealed clues about pathophysiology and increased the etiologic yield of the diagnostic evaluation of patients with infantile spasms. Adrenocorticotrophic hormone remains the treatment of choice for many neurologists. Recent controlled studies support vigabatrin as first-line therapy, and open-label studies suggest that topiramate, lamotrigine, and zonisamide may be useful in treating spasms. Recent reports of visual-field constriction with vigabatrin may limit its use. Surgical treatment has been used successfully in a select subgroup of patients with secondarily generalized spasms from a single epileptogenic zone. Although the prognosis for most patients with infantile spasms remains poor, further studies identifying predictors of favorable prognosis and recent advances in understanding the pathophysiology of infantile spasms offer hope of safer and more-effective therapies that improve long-term outcome. © 2001 by Elsevier Science Inc. All rights reserved.**

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## Introduction

In 1841, West described infantile spasms as a unique seizure type with associated devastating developmental

consequences in his own son [1]. Uncertainty remains regarding many aspects of infantile spasms, including basic definitions and classification, seizure phenomenology, etiology, and pathophysiology, and the impact of treatment on eventual developmental outcome. Within the past decade, some of these controversial issues have been clarified, but many questions remain. This article reviews the major features of infantile spasms, focusing on how recent developments have improved our understanding and approach to this challenging condition.

## Terminology and Classification

The term *infantile spasms* has been used to refer to either a seizure type or an epilepsy syndrome, causing confusion among clinicians and in the medical literature. 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, seizures indistinguishable from infantile spasms may occur in other noninfantile epileptic syndromes. Partial seizures with secondary spasmlike manifestations that require electroencephalogram (EEG) video monitoring for proper classification also may occur [2]. In addition, gastroesophageal reflux, movement abnormalities in spastic infants, and other nonepileptic disorders may mimic infantile spasms and require EEG video monitoring for proper diagnosis [3].

Individual spasms typically are characterized by symmetric, salaamlike contractions of the trunk, with extension and elevation of the arms, and tonic extension of the legs. An individual spasm typically lasts for less than 1 second to up to 5 seconds, and with clusters of 3-20 spasms typically occurring several times per day in untreated patients (see next section). Although often confused with myoclonic or tonic seizures, clinical spasms represent a distinct seizure type.

When defined as an epileptic syndrome, infantile

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spasms are often referred to as *West syndrome*. West syndrome classically consists of the clinical-electroencephalographic triad of spasms (the seizure type), hypsarrhythmia, 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 would still be considered to have an age-specific epileptic encephalopathy or epileptic syndrome with infantile spasms but would not be labeled with West syndrome.

The confusing terminology of infantile spasms is reflected in the evolving scheme of classification of epilepsy syndromes proposed by the International League Against Epilepsy (ILAE). In 1970 the ILAE considered infantile spasms to be generalized seizures in its first proposed classification of seizures [4] but then dropped spasms altogether from the revised classification of epileptic seizures of 1981 [5]. The 1989 ILAE classification scheme for epileptic syndromes defined West syndrome as an age-related generalized epilepsy [6]. Recognizing the ambiguities in defining infantile spasms, the ILAE held a special workshop devoted entirely to infantile spasms in 1991 [7]. On the basis of this workshop, it was concluded that infantile spasms should be reintroduced as a specific seizure type in addition to the syndrome classification. To clearly distinguish between these two meanings, it has been proposed that spasms or epileptic spasms should be used to refer specifically to the seizure type, which primarily but not exclusively occurs in infancy and that infantile spasms and West syndrome should represent age-related epilepsy syndromes [8]. Furthermore, although West syndrome and infantile spasms may be used interchangeably, the term *West syndrome* should be reserved for patients with documented hypsarrhythmia in combination with epileptic spasms, whereas infantile spasms constitutes a more general term for age-related epilepsy syndromes that involve epileptic spasms. We support these guidelines for terminology and will use these conventions in the remainder of this article.

The etiologic classification of infantile spasms may also be confusing. The etiology of infantile spasms has been divided into symptomatic, cryptogenic, and idiopathic. In most earlier studies the symptomatic group included patients with known etiologies, as well as with developmental delay at onset without an identified etiology, leaving the cryptogenic patients group to include those patients with normal development and no known etiology. Some earlier studies also used a designation of “doubtful” for the subgroup of symptomatic patients with developmental delay but 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 typically are attributed to a known or presumed genetic predisposi-

tion with generally favorable prognoses [6]. Using these assumptions, the ILAE revised classification of epileptic syndromes only recognized infantile spasms as being a symptomatic or cryptogenic epilepsy. The previous “doubtful” group would most appropriately be included in the cryptogenic group under the revised classification. Finally, the 1991 ILAE workshop on infantile spasms recommended the creation of an idiopathic group consisting of patients with normal development at onset, normal examination and neuroimaging, and hypsarrhythmia on EEG without focal epileptiform abnormalities [7].

## Epidemiology

Incidence rates of infantile spasms are remarkably similar among different studies from various regions of the world, ranging from approximately two to five per 10,000 live births [9-14]. The lifetime prevalence of infantile spasms at age 10 years has been estimated at 1.5 to 2 per 10,000 children [10,13]. The consistently lower prevalence rates of infantile spasms among children compared with incidence can most likely be attributed to the relatively 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 the peak onset occurring between 4 and 6 months of age [10]. Although the age of onset of West syndrome has been reported to range from 1 day to more than 6 years [15], infantile spasms rarely presents at less than 2 weeks or after 18 months of age [10]. Several case series of infantile spasms report a strong male predominance, but most population-based studies report either no sex difference [13,14] or a moderate male predominance [9,12].

## Clinical Manifestations

Spasms may have variable features but generally consist of brief muscle contractions involving the neck, the trunk, and the extremities in a symmetric bilateral fashion [16]. Using EEG video analysis, spasms have been categorized into three subtypes (flexor, extensor, and mixed flexor-extensor) on the basis of postural manifestations and patterns of muscle involvement during the seizure [16-18]. Flexor spasms typically involve flexion of the neck, trunk, and extremities, resulting in jack-knifing at the waist and a self-hugging motion from adduction of the arms. Extensor spasms consist of extension of the neck, trunk, and extremities. Mixed flexor-extensor spasms involve combinations of neck, trunk, arm flexion and leg extension, or leg flexion and arm extension.

Asymmetric spasms are seen almost exclusively in patients symptomatic from focal brain lesions. Isolated contraction of neck or abdominal muscles may result in subtle head nods or slight trunk movements only. Arrest phenomena with akinesia and decreased responsiveness

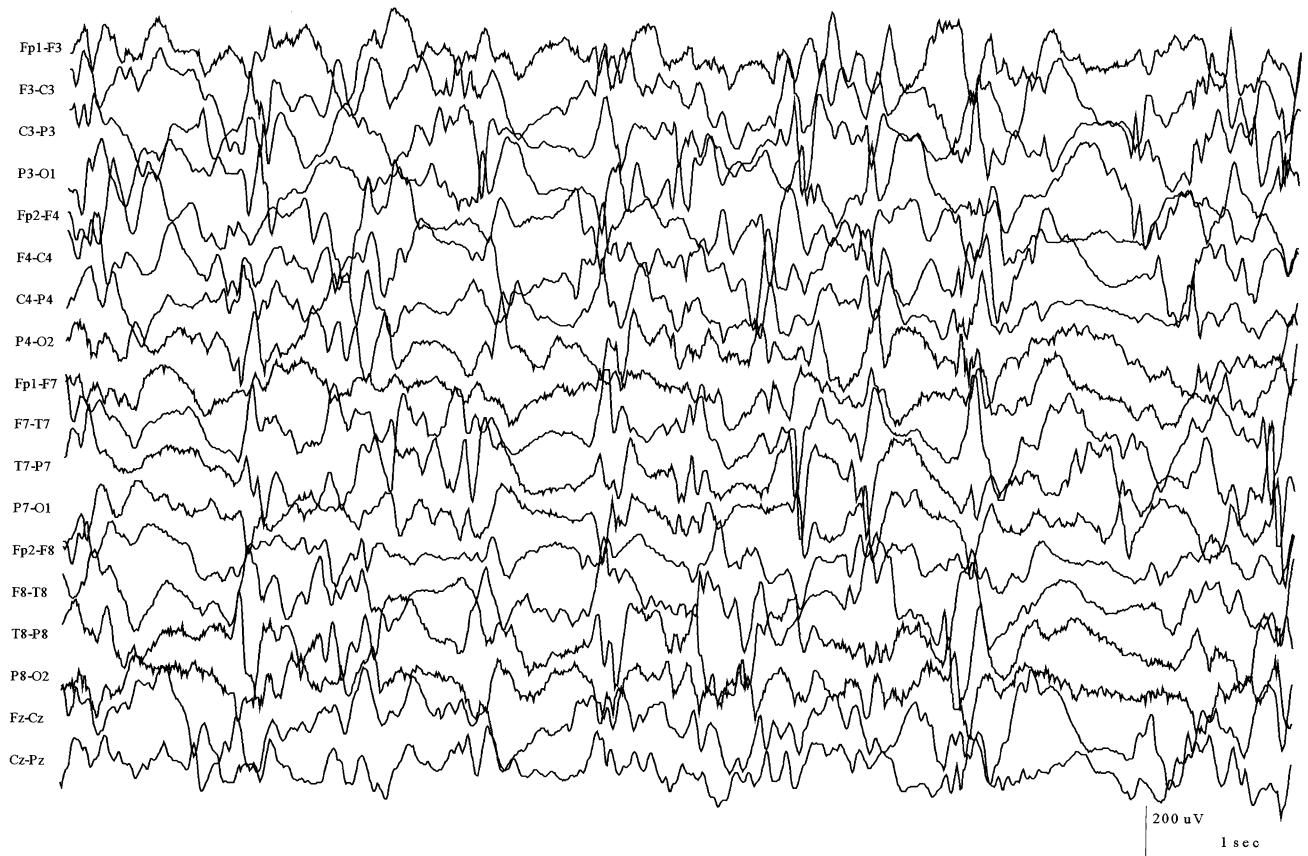


Figure 1. Hypsarrhythmia in a 4-month-old female infant with cryptogenic infantile spasms.

may follow motor spasms or occur independently as a second seizure type. Other associated features of spasms that may occasionally occur in isolation include abnormal eye movements, such as eye deviation or nystagmus, and autonomic changes, including alterations in respiratory and heart rate, diaphoresis, and lacrimation.

In many patients, spasms exhibit characteristic temporal patterns. Fifty to 80% of epileptic spasms occur in clusters of two to more than 100 seizures [17,18]. Patients may have dozens of clusters and several hundred spasms per day, but individual variability in seizure frequency is often large. Although spasms rarely occur during sleep, clusters of spasms are frequently activated after arousal from sleep. Spasms are occasionally triggered by loud noises with associated arousal from drowsiness and sleep but are not sensitive to photic stimulation.

Approximately one third to one half of patients with epileptic spasms also have other seizure types preceding or accompanying the onset of the spasms [19-22]. Associated seizure types include partial, myoclonic, tonic, and tonic-clonic seizures. Spasms usually cease spontaneously by 5 years of age 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].

### EEG Features

The classic interictal EEG pattern of patients with epileptic spasms is hypsarrhythmia (Fig 1). Although it is widely accepted that epileptic spasms are typically associated with hypsarrhythmia, there are little data on the proportion of patients with clinical spasms that do not have hypsarrhythmia because almost all studies of infantile spasms include hypsarrhythmia as a diagnostic criteria. Although the combination of epileptic spasms and hypsarrhythmia constitute the essential features of West syndrome, epileptic spasms have been reported to occur in patients with other epilepsy syndromes that do not feature hypsarrhythmia [24]. Conversely, hypsarrhythmia is not specific for infantile spasms because it may also be seen in other disorders [25].

Hypsarrhythmia was originally defined by Gibbs and Gibbs in the 1950s [26,27] as a completely chaotic and disorganized background pattern consisting of high amplitude slow waves and spikes that are asynchronous, non-rhythmic, and variable in duration and topography. The spikes usually alternate randomly between focal, multifocal, and generalized discharges at different moments within a brief record. Hypsarrhythmia represents a dynamic pattern that may change dramatically on a time scale of minutes, hours, weeks, or longer. It is most

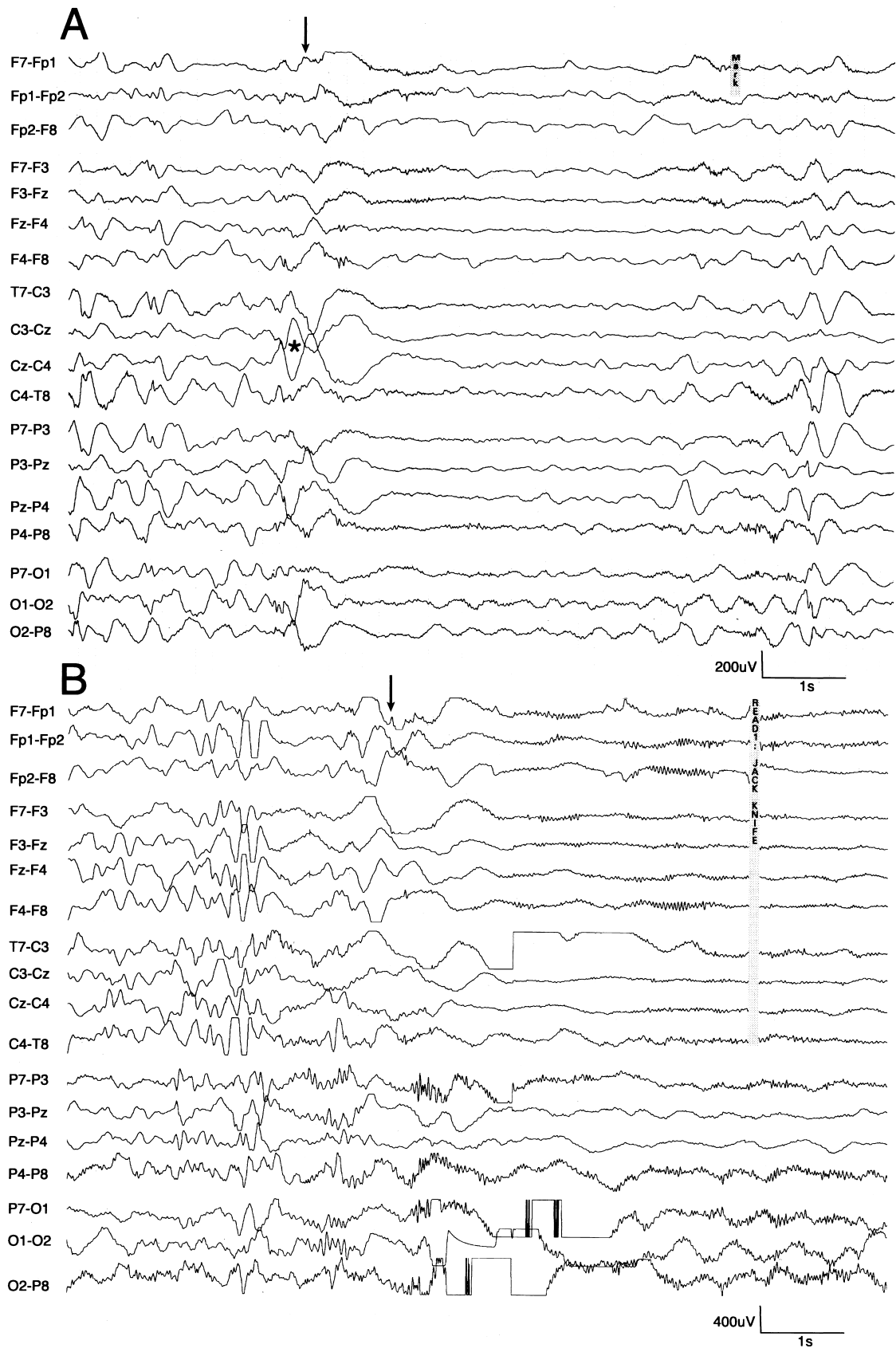


Figure 2. Ictal EEG patterns during epileptic spasms. (A) Ictal EEG from a 10-month-old female with infantile spasms and Down syndrome. Arrow ( $\downarrow$ ) denotes the onset of the clinical seizure that involved bilateral flexor spasms of the trunk and extremities. The electrographic seizure starts with a positive vertex wave, marked by the asterisk (\*), followed by a generalized electrodecremental response. (B) Ictal EEG from a 4-month-old female with cryptogenic infantile spasms. Arrow ( $\downarrow$ ) 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.

pronounced in slow-wave sleep and is diminished or completely suppressed during rapid eye movement sleep. Hypsarrhythmia may also be absent during the awake state or transiently disappear on arousal from sleep or during a cluster of spasms. On a larger time scale, hypsarrhythmia usually develops during early infancy and disappears by early childhood. Through serial EEGs in the same patients, hypsarrhythmia has been demonstrated to evolve from and to other abnormal EEG patterns, such as a burst-suppression pattern in the neonatal period or in Ohtahara syndrome and the slow spike-wave of Lennox-Gastaut syndrome [28,29].

A number of variations on the prototypical pattern of hypsarrhythmia have been described and previously labeled *modified hypsarrhythmia* [30,31]. Such variations include increased interhemispheric synchronization, episodes of attenuation, presence of a consistent epileptiform focus, asymmetric hypsarrhythmia (e.g., hemihypsarrhythmia), burst-suppression, and high-voltage slow activity with minimal spike activity. In fact, modified hypsarrhythmia occurs frequently and may be seen in patients who have typical hypsarrhythmia at other times. Furthermore, variant patterns of hypsarrhythmia appear to impart limited additional prognostic information [32]. Therefore the ILAE 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 EEG video monitoring [16-18]. Kellaway et al. [17] first described 11 different types of ictal EEG patterns consisting of various combinations of generalized sharp or slow wave discharges, generalized voltage attenuation (electrodecremental discharges), and fast activity. Overall, electrodecremental discharges represented the most common ictal feature, occurring in over 70% of recorded spasms, but could also occur in the absence of an obvious clinical seizure.

Fusco and Vigeveno [16] recently reported that a focal high-amplitude positive slow wave over the vertex-central region preceding the electrodecremental discharge was the most consistent ictal EEG feature of spasms, and correlated precisely to the clinical onset of the spasms. Although the more classic electrodecremental discharges were frequently observed in patients with spasms, Fusco and Vigeveno argued that electrodecremental discharges actually represent a postictal phenomenon. In our own experience, we have noticed both patients whose ictal EEG demonstrated the typical positive vertex slow wave at the clinical onset of the spasm (Fig 2A), and those for whom there is no detectable positive vertex slow wave (Fig 2B). The significance of the positive vertex wave at the ictal onset is uncertain and is likely one of the varied manifestations of this heterogeneous syndrome. Because the electrodecremental discharge is often time-locked with the continuing tonic spasm, we suspect that this EEG manifestation is an ictal phenomena in most patients (Fig 2B).

## Etiology and Pathophysiology

The reported percentage of total infantile spasms cases classified as symptomatic has risen over the years as etiologies have become identified more readily. In the early 1980s, most studies found identified symptomatic etiologies in approximately 45-60% of patients [15,19,21]. More recent studies have consistently classified 70-80% 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. Magnetic resonance imaging has a higher sensitivity for detecting focal abnormalities in West syndrome patients compared with computed tomography [33]. In a highly selected group of patients with infantile spasms referred to a tertiary care center the use of positron emission tomography alone increased the percentage of symptomatic cases from 30% to 95% [34].

Within the symptomatic group the etiologies for infantile spasms have traditionally been divided into prenatal, perinatal, and postnatal causes. Most studies identify prenatal etiologies as the most common, accounting for almost 50% of symptomatic cases [15,19], although perinatal causes have been reported to be on the rise [35]. In terms of general categories of disease, prenatal causes include intrauterine insults and infections, malformations of cortical development, neurocutaneous syndromes, metabolic disorders, and other genetic or chromosomal defects. The perinatal group consists primarily of hypoxic-ischemic encephalopathy, obstetric trauma, and other labor complications. Postnatal etiologies include infection, trauma, hypoxic-ischemic insults, and tumors.

Patients with cryptogenic or idiopathic infantile spasms represent a relatively small proportion of total infantile spasms cases [35]. In the absence of an identified etiology, cryptogenic and idiopathic infantile spasms are usually presumed to have an age-related multifactorial genetic predisposition. Recent advances have begun to provide insight into the genetic basis of cryptogenic and idiopathic infantile spasms. Although most cases of infantile spasms are sporadic, some familial cases have been identified. In particular, a recent report has presented evidence for an X-linked form of infantile spasms in two separate families that localizes to the distal part of the short arm of the X chromosome [36].

Although the list of specific diseases potentially causing infantile spasms is enormous, diagnostic evaluation does not necessarily have to be exhaustive. A recent study examined the effectiveness of using a staged diagnostic evaluation for infantile spasms [37]. History and physical examination alone identified the majority of symptomatic etiologies. Neuroimaging increased the etiologic yield by 20%, but other testing, such as cerebrospinal fluid analysis and comprehensive metabolic studies, revealed no additional etiologies. Chromosomal analysis and ophthalmologic evaluation did find specific abnormalities, but these merely confirmed the pre-existing clinical diagnoses.

During the diagnostic evaluation, a number of disorders that may mimic infantile spasms need to be considered in the differential diagnosis. Ohtahara syndrome is also a severe epileptic encephalopathy with frequent tonic spasms, but, in comparison to infantile spasms, Ohtahara syndrome usually has an earlier onset in the neonatal period and exhibits burst-suppression on interictal EEG [38]. Benign disorders may also mimic infantile spasms. Lombroso and Fejerman [39] have described infants with benign nonepileptic infantile spasms, who developed flexion spasms with normal associated EEGs during waking and sleep and normal intellectual outcome. Dravet et al. [40] have also reported infants with benign spasms with associated normal EEGs and good cognitive outcomes. Benign neonatal sleep myoclonus, also associated with normal waking and sleep EEGs, may be confused with infantile spasms [41].

Although many hypotheses abound, relatively little has been established about the pathophysiology of infantile spasms. Given the diverse etiologies of infantile spasms, a popular but unproven idea is that infantile spasms represents a nonspecific age-dependent reaction of the immature brain to injury. This hypothesis must take into account the fact that although most insults causing infantile spasms are multifocal or diffuse in nature, focal or unilateral damage may also lead to infantile spasms. Many pathophysiologic models for infantile spasms have focused on subcortical structures, especially the brainstem, as the primary central mechanisms for generating clinical spasms and hypsarrhythmia. In turn, abnormal brainstem function could influence the cerebral hemispheres diffusely through widespread cortical projections. A number of case reports have identified pathologic alterations in the brainstem of infantile spasms patients, such as the pons [42,43]. The involvement of specific brainstem nuclei containing serotonergic, noradrenergic, or cholinergic neurons has been hypothesized but not definitively substantiated [44].

The role of other subcortical structures in infantile spasms has also been considered. Given the dramatic effects of adrenocorticotrophic hormone (ACTH) and glucocorticoids on spasms, the hypothalamus and the associated pituitary-adrenal axis have been implicated in pathogenesis of infantile spasms, with a variety of stressors being hypothesized to result in excessive release of corticotrophin releasing hormone, a known convulsant [45]. The involvement of the lenticular nuclei also has been suggested, because hypermetabolism in these nuclei was the most prominent and consistent finding in PET studies of patients with infantile spasms [46]. Despite the abundance of hypotheses, no comprehensive or unifying mechanism for the pathophysiology of infantile spasms has been established.

## Treatment

Because of the poor prognosis of infantile spasms, treatment is usually initiated quickly and aggressively

**Table 1. Drugs used for infantile spasms**

	Reference Number
<b>First-line therapy</b>	
Evidence from randomized controlled studies	
Vigabatrin	69, 71
Adrenocorticotrophic hormone	50, 52, 63, 69
Prednisone	50, 52
Nitrazepam	63
Evidence from open-label studies	
Pyridoxine	64, 65
Valproate	59, 61, 62
Zonisamide	80, 81
<b>Add-on therapy</b>	
Evidence from randomized controlled studies	
Valproate	60
Evidence from open-label studies	
Felbamate	77
Lamotrigine	78
Topiramate	79

after diagnosis, often at the risk of serious side effects, with the hope of changing the natural history of the disease. Although a vast literature concerning treatment of infantile spasms exists, there has been an abundance of methodologic problems and a paucity of well-designed clinical trials. The often subtle nature of epileptic spasms makes uncontrolled clinical reports of spasm frequency unreliable and subject to a large placebo effect. Despite the ethical issues of performing placebo-controlled studies in infantile spasms, innovative clinical trials have been published.

Table 1 summarizes drugs that have been reported to be efficacious for infantile spasms in either controlled or open-label studies. For approximately 50 years hormonal therapy has been the staple of treatment for infantile spasms, at least in North America. ACTH was first reported to have dramatic, rapid effects on spasms in the 1950s [47]. 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. Many controversies still exist concerning the relative efficacy, optimal dose and timing, and predictive factors for good responsiveness to ACTH and corticosteroids. No placebo-controlled trials of ACTH or steroids have been performed. In most open-label or retrospective studies, ACTH or prednisone induces a reduction or complete cessation of spasms, as well as an improvement in the EEG, in approximately 50-75% of patients [15,19,23, 48-51]. This effect is usually realized within a couple of weeks [50]. Although some studies report similar efficacy of ACTH and prednisone [19,50], others indicate that ACTH is more effective [51,52]. Some patients who do not initially respond to ACTH may respond to prednisone and vice versa [50]. A large variety of doses of ACTH have been used, but there is no evidence that larger doses (150 U/meter<sup>2</sup> per day) are more effective than lower

doses (20-30 U/day) [23,53]. Longer treatment periods usually do not improve remission rates [53]. Although relapses occur in about one third to one half of patients, a second course of ACTH is often effective [50].

A variety of findings have been reported with regard to predicting responsiveness to ACTH or steroids. Some studies [54], but not others [50], demonstrate that shorter time lag between diagnosis and treatment improves initial remission rate. Age of onset of the spasms has occasionally been correlated with treatment efficacy, with later onset (older than 8 months) having a better seizure control [54]. Whether etiology of the infantile spasms influences responsiveness to treatment is also controversial; some studies report equal efficacy in symptomatic and cryptogenic groups [50], but others find a better response in the cryptogenic group [22,23,51]. Finally, the effect of hormonal therapy on long-term neurodevelopmental outcome is unclear. Although some studies report an association between initial responsiveness to ACTH and improved long-term intellectual development [19,22,23,55], others found no significant difference in prognosis between initial responders and nonresponders to hormonal therapy [15,21,56].

Hormonal therapy with ACTH or corticosteroids may have significant, potentially fatal, side effects [57]. Although cushingoid features are among the most common side effects, ACTH or corticosteroids may also produce hypertension, metabolic abnormalities, severe irritability, osteoporosis, sepsis, and congestive heart failure. A non-depot form of ACTH has recently been reported to have less severe adverse effects [58]. Given the serious morbidity of hormonal therapy, a number of other therapies have received attention for infantile spasms.

Among conventional antiepileptic drugs, valproate and nitrazepam have been found to be effective in controlled clinical trials of spasms [59-63]. Pyridoxine has also been used successfully in some patients [64,65]. Few studies have directly compared these other agents with hormonal therapy, making conclusions about relative efficacy difficult. Because of the risk of hormonal therapy and the almost certain poor developmental outcome in symptomatic infantile spasms, we reserve the initial use of ACTH for cryptogenic cases.

The most exciting recent development in the treatment of infantile spasms has been the emergence of vigabatrin as a potential first-line therapy, comparable with ACTH. In 1991, vigabatrin was first reported to be effective as add-on therapy in resistant infantile spasms [66]. Over the past decade, vigabatrin has been repeatedly documented to also be effective as first-line therapy for infantile spasms [67-71]. Studies directly comparing vigabatrin and ACTH have found either similar efficacy between the two drugs [68] or superiority of ACTH [69]. All studies report that vigabatrin is better tolerated with fewer side effects than ACTH [68,69]. In a unique double-blind placebo-controlled trial, vigabatrin or placebo was used for the first 5 days of treatment before conversion to open-label vigaba-

trin therapy. During the double-blind 5-day period, vigabatrin caused a 78% reduction in spasm frequency with 35% having complete control, compared with a spasm reduction of 26%, and complete control in 10% of patients on placebo [71]. 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 [67,72].

When available, ACTH remains a treatment of choice for infantile spasms in the United States [73], and vigabatrin has become a first-line therapy in many European countries [74]. Unfortunately, recent reports of visual-field constriction associated with vigabatrin therapy may not only prevent vigabatrin from becoming an approved treatment in the United States but also may limit its utility in other countries [75,76]. Thus other new antiepileptic drugs may be investigated more thoroughly as potential first-line therapy for infantile spasms. Open-label studies have already provided preliminary evidence for the efficacy of felbamate, lamotrigine, topiramate, and zonisamide in infantile spasms [77-81].

As the identification of focal cortical lesions associated with infantile spasms has increased, interest in the potential surgical treatment of patients with infantile spasms has correspondingly risen. Reports of cessation of spasms after surgical treatment of obvious cerebral lesions, such as brain tumors or cysts, have been reported [82-84]. More recently surgery has been used successfully in patients previously believed to have cryptogenic infantile spasms but subsequently found to have small lesions detected by PET scan and identified mainly as cortical dysplasias on neuropathologic examination [85,86]. For patients without a surgically resectable lesion, corpus callostomy has been reported to dramatically improve spasms, as well as other seizure types, such as drop attacks [87].

## Prognosis

Many studies have examined the long-term prognosis of patients with infantile spasms. Although there is substantial variability in specifics reported from different studies, by all accounts the majority of patients with infantile spasms suffer a poor outcome with respect to chronic epilepsy, mental retardation, and other neurodevelopmental disabilities.

Epileptic spasms resolve spontaneously without treatment or with treatment in the majority of patients, usually by midchildhood [20,23,88]. However, other seizure types arise in 50-70% of patients [21,22]. Similarly, on long-term follow-up, chronic intractable epilepsy is present in approximately 50% of patients with a history of infantile spasms [15,21-23]. A close relationship between infantile spasms and Lennox-Gastaut syndrome has been consistently observed [24,89] because these two syndromes share parallel clinical and electrographic features, such as intractable seizures, strong association with mental retardation, and characteristic interictal EEG abnormalities.

Approximately 20-50% of patients with infantile spasms evolve into Lennox-Gastaut syndrome [13,14,19,89] and conversely, a similar percentage of patients with Lennox-Gastaut syndrome have a history of infantile spasms [79,90].

Mental retardation occurs in 70-90% 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 30-50% of patients [13,22,23]. By far the most important factor in predicting neurologic prognosis, including developmental outcome and long-term epilepsy, is etiology. In some studies, patients with cryptogenic infantile spasms have only a 30-50% chance of mental retardation compared with 80-95% for patients with a symptomatic etiology [12,14, 23,22]. 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 [91,92]. Other factors that have been associated with a good prognosis include 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 mortality rate associated with infantile spasms has been estimated to be between 5% and 30% [13,51,52]. Although the higher mortality figures understandably come from a study that followed patients into adulthood [51], about one third of the deceased patients from that study died before 3 years of age and more than 50% died before 10 years of age. The most common cause of death is infection, followed by reasons related to the underlying disease process [51].

## Conclusions

Children with infantile spasms represent one of the greatest challenges for pediatric neurologists. Accurate diagnosis depends on a thorough understanding of the clinical and electrographic features of spasms. Diagnostic evaluation should use a rational approach for identifying potential etiologies of symptomatic infantile spasms. Decisions about treatment should take into account the poor prognosis of infantile spasms, conflicting data about the impact of treatment on long-term outcome, and the potentially serious side effects of treatment. As more is learned about the pathophysiology of infantile spasms, there is hope that more effective and safer treatments (including perhaps neuroprotective agents) will be developed. Given the profound neurodevelopmental sequelae of infantile spasms, the ultimate goal should be the primary prevention of infantile spasms.

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