Infantile Spasms: Little Seizures, BIG Consequences

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Infantile spasms is one of the "catastrophic childhood epilepsies" because of the difficulty in controlling seizures and the association with mental retardation. However, early recognition, a careful diagnostic evaluation, and proper treatment may allow some children to attain seizure control and to achieve a normal, or at least much improved, level of development. Thus, there is the opportunity to have an important impact in the lives of these unfortunate children and their families.

Infantile spasms is arguably the most interesting, but also the most enigmatic, of all the epilepsy syndromes. Infantile spasms was one of the first epilepsy syndromes described. In a letter to the editor of *The Lancet* in 1841, Dr. WJ West's description is as clear as any modern portrayal. He recounted that the patient had "bobbings" that "cause a complete heaving of the head forward towards his knees, and then immediately relaxing into the upright position . . . these bowings and relaxings would be repeated alternately at intervals of a few seconds, and repeated from 10 to 20 or more times at each attack, which attack would not continue more than 2 or 3 minutes; he sometimes has 2, 3 or more attacks in the day (1)." West also reported on the consequences of infantile spasms: marked developmental delay and mental retardation. Sadly, the patient who West was describing was his own son, and the letter was a request for help in treatment. The letter was written more than a century before adrenocorticotropic hormone (ACTH) was identified as the first effective therapy.

Infantile spasms has been known by many names over the years, including salaam attacks, salaam convulsions, generalized flexion epilepsy syndrome, Blitz-Nick-Salaam-Krämpfe, eclampsia nutans, flexion spasm, infantile spastic epilepsy, jackknife convulsion syndrome, jackknife spasm, massive myoclonia syndrome, and nodding spasms (2). Infantile spasms is now the preferred term, but West syndrome is often used synonymously. A more general term, "epileptic spasms," includes infantile spasms as well as clinically similar seizures that occur in older patients (3).

In the 165 years since the initial description of infantile spasms, clinicians have made remarkable progress in recognizing infantile spasms and evaluating patients for underlying causes. However, more remarkable is how little is really known about the neuroanatomic and electrophysiologic mechanisms that trigger infantile spasms. This lack of understanding may well result from the fact that no animal model has been created that is similar to the human disorder. It is possible that the underlying mechanisms of infantile spasms exist only in the context of the complexities of the developing human nervous system.

Diagnosing Infantile Spasms

Although the epileptogenic mechanisms of infantile spasms is not well understood, an etiologic diagnosis can be identified in more than 70% of cases (4,5), which may lead to a specific therapy that can have a dramatic influence on the outcome of the patient. It is, therefore, essential that an appropriate diagnostic evaluation be performed in every patient. Because infantile spasms has such characteristic clinical and electrographic features, it is easy to make the diagnosis if the epileptic nature of the spells is recognized. However, sometimes the spasms are subtle enough that the syndrome is not even considered.

Three key factors lead to the diagnosis. The first factor is age. Infantile spasms is a disorder of the developing nervous system and the spasms typically begin in the first year of life, most commonly between 4 and 8 months of age (6). Occasionally, they may begin in the neonatal period (7) or, rarely, much later in childhood (8). An atypical age of onset may help with etiologic diagnosis. For example, neonatal onset is associated with cortical dysplasia (9), whereas late onset (after 1 year of age) often is associated with genetic anomalies, hypoxic ischemic encephalopathy, and cortical dysplasia.

The second factor is the semiology. Clusters of flexion jerks of the neck, trunk, and extremities lasting 1–2 seconds are typical. Variations occur, such as extension of upper and lower extremities or both. Or, the spells may be very subtle, such as just a brief head drop (so-called Blitz-Nick-Krämpfe or "lightening neck spasms"), and often are misdiagnosed as a Moro reflex or simple startle reflex. In such cases, the epileptic nature of the spells may remain unappreciated for weeks or months. Although the spasms may happen as single jerk event, clusters

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are more common and often occur on awakening in the morning or after a nap (6). Other seizure types may arise concurrently or sequentially with infantile spasms (10–12).

The third factor is a very distinct EEG pattern. It is interesting to note that infantile spasm syndrome was not recognized as an epileptic disorder until the 1950s when Gibbs et al. described the characteristic and pathognomonic EEG abnormality called hypsarrhythmia (13). Hypsarrhythmia is a very high-voltage, disorganized pattern of EEG abnormality. A less chaotic pattern, called modified hypsarrhythmia, actually may be more common than hypsarrhythmia (14). Hypsarrhythmia or modified hypsarrhythmia is seen in about two thirds of cases. Other patterns, such as multifocal independent spike discharges (MISD), are present in the remainder. Although infantile spasms may be associated with other EEG abnormalities, hypsarrhythmia virtually never occurs in other epilepsy syndromes. Because infantile spasm seizures are frequent, it is common to capture the spells on a routine EEG, revealing the characteristic feature of electrodecrement immediately after the individual clinical spasm. If the EEG is normal, the diagnosis of infantile spasms should be reconsidered, as there are benign disorders that may appear clinically similar to infantile spasms (e.g., benign infantile myoclonus (15) or benign familial infantile convulsions (16)).

These three factors are so distinctive that the clinical diagnosis of infantile spasms can be made with certainty in the vast majority of cases. Whereas the diagnosis of infantile spasms syndrome is usually easy, determining an etiologic diagnosis may be difficult. However, the etiologic diagnosis has such a profound impact on treatment and prognosis that an appropriate evaluation is essential in all cases.

The Etiologic Diagnosis

An etiologic diagnosis is very important because it can lead to initiation of a specific therapy that may markedly improve the long-term developmental outcome. In fact, some children with infantile spasms may ultimately lead normal lives, but only if they are diagnosed and treated correctly. Examples of specific therapy include: pyridoxine-dependent seizures, treated with pyridoxine; tuberous sclerosis, treated with vigabatrin; and focal cortical dysplasia, treated by surgical resection. Another important reason for establishing an etiologic diagnosis is that some of the disorders are genetic in nature, which may carry a significant risk of recurrence in offspring. Genetic counseling is essential if recurrence is to be avoided.

In some cases, an etiologic diagnosis cannot be identified; such cases are labeled as "cryptogenic." However, as previously noted, an etiology can be identified in more than 70% of cases, which are then labeled as "symptomatic." The reported causes of infantile spasms are extensive and broad categories of etiologies, including (i) CNS infection, which may have occurred prenatally (e.g., transplacental infections), perinatally (e.g., herpes simplex virus), or postnatally (e.g., meningitis or encephalitis); (ii) brain developmental abnormalities, such as lissencephaly, focal cortical dysplasia, or hemimegalencephaly; (iii) neurocutaneous syndromes, including tuberous sclerosis, neurofibromatosis, and incontinentia pigmenti; (iv) hypoxic ischemic encephalopathy; (v) chromosomal or genetic abnormalities, such as Down syndrome, Miller–Dieker syndrome, or ARX mutation; and (vi) rarely, a metabolic disorder. While the metabolic disorders are important, they represent only a small percentage of patients. Metabolic workup and specific chromosomal or gene testing is quite expensive and should be reserved for patients for whom an etiology is not identified in the initial evaluation.

Patient History

As with most neurologic disorders, patient history is a key aspect of the assessment. Although there are many disorders associated with infantile spasms, two stand out as particularly important: (i) a history of hypoxic ischemic encephalopathy (e.g., perinatal hypoxic ischemic encephalopathy, postcardiac arrest) and (ii) CNS infections, as previously described. Special attention should be paid to these issues in taking the history.

Physical and Neurologic Examination

Several etiologic diagnoses can be identified by careful examination. Many patients are developmentally delayed and have evidence of cerebral palsy (17). Examination of the skin, especially for evidence of neurocutaneous disorders, is particularly important. The most common neurocutaneous disorder is tuberous sclerosis, which typically has characteristic "ash leaf" spots (18). But neurofibromatosis, with its associated café au lait spots, and incontinentia pigmenti, characterized by swirling pigmented skin, also may be identified. Dysmorphic features might suggest Down syndrome or Miller–Dieker syndrome.

Magnetic Resonance Imaging

Neuroimaging has been a significant advancement in the last several decades in the diagnosis of the underlying etiologies of infantile spasms. A very extensive list of neurologic abnormalities can be seen on MRI scan, including cortical dysplasia, porencephalic cyst, and evidence of brain injury events, such as hypoxic ischemic encephalopathy, trauma, or infection.

Metabolic Workup

If examinations and imaging are unrevealing, then—and only then—should the patient have a metabolic workup. More than 50 genetic/metabolic diseases have been associated with infantile spasms (19). A good first step is to administer 100-mg pyridoxine intravenously to identify pyridoxine-dependent seizure

disorder. If that is unsuccessful, then routine blood work, looking especially for an anion gap, urine for organic acids, serum for amino acids, lactate, pyruvate, and ammonia, should be performed. A lumbar puncture to assess for glucose, amino acids (specifically for glycine, since hyperglycinemia may be detected only in CSF (20)), as well as evidence of infection may be revealing. If, at the conclusion of the history, EEG, MRI, and metabolic testing, no etiology has been identified, the patient then appropriately is labeled cryptogenic.

Treatment

The treatment plan is influenced by the answers to two questions. First, is there an etiologic diagnosis that lends itself to specific therapy? Second, what is the potential for normal or much improved developmental outcome? Appropriate long-term developmental goals should be defined prior to initiation of therapy. Unlike treatment of other seizure types, there is only one goal for treatment of infantile spasms: the complete control of spasms. If spasms cannot be controlled, the child is unlikely to do well developmentally, and a 50% or 90% reduction does not provide for this possibility. Unfortunately, for many patients, the only goal that can be obtained is amelioration of seizures, because the underlying diagnosis precludes normal development (e.g., lissencephaly or status posthypoxic ischemic encephalopathy, with severe brain damage). Nevertheless, seizure control should still sought because it greatly improves the parents' life; however, expectations should be explained in advance. For other patients, there may be an opportunity to significantly improve the developmental outcome. The patients with the best prognosis are those with a cryptogenic etiology and possibly some patients with tuberous sclerosis or a localized cortical dysplasia.

Medical treatment options are somewhat different for infantile spasms than for other seizure types. There are two drugs with solid evidence of efficacy: ACTH and vigabatrin. Older medications, such as phenobarbital, carbamazepine, or phenytoin, are rarely helpful. There is growing evidence that some of the newer drugs, high-dose intravenous immunoglobulin, and the ketogenic diet may be effective. For patient with localizable brain abnormalities, cortical resection offers the possibility of seizure control if medications fail.

Adrenocorticotropic Hormone

In 1958, Sorel reported administering ACTH to seven patients, four of whom responded within a few days and only one of whom had no response at all (21). Despite nearly a half century of use, there is no agreement about dose or duration of treatment. Dosing ranges from 0.2 IU/kg/day (22) to 150 IU/m^2 (23). However, the very low doses are not really comparable with the higher ones, as most of the very low-dose studies were performed in Japan where they used synthetic ACTH, which requires a much lower dose (~1:40) compared with the natural product available in the United States. A commonly used ACTH dose is 40 IU/day. Riikonen reviewed seven studies and could not verify a better response using 150 IU/day compared with 40 IU/day (24). The overall long-term response rate is 53 to 91 percent. A frequently used approach is to begin with 40 IU/day for 1 to 2 weeks. If there is an incomplete response, the ACTH may be increased to 60 IU/day or even to 80 U/day. If ACTH is successful in completely controlling the spasms and the hypsarrhythmia disappears from the EEG, then the ACTH is tapered over 1 to 4 months. If ACTH has not been successful, it should be rapidly tapered, discontinued, and another medication should be tried.

ACTH side effects are significant. The majority of children will develop cushingoid obesity and become very irritable. More serious side effects may develop, including arterial hypertension, electrolyte imbalance, gastric ulcer, growth retardation, cardiomyopathy, and immunosuppression. In one study, the risk of serious side effects with ACTH was 43% in the children treated with 160 IU/day (25) but lower in children treated with lower doses. By keeping the dose as low as efficacy allows and the duration as short as possible, morbidity and mortality can be minimized. Patients receiving ACTH should be comedicated with a proton pump inhibitor to prevent gastrointestinal bleeding and should have follow-up visits, with regular blood pressure measurements and blood workup for electrolytes.

Vigabatrin

In 1991, Chiron et al. reported that vigabatrin showed remarkable efficacy with infantile spasms (26). Sixty-eight medically refractory patients were treated with vigabatrin as add-on therapy, and 29 of them (43%) showed complete resolution of the spasms. The authors also noted that 12 of 14 patients who had tuberous sclerosis responded with complete control. Numerous other studies confirm the observations of Chiron and colleagues (27,28). Vigabatrin also may improve developmental outcome in patients with tuberous sclerosis (29). However, an important issue is how vigabatrin compares with ACTH. Vigevano et al. performed a randomized study of children with newly diagnosed infantile spasms. The patients were given either ACTH 10 IU/day or vigabatrin 100 to 150 mg/kg/day. Eleven of 23 vigabatrin patients responded (1 later relapsed) compared with 14 of 19 patients treated with ACTH (6 later relapsed). After relapses were taken into account, the long-term response rate was similar for the two groups (i.e., 10 of 23 with vigabatrin; 8 of 19 with ACTH) (30). ACTH was more effective for patients with perinatal hypoxic ischemic encephalopathy. There was no difference in the cryptogenic cases.

Vigabatrin generally is well tolerated in young children. There are reports of hypotonia, somnolence, or insomnia (26)—all of which would be expected from a drug that enhances GABA activity. Visual field constriction is the one serious side effect that substantially limits the use of vigabatrin. The visual loss is usually very subtle, so it took more than a decade to recognize the side effect (31). Since 1997, there have been numerous reports indicating that peripheral visual fields are constricted in 15 to 50 percent of adult patients. No one knows if visual field constriction occurs in very young children because there is no effective method of testing for it. However, given the catastrophic nature of infantile spasms, even if it is proven to occur in infants, visual field constriction may be an acceptable side effect to trade for seizure control and an improved opportunity for normal development (32). Thus, the visual field issue notwithstanding, many pediatric epileptologists consider vigabatrin to be the drug of choice for children with infantile spasms that are due to tuberous sclerosis and for other conditions as well.

Pyridoxine

Pyridoxine (vitamin B6) dependency is a very rare cause of infantile spasms. A trial of 100-mg pyridoxine given intravenously should be administered if diagnosis remains in doubt after the history, examination, and MRI scan have been performed (33). An immediate normalization of the EEG suggests pyridoxine-dependent epilepsy. However, chronic oral administration of high doses of pyridoxine also may be effective for some patients who do not have pyridoxine-dependent seizures (34,35). In Japan, high-dose pyridoxine is considered the initial drug of choice by many pediatric neurologists (36), with reports that approximately 15% respond. While this response rate is clearly inferior to either ACTH or vigabatrin, pyridoxine is their first choice based on the safety profile. Side effects include loss of appetite, irritability, and vomiting—all of which are relatively common but modest compared with those associated with ACTH or vigabatrin. Pyridoxine has not found favor outside of Japan and a few other epilepsy centers. But, given the low risk associated with its use, it seems reasonable to give patients a 1 to 2 week trial of 100 to 400-mg pyridoxine before starting other medications.

Other Drug Therapies

If these "standard" medications fail, other therapies must be considered, including other AEDs. Valproic acid probably has the best anecdotal evidence of efficacy, but there have been no prospective randomized studies of efficacy for infantile spasms. Doses range from 20 mg/kg/day to 100 mg/kg/day (37–39). Although none of the reported patients developed liver failure, it nevertheless is a risk in children less than 2 years of age (40) and should be used with caution for children with infantile spasms—virtually all of whom are less than 2 years of age. Thus, the risk/benefit ratio should be determined.

One of the earliest nonsteroid treatments for infantile spasms were the benzodiazepines (41) but are only occasionally successful. Clonazepam and nitrazepam both have anecdotal evidence of efficacy (42,43). However, nitrazepam is associated with an increase in oral secretions and a higher incidence of aspiration and pneumonia, with several deaths reported in one series (44). Rintahaka et al. reported that the incidence of mortality with nitrazepam was 3.98 deaths per 100 patient years compared with 0.26 deaths per 100 patient years if the medication was discontinued (45). Thus, nitrazepam and possibly other benzodiazepines carry a significant risk of aspiration pneumonia and mortality and should be used with caution.

Several of the new anticonvulsants have some evidence of efficacy.

- **Zonisamide** has shown some promise as an effective therapy for infantile spasms, but there have been no controlled or comparison trials to date. The Japanese experience suggests that zonisamide may be effective in about a third of patients (46). A recent report indicated that 5 of 25 patients with infantile spasms had a complete clinical and electrographic response to zonisamide within 1 to 2 weeks, with doses ranging from 8 to 32 mg/kg/day (47). Zonisamide is generally well tolerated. If the 30% or greater efficacy rates hold up in controlled studies, zonisamide could become a first-line therapy.
- **Topiramate** was shown to be effective in 4 of 11 intractable infantile spasms patients in doses up to 25 mg/kg/day in a study by Glauser et al. (48). Mikaeloff et al. reported that topiramate reduced seizures in 43% of 14 infantile spasms patients, but 29% were made worse and none became seizure free (49).
- **Felbamate** was considered promising as a therapy for infantile spasms—with three of four medically intractable patients, in one study, responding to it as an add-on therapy (50)—until aplastic anemia was identified as a serious side effect of the drug. Now that it is clear that the aplastic anemia does not affect prepubertal patients, felbamate actually may be as safe as some of the more commonly used drugs and could be recommended if other medications have failed.
- **Lamotrigine** is another of the newer antiepileptic drugs with some anecdotal evidence of efficacy for infantile spasms, although there are no prospective controlled trials. One report of 3 patients who had failed vigabatrin and ACTH responded to lamotrigine in 1 dosage (51). The usual dose of lamotrigine is 6 to 10 mg/kg/day (52). The major side effect is rash, which is dependent

to some extent on how rapidly the dose is increased. The usual recommendation is to increase the dose slowly over 2 months to the minimum expected therapeutic dose. Given the severe nature of infantile spasms and the need to achieve control as soon as possible, taking 2 months to get to a therapeutic level obviously decreases the value of lamotrigine as a therapeutic option. However, if the lowest dose is effective, then lamotrigine becomes a drug to try when standard therapies have failed.

Nondrug Therapies

There are three nondrug therapies that should be considered as options when other therapies have failed: the ketogenic diet, high-dose intravenous immunoglobulin, and surgery.

The ketogenic diet is a decades-old therapy that has had a resurgence in popularity. Two recent retrospective reports of 40 children with infantile spasms indicate that the diet may control spasms in 20 to 35 percent of patients who are intractable to other therapies (53,54). In the past, there had been a question as to whether children less than 1 year of age could achieve and maintain ketosis. The recent reports indicate that young children can indeed achieve ketosis and may benefit from the diet. Most of the children tolerated the diet well, but there were adverse events, including renal stones, gastritis, hyperlipidemia, and gastroesophageal reflux.

High-dose intravenous immunoglobulin has been reported to be helpful in a variety of seizure disorders. Ariizumi et al. reported that all six children in their study who had cryptogenic infantile spasms achieved complete remission, but only one of five symptomatic patients responded (55). Intravenous immunoglobulin doses ranged from 100 to 200 mg/kg/dose administered every 2 to 3 weeks to 400 mg/kg/day for five consecutive days. Although the data are extremely limited, intravenous immunoglobulin could be considered a possible therapeutic option in patients who have failed other medical therapies, but the actual efficacy is unclear and the most appropriate dosing and duration have not been defined.

The final nondrug therapeutic option is cortical resection and should be considered for patients who have failed ACTH and Vigabatrin or both, and have evidence of localizable abnormalities, such as cortical dysplasia, porencephaly, or tuberous sclerosis. Not many years ago, infantile spasms was considered to be a generalized seizure disorder, and thus not surgically remediable. It has become clear in the last several years that in spite of the generalized nature of the seizures, an area of cortical abnormality can often be discovered and that its removal may lead to control of seizures (56,57) as well as possibly to improved developmental outcome (58,59). The majority of patients who have cortical resection have evidence of focal cortical abnormalities prior to surgical evaluation (60), and for these patients, surgery should be considered early in the course rather than waiting for months or years. Selecting the appropriate candidates for surgery is usually more difficult in infantile spasms than for other types of epilepsy because of the generalized nature of the EEG abnormalities. A careful review of the history (especially history of partial seizures that preceded or accompanied infantile spasms) and the presence of cortical disturbances on MRI scan and of localized EEG abnormalities that suggest a localized cortical defect, all should lead to referral to a pediatric epilepsy surgery center for further evaluation.

Prognosis

Infantile spasms is associated with a significant risk of mortality and morbidity. Riikonen has followed 214 infantile spasms patients for 20–35 years and has accumulated the best long-term follow-up studies of these patients (4,24). In her series, nearly one third of the patients died during the follow-up period, many in the first 3 years of life. Eight of the 24 patients who died by age 3 died of complications of therapy with ACTH. (Those who treat large numbers of infantile spasm patients do not see such a high mortality rate, which largely is due to improved medical capabilities.) Of the 147 surviving patients, 25 (17%) had a favorable developmental outcome with an IQ of 85 or greater. Eleven others were in the dull–normal range, with an IQ of 68–84. Thus, of the 214 patients diagnosed with infantile spasms, 31% died, 45% were retarded, but 24% had a reasonably favorable outcome. The outcome is dependent on two major factors. First and foremost is the underlying etiology. Some etiologies will lead to death or mental retardation, whether or not the patient developed infantile spasms. However, children with cryptogenic infantile spasms or infantile spasms that is due to remediable etiologies, such as focal cortical dysplasia, may have a normal or near normal developmental outcome if seizures are controlled. Thus, the goal of therapy is to achieve control as soon as possible, especially for children who may have the potential for normal intellectual development.

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