Infantile spasms[1]

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West's syndrome is an age-specific set of symptoms consisting of myoclonic epilepsy (infantile spasms), an interictal electroencephalographic pattern (hypsarrhythmia), and moderate-to-severe mental retardation. Infantile spasms were first reported in 1841, but all three characteristics were not described until 1951. The basic pathophysiology of and ideal therapy for the seizures remain undefined. The author reviews the historical aspects, clinical manifestations, etiology, diagnostic evaluation, and treatment of West's syndrome.

Index terms: Epilepsy, myoclonus · Mental retardation · Spasms, infantile

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In 1841, Dr. W. J. West gave the first clinical description of infantile spasms.[1] He described "a peculiar form of infantile convulsions" that affected his son. Through the next 100 years, an abundance of writings, mainly in European medical journals, described various aspects of infantile spasms, and a number of descriptive terms (salaam spasms, lightening fits, jack-knife convulsions, *Blitz-Nick-Salaam Krömpfe* [BNS], *encephalopathie myoclonique infantile avec hypsarythmie* [EMIH], and West's syndrome) were used to describe this malady. The three main characteristics of West's syndrome (myoclonic epilepsy [infantile spasms], an interictal electroencephalographic [EEG] pattern, and moderate to severe retardation) were not described fully until 1951.[2] The following year, Gibbs et al[3] further defined the interictal EEG pattern and coined the word

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"hypsarrhythmia." Sorel and Dusaucy-Bauloye[4] first reported successful treatment of infantile spasms with the adrenocorticotropic hormone (ACTH) in 1958. During the past 25 years, little pertinent data concerning the anatomic or physiologic basis of infantile spasms or an advance in treatment have appeared.

Clinical manifestations[5–10]

Infantile spasms occur at an estimated incidence of 1:4,000–6,000. The age of onset ranges from 24 hours to five years; however, the syndrome first develops between two and seven months old in 77% of all afflicted infants. Nearly 90% of all patients first experience seizures before their second birthday. Most studies report that 60% of the patients are boys. No racial or ethnic predominance seems evident. In addition, no clear familial tendency seems apparent; approximately 3%–6% of cases have been reported to occur in the same family.[10]

Seizure types

Three seizures types have been defined clinically. The *flexor spasms* consist of flexion of the neck, trunk, arms, and legs, and contraction of the abdominal muscles. The arms may either abduct or adduct. The *extensor spasms* are defined by predominant activity of the extensor muscles of the trunk and extremities. The *mixed spasms* consist of flexion of the upper trunk and extension of the legs; infrequently, the reverse may occur. Other seizure patterns, or *atypical spasms*, include head nodding, unilateral or focal myoclonic jerks of an extremity, and head or eye deviation. The same child usually experiences more than one seizure type, but the type has no correlation with other aspects of the syndrome.

Commonly associated features include a cry or scream, a change in facial expression, eyelid flutter, jerky eye movements, or autonomic symptoms. Contact with the environment is altered, but loss of consciousness does not clearly occur. The seizures are brief, lasting from one-half to 12 seconds, but occur in clusters which may continue for 30 minutes and often happen when the person is drowsy.

Etiology[11–16]

Multiple potential encephalopathic events or pathologic states have been implicated as associated with infantile spasms, but no specific etiology has been identified. Prenatal factors can include genetic disorders (tuberous sclerosis), developmental central nervous system anomalies (agenesis of the corpus callosum), or acquired intrauterine infections (cytomegalic inclusion disease). Perinatal factors most commonly include a hypoxic-ischemic event during delivery. Postnatal factors can include central nervous system infections, head trauma, or manifesting metabolic disease. If an associated condition can be identified, infantile spasms are classified as "symptomatic." This is the case in approximately 60% of all patients.

The most commonly identified single factor in most studies is hypoxic-ischemic encephalopathy. Tuberous sclerosis has been reported in nearly 10% of cases. Since characteristic physical findings or computed-tomographic (CT) scan observations are often lacking, tuberous sclerosis may, in fact, be an even more frequent cause. Aminoacidurias (i.e., phenylketonuria, histidinemia,[13] and hyperonithinemia) have been mentioned rarely in case reports of infantile spasms, but should be considered. Intrauterine TORCH infections (toxoplasmosis, rubella, cytomegalic inclusion disease, and herpes), particularly cytomegalic inclusion disease, may be more common than initially suspected. Pyridoxine dependency or congenital brain tumors have also been reported in isolated instances.[14,15]

The role of immunizations,[16] more specifically pertussis, in the cause of infantile spasms deserves specific comment. An association was first suggested in 1957 and has been repeatedly suggested through the years by various authors. Yet, such an association is difficult to prove statistically because the age for receiving immunizations and the onset of infantile spasms coincide.

When a causative factor cannot be determined (40% of the cases), infantile spasms are labeled "idiopathic." Children who have developed normally prior to the onset of the spasms and have no associated or identified etiologic factors have been identified as having "cryptogenic" infantile spasms. A favorable prognosis is implied by this designation.

Diagnostic evaluation

History/physical: The child commonly presents with a history of developmental regression and irritability. Results of the general examination, such as the identification of the hypopigmented spots of tuberous sclerosis, may be more useful than the results of the neurologic examination, which in 70% of all cases are abnormal, when attempting to establish the cause of infan-

tile spasms. General findings often include alterations in muscle tone (spasticity, hypotonia, or athetosis), microcephaly, or macrocephaly. When searching for hypopigmented spots, a Wood's lamp should always be used.

Tests: The EEG is the most important test used to help substantiate a diagnosis of infantile spasms.[17] The interictal pattern (hypsarrhythmia), defined as a chaotic, continuous, slow wave and spike characteristic, is of greater diagnostic significance than the ictal pattern. The amplitude is always greater than 200 μV and can exceed 1,000 μV (1 mV). The slow waves vary from 0.75 to 3.00 cycles per second. The spikes are irregular and differ in size and location. At times, there may be a rhythmicity to the pattern that alternates with normal background activity. This has been called "modified hypsarrhythmia" and has the same diagnostic significance as the more classic pattern.The EEG may be more abnormal during sleep; in fact, the abnormalities may only be present at that time. Only 50%–60% of the initial EEGs, if obtained shortly after the onset of infantile spasms, show hypsarrhythmia, although the pattern is usually present on repeat EEGs. The interictal pattern usually resolves with time and rarely occurs after a patient is more than four years old. The presence of hypsarrhythmia is not required for the diagnosis of infantile spasms. Focal or multifocal spike and wave discharges may occur. Between 1%–8% of afflicted children reportedly have normal EEGs.

The common ictal pattern is a high-amplitude spike, sharp wave, or slow wave followed by low-amplitude background activity with paroxysmal 14–20-cycle-per-second fast activity. A polyspike and slow wave or suppression of the background activity may also be evident.

A CT scan should be obtained initially in all cases.[18–22] An abnormal scan has been reported in approximately 70% of cases and indicates that a child does not have cryptogenic infantile spasms. Cerebral atrophy (49%), congenital anomalies (18%), and hydrocephalus (6%) have also been detected. The CT scan should be obtained early in the course of these spasms because enlarged ventricles and an expanded subarachnoid space may occur during ACTH or steroid therapy, but reverse with the discontinuance of this therapy. These changes may be due to an alteration of brain fluid.

With the onset of seizures, pyridoxine (100 mg, administered intramuscularly) should be given along with EEG monitoring. If pyridoxine is effective, clinical symptoms should subside and brain-wave improvement should occur soon. Serum amino-acid and blood glucose levels should be determined along with calcium, magnesium, electrolytes, and liver function, and cerebrospinal fluid should be obtained. Occasionally, lysosomal-enzyme evaluation should be done if a neurodegenerative syndrome is suspected.

Differential diagnosis

The differential diagnosis takes into account conditions which can resemble infantile spasms (e.g., colic, an accentuated startle reflex, or patient irritability) and the various causes of symptomatic infantile spasms as mentioned previously. If the child *is* having myoclonic seizures, infantile spasms must be differentiated from other myoclonic-associated neurodegenerative disorders and benign infantile myoclonus of early infancy.[23] This latter disorder can clinically resemble West's syndrome initially. The myoclonic jerks are quite similar to infantile spasms, but head and neck movements predominate. The age of onset is similar, however. The EEG remains normal. No regression or slowed development is apparent.

Natural history[24,25]

Prior to the onset of infantile spasms, approximately 30% of the patients will have a history of a seizure disorder, and 80% will have no delay in development. With the onset of infantile spasms, previously developed mental capabilities regress noticeably. Generally, the number of seizures increases and then a plateau is reached. Eventually, even without specific treatment, the seizures tend to become less frequent and less severe. In 1961, Jeavons and Bower[24] reported a series of 30 patients who did not receive ACTH or steroid therapy. These patients were followed for between three and six years. One third of the patients no longer had infantile spasms 36 months after the onset of symptoms; two thirds of the patients no longer had infantile spasms 42 months after the onset of symptoms. Other seizure types eventually developed in one sixth of the patients. An improved EEG correlated with the clinical picture. By 36 months after the onset of seizures, a normal EEG was obtained in one third of the cases. Hypsarrhythmia was persistent in three cases. Other abnormal epileptic patterns developed in the remaining patients. Focal abnormalities tended to develop on the EEG over

time in those children who continued to have seizures.

Treatment[26–38]

In 1841, West treated his children with calomel purgatives, gum lancing, and leeches. In the early 1950s, several of the tetracycline antibiotics[26] and pyridoxine were reported to be effective. In the 1950s, Livingston et al[27] reported that seizures were controlled in 50% of their patients on the ketogenic diet; patient compliance was a problem, however.

The earliest form of drug treatment that was clinically effective was corticotropin therapy; a rapid improvement in clinical seizure activity, corresponding normalization of the EEG, and an improved outlook for normal intelligence were reported.[4] Since this initial report, abundant documentation showing the effectiveness of hormonal therapy has been published. Improved patient intellect, however, has not been generally observed. The agent of choice, optimum dosage, and duration of therapy have not been determined.

Recently, ACTH therapy has been recommended and has become the standard treatment for infantile spasms. Effective ACTH doses have varied from 5 to 180 units. Twice daily, daily, and every-other-day dosage schedules are advocated. The differences in effectiveness and side-effect incidence between the natural and the synthetic ACTH preparations have not been clearly established. Duration of therapy has varied between two weeks and 18 months. Most studies have reported striking clinical and EEG improvement with hormone therapy. After three weeks of treatment, ACTH therapy has resulted in clinical improvement with a close EEG correlation.[30] In general, the results have been excellent for 70%–90% of patients. Yet, relapses are frequent (as much as 30% of the patients), and accurate interpretation of treatment efficacy is difficult because the methods of patient evaluation are variable and uncontrolled. Recently, ACTH fragments (ACTH 1–24)[31] have been used to treat infantile spasms; significant benefits have not resulted. The reasons for ACTH effectiveness remain unknown. Speculations include correction of an enzymatic process, changes in intracellular-extracellular electrolyte ratios, an anti-inflammatory action, and changes in intracellular glucose concentrations. Therapeutic response has not correlated with serum cortisol levels which have shown similar elevations to 12–100 times the baseline values with an ACTH dosage of 20–40 units per day. Recently, a direct neuronal, extra-adrenal effect of ACTH peptides has been proposed. Significant side effects[32] from ACTH are usually infrequent; however, severe complications and even fatalities have occurred. Approximately 30%–40% of all patients may experience sepsis, pneumonia with uncommon organisms (*Pneumocystis carinii*), urinary tract infections, hypertension, osteoporosis, electrolyte disturbances (hypokalemia alkalosis), hyperglycemia, and central nervous system hemorrhage. Other side effects have included hirsutism, acne, cutaneous pigmentation, cushingoidism, seborrheic dermatitis, and irritability. Rapid withdrawal of ACTH therapy has been associated with renal failure secondary to suppression of the renin-angiotensin-aldosterone axis with hypo-osmolar contraction of the intracellular volume.

Oral steroid preparations (prednisolone [2 mg/kg], prednisone [2 mg/kg], hydrocortisone [1–3 mg/kg], and dexamethasone [0.3 mg/kg]) have been reported to have equal, or even superior, effectiveness when compared with ACTH.[33–35] Some therapy protocols have used ACTH followed by ingestion of these preparations. More recent studies have shown oral steroids to be less effective when compared to ACTH.[36]

Treatment with anticonvulsant drugs[37,38] has not been as dramatically beneficial as ACTH. Excluding recent reports of improvement with the benzodiazepines and valproic acid, treatment with the standard anticonvulsants has not significantly modified infantile spasms. The most effective anticonvulsant has been nitrazepam (Mogadon), with approximately 60% of the infantile spasms showing significant improvement (1–3 mg/kg/24 hrs). Sedation and drooling have been the major side effects. Clonazepam (Clonopin) has also been effective, but similar side effects have been more prevalent. Diazepam (Valium) has been evaluated less than other benzodiazepines. Valproic acid (Depakene), in limited studies, has been reported to be effective; however, because of potential hepatotoxicity, it should be used with extreme caution in the child who is less than two years old.

Prognosis[39–43]

Despite the 90% initial seizure and improved EEG response to ACTH, the long-term prognosis for infantile spasms remains grim. With discon-

tinuance of ACTH, nearly 30% of these children experience infantile spasms again. Nearly 65% of all afflicted children experience other seizure types later in life (usually partial seizures or generalized clonic seizures and less often minor motor seizures with slow spike and wave EEG [Lennox-Gastaut syndrome]). Eighty per cent are significantly retarded mentally. The cumulative mortality rate is high; nearly 20% of these children die, mostly due to infections (e.g., aspiration pneumonia) that develop before they are five years old.

The etiology of infantile spasms has not been a significant prognostic determinant. The condition of those with idiopathic (including cryptogenic) and symptomatic spasms has been poor. The condition of those with malformations or infections of the central nervous system or tuberous sclerosis has been worse. No clearly favorable factors have been defined, although an interval of less than one month from the onset of infantile spasms to initiation of treatment is important. Other positive signs include idiopathic (cryptogenic) infantile spasms with normal development prior to the onset of seizures, absence of other seizure types, and a prompt response to ACTH therapy.

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