



Infantile spasms

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INFANTILE spasms are a relatively rare seizure disorder of infancy and early childhood. Referred to in the literature as massive spasms, flexion spasms, jackknife seizures, infantile myoclonic seizures, etc., they have been recognized as an epileptic phenomenon since they were first described by West in 1841.¹ The triad of infantile spasms, retardation, and the electroencephalographic (EEG) pattern, hypsarrhythmia, has become known as West's syndrome.

Although a considerable amount of world literature pertaining to this disorder has accumulated, the classifications and clinical descriptions of the seizures, based largely on routine bedside observation, have been highly variable, and this lack of uniformity has led to confusion and controversy.

The development of long-term polygraphic/video monitoring techniques in the 1970s² improved our understanding of the clinical manifestations of this disorder and also provided, for the first time, an objective means of studying the effects of therapy on the EEG and on seizure frequency.

In this chapter, we will characterize infantile spasms briefly and address some of the more controversial and still unresolved issues, including therapy and pathophysiology.

EPIDEMIOLOGY

Infantile spasms usually begin within the first 6 to 8 months of life; the incidence has been estimated to be 1 per 4,000 to 6,000 live births.³ Familial occurrence of infantile spasms is rare, and there is no clear evidence to suggest a preponderance of one sex over the other.⁴

CLINICAL MANIFESTATIONS

The spasm of infantile spasms is usually a brief contraction of the muscles of the neck, trunk, and extremities, typically occurring bilaterally and symmetrically. The character of the seizure depends on whether the flexor or extensor muscles are predominantly affected and on the number and distribution of the muscle groups involved.^{2,5} Thus, the spasms may vary from a massive contraction of all flexor muscles to a minimal contraction of only the neck muscles or the abdominal recti.

There are three main types of spasms: flexor, extensor, and mixed flexor-extensor. Mixed spasms are the most common type (about 42%); flexor spasms are the next most common (about 34%); and extensor spasms are the least common (about 23%).^{2,5} Most infants with this disorder have more than one type of spasm, and the type observed at any given moment may be influenced by body position.

Asymmetrical infantile spasms are rare (<1%). Periods of attenuated responsiveness (arrest phenomena), which usually follow a motor spasm, may also occur as independent phenomena.

Eye movements, consisting of deviation alone or followed by rhythmic nystagmoid movements, occur in

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approximately 60% of motor spasms. Alterations in respiration accompany about 60% of the spasms; changes in heart rate are rare (<1%). A cry may frequently follow a spasm, but crying does not occur as an ictal phenomenon.

Although there is little variation in the number of spasms occurring in consecutive 24-hour periods, there is a marked variation in the number recorded at 2-week intervals.⁶ The number of spasms recorded during 24-hour periods has ranged from three to 763.

About 80% of infantile spasms occur in clusters, i.e., the interval between successive spasms is less than 60 seconds. The number of spasms per cluster has varied from two to 138, with succession rates of up to 15 per minute. Usually the intensity will initially wax and then wane within a given cluster.

The frequency of spasms is approximately the same during the night as during the day. Although they rarely occur when the infant is actually asleep (<3%) they frequently occur immediately upon arousal or soon thereafter. Infantile spasms are not precipitated by feeding or photic stimulation but may infrequently be elicited by unexpected loud noises or tactile stimulation.

EEG FINDINGS

Interictal

Although a variety of EEG patterns may be seen in association with infantile spasms,⁴ the most characteristic finding is hypsarrhythmia.⁷ This prototypic pattern, as originally described by Gibbs and Gibbs in the 1950s,⁷ is frequently restricted to the early stages of the disorder and is seen more often in younger infants (<1 year). More commonly, the EEG shows variations of the pattern (modified hypsarrhythmia); these include hypsarrhythmia with increased interhemispheric synchronization, asymmetrical or unilateral hypsarrhythmia, hypsarrhythmia with a consistent focus of abnormal discharge, hypsarrhythmia with episodes of generalized, regional, or localized voltage attenuation (suppression-burst variant), and hypsarrhythmia composed primarily of high-voltage, bilaterally asynchronous, slow-wave activity.⁸

In addition to these basic variations, transient alterations in the pattern typically occur throughout the day. The hypsarrhythmic pattern is most pronounced, and persists to the latest age, in slow-wave sleep, and is least evident or completely absent during rapid eye movement (REM) sleep, when the background EEG

activity may appear normal.⁹ Also, a marked reduction or transient disappearance of the hypsarrhythmic pattern often occurs upon arousal from slow-wave or REM sleep or during a cluster of spasms.⁸

Ictal

Eleven different ictal EEG patterns have been described.⁵ Generalized slow-wave transients, sharp-and-slow-wave transients, attenuation episodes, or attenuation episodes with superimposed faster frequencies occur singly or in various combinations. The most common EEG event associated with infantile spasms is a high-voltage, generalized, slow-wave transient followed by an abrupt attenuation of background activity in all regions that may last from one to many seconds. There is no close correlation between the character of the ictal EEG event and the type of spasm. The duration of the ictal EEG event ranges from 0.5 to 106 seconds, the longer episodes being associated with the arrest phenomenon.

PATIENT CLASSIFICATION

In the past, the classification of patients was somewhat variable and inconsistent.⁴ At present, patients can best be classified on the basis of computed tomographic (CT) scan findings, medical history, developmental history, and the neurologic examination. On the basis of this information, patients can be divided into two groups, cryptogenic and symptomatic. A patient is classified as cryptogenic if there is no known associated etiologic factor, development is normal prior to onset of the spasms, there is no abnormality on neurologic examination, and the CT scan is normal prior to therapy. Using these strict criteria, approximately 10% to 15% of patients can be classified as cryptogenic.¹⁰⁻¹³ The remainder are classified as symptomatic. The classification of patients as cryptogenic or symptomatic is crucial to the prediction of long-term outcome.

ASSOCIATED ETIOLOGIC AND CLINICAL FACTORS

In about 60% of patients, potential etiologic factors can be clearly identified, and various pre-, peri-, and postnatal conditions have been implicated.⁴ Prenatal factors include intrauterine infection, prematurity, cerebral dysgenesis (e.g., lissencephaly), hypoxia-ischemia, and genetic disorders (e.g., tuberous sclerosis).

Perinatal factors include hypoxia-ischemia and traumatic delivery, while postnatal factors include head injury, inborn errors of metabolism (e.g., nonketotic hyperglycinemia), central nervous system infection, hypoxia-ischemia, and intracranial hemorrhage. Approximately 85% to 90% of patients with infantile spasms show some degree of mental and developmental retardation. About 50% have major neurologic defects, and another 40% have minor ones.^{4,14}

In our earlier studies of 54 patients with infantile spasms, CT scans revealed the following: no abnormalities in 17 patients (31%); generalized atrophy in eight (15%); predominantly focal atrophy in 19 (35%); and congenital anomalies in ten (19%). These findings are comparable to those previously reported.^{15,16}

IMMUNIZATION

During the past several decades, there has been major disagreement as to whether immunization is an etiologic factor associated with infantile spasms. This issue is important not only from a medical standpoint but also from a legal one, as evidenced by the increasing number of lawsuits against manufacturers of vaccines. Infantile spasms have been reported to be associated with various vaccines; however, the one most frequently implicated has been the diphtheria-pertussis-tetanus (DPT) vaccine. The pertussis agent has generated the most concern, and a number of publications have reported its apparent relationship to the development of infantile spasms.¹⁷⁻²³

The major problem in determining whether there is a relationship between infantile spasms and DPT immunization is that the vaccine is given at a time when infantile spasms usually have their onset (before the age of 6 to 8 months). Although few studies have approached this problem in a manner amenable to statistical analysis, those that have done so²⁴⁻²⁷ demonstrated that the apparent association between infantile spasms and DPT immunization is coincidental and that the two are not causally related.

PATHOPHYSIOLOGY

A large number of pathologic abnormalities have been identified in infantile spasm patients.⁴ However, considerable evidence implicates the brain stem as the area giving rise to infantile spasms and the hypsarrhythmic EEG pattern.^{9,14,28-30} Our recent work, utilizing

long-term monitoring,⁹ provides supportive evidence that dysfunction of certain monoaminergic or cholinergic regions of the brain stem implicated in the control of sleep cycling may also be responsible for the generation of the spasms and the EEG changes seen in infantile spasms. The pathophysiologic model of infantile spasms based on these data has been described in detail elsewhere.^{9,31} Various other authors have suggested that dysfunction of monoaminergic neurotransmitter systems may be responsible for the generation of infantile spasms.³²⁻³⁶ However, two other major pathophysiologic mechanisms have been proposed. First, it has been suggested that infantile spasms result from a failure, or delay, of normal developmental processes.³⁷ This theory is based largely on the assumption that adrenocorticotrophic hormone (ACTH) and corticosteroids accelerate certain normal developmental events in immature animals.³⁸⁻⁴⁰ Another hypothesis is that infantile spasms are the result of a defect in the immunologic system.^{31,41-48} These hypotheses are not necessarily mutually exclusive. For example, an immunologic reaction to brain tissue could alter the functional activity of neurotransmitter systems so as to produce the clinical manifestations observed in this disorder.

TREATMENT

No aspect of this disorder has generated as much controversy and confusion as the issue of therapy. The opinions concerning the treatment of infantile spasms expressed in numerous studies published during the past three decades have been so diverse that no consensus of opinion exists, nor has a "standard of care" been established. We will not attempt to provide an extensive review of the literature concerning treatment of this disorder; nor is such a review warranted, because of the many methodological problems present in most of the published studies. However, we will review the prevailing attitudes and opinions, and recommend the most appropriate therapy based on the best available data.

Hormonal therapy

Acute effects. In 1958, Sorel and Dusaucy-Bauloye⁴⁹ reported that treatment of infantile spasms with ACTH resulted in cessation or amelioration of seizures and disappearance of the hypsarrhythmic EEG pattern. Extensive literature concerning the treatment of this disorder with ACTH and corticosteroids has

subsequently appeared; most studies, however, have been plagued with methodological problems, making it difficult to interpret the results.

In spite of these methodological shortcomings, several major opinions have evolved concerning hormonal therapy for infantile spasms. Some individuals consider ACTH and prednisone to be equipotential, whereas others consider ACTH to be superior.^{4,50-55} Furthermore, two therapeutic approaches have evolved for the treatment of infantile spasms with ACTH. Some researchers suggest using high dosages of ACTH (40 to 160 units/day) and long durations of therapy (3 to >12 months).^{51,53,56-60} Others utilize low-dosage ACTH therapy (5 to 40 units/day) for relatively brief periods (1 to 6 weeks).^{40,55,61,62} Some proponents of high-dosage/long-duration ACTH therapy report better control of seizures and greater EEG improvement with such treatment compared with low-dosage/short-duration therapy.^{51,53}

Our own controlled study of the relative efficacies of low-dosage ACTH and prednisone, utilizing serial 24-hour polygraphic/video monitoring studies to determine the response objectively,¹³ revealed the following:

1. Response to hormonal therapy is all or none: complete control or no control. We did not observe a graded response.

2. It was impossible to demonstrate a major difference in therapeutic efficacy between ACTH (20 to 30 units/day) and prednisone (2 mg/kg/day) in stopping the spasms and improving the EEG.

3. About 60% to 70% of infantile spasm patients respond to either ACTH or corticosteroid therapy.

4. Only a short course (2 weeks) of hormonal therapy is required for most patients to obtain a response.

5. Once a response to hormonal therapy is documented, the therapy can be immediately discontinued and the response maintained.

6. If a patient fails to respond to a course of ACTH, he or she may respond to prednisone, and vice versa.

7. About one third of patients will experience a relapse. This figure is comparable to that previously reported by Lacy and Penry.⁴ If a relapse occurs, a second course of therapy is usually effective.

8. Etiology and treatment lag (the time from onset of spasms to initiation of treatment) are not useful predictors of response. Symptomatic patients responded just as well as cryptogenic patients, and patients with long treatment lags responded as well as those with short treatment lags.

9. Relative normalization of the EEG may occur in

patients who continue to have spasms. This is an important point, because many physicians rely heavily on the EEG to determine whether a response to therapy has occurred.

Although this study provided valuable information concerning the acute effects of low-dosage ACTH compared to prednisone, it did not address the issue of high-dosage/long-duration ACTH therapy *v* low-dosage/short-duration ACTH therapy. Unfortunately, no comparable prospective, blinded, objectively controlled studies of high-dosage/long-duration ACTH therapy are available. In the only retrospective analysis of the results of high-dosage *v* low-dosage ACTH therapy, Riikonen⁴⁰ showed that higher dosages of ACTH (120 to 160 units/day) produced no better results than smaller dosages (20 to 40 units/day) in patients with infantile spasms.

Long-term outcome. When lower dosages and shorter durations of hormonal treatment are used, about 9% to 13% of patients with infantile spasms have been reported to show normal development.^{50,63-68} Some investigators have found similar outcomes in treated and untreated patients.^{50,63,69} Others have reported an improved prognosis for long-term mental and motor development with the use of high-dosage/long-duration ACTH therapy.^{51,60} Also implicit in many reports is that long-term outcome is adversely affected when the treatment lag is prolonged.^{4,51,60} Like the studies that evaluated the acute effects of hormonal therapy in infantile spasm patients, however, the design of most studies concerned with long-term outcome does not permit definitive conclusions to be drawn. Reports of long-term prognosis have usually been retrospective or have not used diagnostic evaluations such as CT scans to aid in classifying patients as cryptogenic or symptomatic. Our own study of the long-term outcome in 64 patients followed prospectively and treated with ACTH (20 to 30 units/day for 2 to 6 weeks) and prednisone (2 mg/kg/day for 2 to 6 weeks)¹⁰ revealed the following:

1. The overall prognosis is poor, with only 5% of the total population having normal outcomes.

2. Severe or very severe impairment was observed in 69% of the patients.

3. There was no significant difference between responders and nonresponders with respect to long-term outcome.

4. There was no significant difference in outcome between patients treated within 5 weeks of the diagnosis of infantile spasms and those treated more than 5 weeks after the diagnosis. Early treatment (within 5

weeks), even in the cryptogenic group, did not insure a normal long-term outcome.

5. The only factor that appears to affect long-term outcome is whether a patient is classified as cryptogenic or symptomatic.^{51,54,63,70} In our study, cryptogenic patients had a significantly better long-term outcome than symptomatic patients; 38% of the cryptogenic patients were normal or had only a mild impairment, in contrast to 5% of the symptomatic patients.

6. There is no way to predict which cryptogenic patients will have normal outcomes and which will be retarded.

The question still remains as to whether higher dosages of hormonal therapy given for longer periods of time will increase the chance for a normal outcome. The answer to this question awaits proper evaluation in prospective, controlled protocols. As noted previously, in a retrospective study of patients with infantile spasms, Riikonen⁴⁰ observed no significant difference in the effects of large dosages of ACTH compared with lower dosages. In fact, patients treated with lower dosages had better outcomes and fewer side effects.⁷¹

Recommended treatment regimen. Until appropriately designed studies are performed to demonstrate that high-dosage ACTH therapy is superior to low-dosage ACTH therapy, the following treatment regimen is recommended for all patients with infantile spasms, regardless of treatment lag, age, or patient classification (cryptogenic or symptomatic).

A baseline EEG should be obtained on all patients prior to initiation of therapy. A CT scan should also be obtained to aid in classifying patients as symptomatic or cryptogenic. Either ACTH or prednisone may be given initially. If ACTH is chosen, the drug is started at a dosage of 20 units/day for 2 weeks; if there is no response at that time, the dosage is increased to 30 units/day for 4 weeks. If prednisone is chosen, the drug is administered at 2 mg/kg/day for 2 weeks; if there is no response, that dosage is continued for an additional 4 weeks. Response is defined as total cessation of infantile spasms and improvement in the EEG. If a patient fails to respond to a course of ACTH, prednisone should be tried after a 1-week washout period, and vice versa. If a relapse occurs after ACTH or prednisone has been discontinued, the effective drug should be restarted at the dosage that produced the initial response.

Throughout the entire course of ACTH or prednisone therapy, the patient's blood pressure should be monitored closely, and serum electrolyte studies should be performed on a weekly basis.

Side effects. The side effects of ACTH or cortico-

steroid therapy, some of which may preclude treatment or require its termination, are hypertension, electrolyte imbalance, suppression of the immune system, ocular opacities, gastrointestinal disturbances, and transient brain shrinkage.⁷² The most common side effect is hypertension, which has been reported to occur in from 10% to 25% of patients with infantile spasms treated with ACTH or corticosteroids.^{4,11-13}

Anticonvulsant and pyridoxine therapy

Of the various traditional anticonvulsants that have been used to treat patients with infantile spasms, only valproic acid^{73,74} and the benzodiazepines, particularly nitrazepam,^{4,57,75-79} have been reported to be effective. Pyridoxine also has been reported to be beneficial in treating a small number of patients with infantile spasms.⁸⁰⁻⁸³ These studies, however, suffer from the same methodological shortcomings previously mentioned in the discussion of hormonal therapy.

At present, there is no clear evidence that standard anticonvulsant or pyridoxine therapy is of benefit in treating infantile spasms. This issue will not be resolved until appropriately designed and objectively evaluated studies are performed.

MORTALITY RATE

Past studies of infantile spasms have reported a significant mortality (11% to 23%).⁴ But in a recent study of long-term outcome we documented a mortality rate of only 5%,¹⁰ a finding probably reflecting the availability of better medical care in today's society.

OTHER SEIZURE TYPES

The occurrence of other types of seizures in patients who stopped having infantile spasms has ranged from 35% to 60%.^{4,40,63,64} The most common types observed are tonic, simple partial, and generalized tonic-clonic. In our recently completed prospective study of long-term outcome, other types of seizures occurred in 53%.¹⁰ None of the cryptogenic patients who responded to hormonal therapy had other types of seizures.

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