The Physician’s Guide to
Infantile Spasms

Visit website at: nordphysicianguides.org/Infantile-Spasms
Introduction

Welcome to the NORD Physician Guide to Infantile Spasms by Cristina Y. Go, MD, and O. Carter Snead III, MD, FAAN.

The authors are members of the Department of Neurology, Hospital for Sick Children, Toronto, Canada.

Infantile spasms is a catastrophic epilepsy syndrome with onset in the first year of life. Prompt diagnosis and urgent treatment of affected children can improve their long-term outcomes.

Publication of this guide was made possible by fundraising conducted by 13-year-old Jacob Maren, who experienced infantile spasms during the first year of his life and benefited from prompt diagnosis. (See acknowledgements for additional information.)

The NORD Guide to Infantile Spasms is part of a series sponsored by the National Organization for Rare Disorders and written by physicians for physicians to promote early diagnosis and appropriate treatment for individuals affected by rare diseases. NORD is a nonprofit organization, established in 1983, which provides programs of education, advocacy, patient services and research.

NORD is grateful to Jacob Maren and his family, the authors, and the American Academy of Neurology for helping make this guide possible.

What are Infantile Spasms?

Infantile spasms is a catastrophic, age-specific epilepsy syndrome that has its onset within the first 12 months of life. This disorder is characterized clinically by epileptic spasms which consist of massive myoclonic jerks of the body, which can be extensor or flexor (or both) in nature. Infantile spasms often are accompanied by developmental regression and a characteristic interictal electroencephalogram (EEG) pattern known as hypsarrhythmia. When all three features are present, the term "West syndrome" is
commonly used. The syndrome is considered to be catastrophic because of the frequent sequelae of global neurodevelopmental delay, significant intellectual disability, and medically refractory epilepsy. In most cases, the initial age of onset is between 3 and 7 months of age, and over 90% of cases begin before 12 months of life. The incidence of infantile spasms is 2 to 3 per 10,000 live births,²³ with a lifetime prevalence of 1.5 to 2 per 10,000 children.⁴ It is slightly more common in males, accounting for about 60% of cases, and a family history exists in 3% to 6% of cases.⁴⁵

Infantile spasms was originally classified as a generalized epilepsy according to the 1989 International Epilepsy Classification.⁶ However, using the revised classification based on the 2001 International League Against Epilepsy (ILAE) report, this epileptic syndrome can be classified as: Level I (ictal phenomenology): clinical spasms, flexor, extensor, mixed or subtle; Level II (epilepsy seizure type): epileptic spasms; Level III (epilepsy syndrome): infantile spasm syndrome.⁷

**Causes**

Infantile spasms may be classified into three groups: symptomatic, cryptogenic, and idiopathic. The term symptomatic is used to describe cases in which there are structural brain abnormalities or metabolic causes seen in a child with preexisting developmental delay. When there are no apparent causes identified in a child with developmental delay or some other neurologic impairment before the onset of spasms, the term cryptogenic infantile spasms is used. Idiopathic infantile spasms are those in which the child is developmentally normal, with a normal neurologic exam prior to onset of infantile spasms.⁸

Cryptogenic cases constitute up to 15% of infantile spasms cases. The number of symptomatic cases has increased over the years due to advancement in neuroimaging technology, better metabolic testing, and the availability of genetic testing.⁸

Symptomatic cases are further subdivided into prenatal, perinatal, and postnatal, depending on the timing of presumed causes. There are numerous disorders associated with symptomatic infantile spasms, but major categories include chromosomal abnormalities and genetic syndromes, disorders of cortical development, infections, metabolic conditions and vitamin deficiencies, trauma, vascular insults, and tumors. Tuberous sclerosis (TS) is a major symptomatic cause of infantile spasms,
with up to 50% of patients with TS presenting with infantile spasms between 4 and 6 months of age. Several gene mutations that have been associated with infantile spasms include ARX, CDKL5, FOXG1, GRIN1, GRIN2A, MAGI2, MEF2C, SLC25A22, SPTAN1, and STXBP1. Children with these genetic disorders were formerly classified as cryptogenic or idiopathic. Classification of cases into these two categories will continue to dwindle as more and more genetic causes of infantile spasms are revealed by more sophisticated genetic screening. In fact, new insights into molecular genetic testing imply that all forms of infantile spasms may actually be symptomatic, and the ILAE has recently recommended replacing the symptomatic, cryptogenic, and idiopathic classification system of epilepsy syndromes. However, most studies on treatment and long-term outcomes of infantile spasms subdivide cases into either symptomatic or cryptogenic, and these studies do point to the etiology as a contributing factor for long-term neurodevelopmental outcomes.8

Symptoms and Signs
Clinically, the spasms appear in clusters and are characterized by brief, sudden contractions of the axial musculature. The clusters may occur several times daily, with up to 100 spasms per day. They appear to be temporally related to sleep, tending to occur as the infant falls asleep or awakens. Depending on the muscle groups involved, the spasms can be further subdivided into flexor, extensor, or mixed. The type of spasms may also be influenced by the position of the body at the time the spasms occur.

In flexor spasms, the infant appears to be in a self-hugging posture with sudden adduction of the arms. The abdominal muscles may be involved, with the infant bending at the waist; the term jackknife seizure is sometimes used for this manifestation. The combination of jackknife seizure plus adduction of the arms with or without neck flexion is called salaam seizures.

Extensor spasms look similar to an exaggerated Moro reflex. Mixed spasms are a combination of flexion of the neck, trunk, and arms, with leg extension. In some cases, the spasms may be subtle, manifesting as head nods and clusters of wide eye opening with eye deviation.

The etiology of infantile spasms does not point to the clinical semiology, or appearance, of the spasms; however, the presence of asymmetry may indicate focal cortical pathology as a cause.

Developmental regression is almost always seen at the onset of infantile
spasms, with decreased visual alertness often being the first symptom. The vast majority of children develop significant cognitive impairment when followed long-term. In many cases, the spasms evolve into other types of medically refractory epilepsy as the children grow older.

**Diagnosis**

Because of the critical importance of early treatment, children presenting with infantile spasms require prompt and comprehensive diagnostic evaluation. This includes a complete history, physical and neurologic examination, and an urgently obtained EEG. The latter is critical because the ultimate diagnosis of infantile spasms is made by the clinical history coupled with the EEG findings.

**EEG:**

The characteristic interictal EEG pattern associated with infantile spasms is hypsarrhythmia, which consists of a disorganized and asynchronous high-amplitude background with spikes and slow waves. This pattern can be seen in wakefulness and is enhanced during sleep. Therefore, an EEG study to rule out infantile spasms should ideally include both awake and sleep recording. Another common EEG pattern associated with infantile spasms is the electrodecremental response or burst suppression, which is a high-voltage sharp or slow-wave discharge followed by generalized voltage attenuation or flattening. In addition to hypsarrhythmia and burst suppression, there are several additional, less dramatic ictal EEG patterns associated with infantile spasms, including combinations of generalized sharp and slow-wave discharges and electrodecremental fast activity. The combination of asymmetric spasms and asymmetric hypsarrhythmia pattern strongly suggests the presence of a focal brain lesion. It is important to emphasize that all of these abnormal EEG patterns represent a dynamic continuum that can occur at any point along the natural history of infantile spasms. Therefore, an EEG diagnosis of hypsarrhythmia is not required for diagnosing infantile spasms and initiating treatment. Any child with the clinical semiology of spasms as described previously and who has any epileptiform activities on his or her EEG, be it hypsarrhythmia or some other paroxysmal abnormality, merits urgent treatment of the spasms, as described next. Conversely, if the child appears to be having spasms by history but results from a waking and sleeping EEG are normal, the child does not have infantile spasms but rather could be experiencing a benign infantile myoclonus.
When a diagnosis of infantile spasms is made by the clinical history and an EEG, an extensive search for the etiology should be undertaken.

**Neuroimaging studies:**

Computerized tomographic (CT) brain scans are not indicated in the diagnostic evaluation of infantile spasms. CT is relatively insensitive to the majority of structural causes of infantile spasms and serves only to expose the child to unnecessary radiation exposure. In comparison with CT, magnetic resonance imaging (MRI) is a more sensitive study to detect lesions, including abnormal myelination, metabolic abnormalities, and neuronal migrational anomalies. As well, MR spectroscopy can help point to a possible metabolic or mitochondrial cause. However, it is important to note that MRI performed in a child less than 2 years of age can still miss subtle cortical migrational anomalies due to immaturity of the white matter. Therefore, a child who has spasms in addition to other neurodevelopmental abnormalities, but a normal MRI scan in the first year of life, should have a repeat MRI at 2 years of age or older. Interictal positron emission tomography (PET) may detect areas of hypometabolism, which may correlate with cortical malformation. PET is not used in the routine diagnostic evaluation of infantile spasms; however, PET may be valuable in a child with spasms for whom the MRI is normal but a structural brain lesion is suggested by the asymmetry of spasms and a focally abnormal EEG pattern.

**Laboratory tests:**

Blood and urine tests are performed for detecting a potential genetic, metabolic, or infectious etiology that can cause symptomatic infantile spasms. These tests also provide baseline results before initiation of treatment.

Blood tests should include but not be limited to complete blood and differential count; tests of glucose, electrolyte, pH, lactate, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine transaminase, bilirubin, and alkaline phosphatase levels; test of thyroid function; and screens of serum amino acid, toxoplasma, and cytomegalovirus IgG and IgM or polymerase chain reaction (or both).

Urine tests should include urinalysis and amino acid and organic acid screens.

Electrocardiogram (ECG) and chest x-ray should be performed, especially when cardiac examination is abnormal. Consultations with ophthalmology, cardiology, and genetics can also be requested as needed.
Chromosomal studies with microarray and genetic tests for infantile epileptic encephalopathies may be indicated when there is a family history or when the above-listed blood, urine, and neuroimaging tests are negative.

**Treatment**

There is considerable variation in the management of infantile spasms, as evidenced by the US Consensus Report and a recent survey done on the current evaluation and treatment of infantile spasms among members of the Child Neurology Society (CNS).⁹,¹⁰ According to these sources, most neurologists use adrenocorticotropic hormone (ACTH) as their preferred first-line treatment for infantile spasms not caused by TS and vigabatrin (VGB) as the first-line treatment of infantile spasms caused by TS.⁹,¹⁰

The 2004 American Academy of Neurology (AAN) and CNS practice parameter on the medical treatment of infantile spasms concluded that ACTH is probably effective for the short-term treatment of infantile spasms and that VGB is possibly effective for the short-term treatment of infantile spasms and for treatment of children with TS.¹¹

A 2012 AAN evidence-based guideline, which updated the 2004 parameter, reported that ACTH or VGB may be useful for short-term treatment of infantile spasms, with ACTH being more effective than VGB, excluding cases with TS.¹²

According to the 2012 guideline, there is insufficient evidence to determine whether other forms of corticosteroids are as effective as ACTH.¹² There is also insufficient evidence to recommend other agents or combination therapy as being effective in the short-term therapy of infantile spasms.¹²

**Adrenocorticotropic hormone**

ACTH is given as an intramuscular injection, and different epilepsy centers show considerable variability in dosage (high vs low), formulation (natural ACTH in the United States vs synthetic ACTH in Canada, Japan, and Europe), and duration of therapy. Side effects are common and include hypertension (up to 37%), irritability (37%–100%), infection (14%), and cerebral atrophy (62%). Higher dosage and longer duration of treatment correlate with higher incidence of side effects.

Questions regarding the optimal dose, formulation, and duration of ACTH treatment remain, although the 2012 updated guideline reported that
low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms.\textsuperscript{12}

**Vigabatrin**

VGB has been used in Europe since the late 1980s and in Canada since 1994 and was approved by the US Food and Drug Administration (FDA) in August 2009. VGB causes retinal toxicity in about one-third of patients. This has led to an FDA black box warning for potential permanent visual impairment in the United States where VGB currently is available only through the Lundbeck Inc. restricted Support, Help and Resources for Epilepsy (SHARE) program. The VGB-induced retinal toxicity results in visual field constriction. The risk of this complication of VGB appears to be lower with short-term use of VGB. In children with infantile spasms being treated with VGB, the risk of retinal toxicity begins to increase after 6 months of chronic administration.

Baseline visual field testing or, in the case of infants, electroretinography (ERG), should be done before initiation of treatment and regularly thereafter to monitor for retinal toxicity. The initial dose of VGB is 50 mg/kg which is rapidly titrated up to 150 mg/kg divided twice a day. In order to minimize the risk of retinal toxicity, VGB should be given for no longer than 6 months.

**Other agents**

Other medical treatments that have been used in infantile spasms include zonisamide, topiramate, valproic acid, nitrazepam, levetiracetam, pyridoxine, sulthiame, ketogenic diet, intravenous immunoglobulin, and combination therapy with ACTH and magnesium sulfate. However, the 2012 updated guideline concluded that the evidence is insufficient to recommend therapies other than ACTH and VGB for the short-term treatment of infantile spasms.\textsuperscript{12}

**Prognosis**

The spontaneous remission rate of infantile spasms in limited natural history studies is 30%. Although clinical spasms and the typical EEG pattern disappear by 3 to 4 years of age, up to 60% of children with infantile spasms go on to develop other types of seizures. The long-term prognosis for infantile spasms in terms of neurodevelopmental outcomes and development of other types of seizures remains dismal, although most studies reported better neurodevelopmental outcomes in idiopathic or cryptogenic cases.
The United Kingdom Infantile Spasms Study reported on the long-term outcomes of 77 patients with infantile spasms at 4 years and noted that whereas there was no significant difference between patients treated with either hormonal therapy or VGB in outcomes for either neurodevelopmental delay or epilepsy, those patients with cryptogenic infantile spasms who received hormonal therapy had higher mean Vineland Adaptive Behavioral Scale (VABS) scores. Also, a 3.9-point decrease in mean VABS score was observed for each increase in category of lead-time duration after controlling for the effects of treatment and etiology.

The 2012 updated guideline recommended a shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB to possibly improve long-term developmental outcomes.

These data emphasize the importance of prompt diagnosis and urgent treatment of children with infantile spasms to improve their long-term outcomes.

**Investigative Therapies**

Information on current clinical trials is posted at www.clinicaltrials.gov

All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

*NORD does not endorse or recommend any particular studies.*
References


Resources

Child Neurology Foundation
2000 West 98th Street
Bloomington, MN 55431 USA
Telephone: (952) 641-6100 or (877) 263-5430
E-mail: jstone@childneurologyfoundation.org
Web: http://www.childneurologyfoundation.org
http://www.infantilespasmsinfo.org/

Epilepsy Foundation
8301 Professional Place
Landover, MD 20785-7223
Telephone: (866) 330-2718 or (800) 332-1000
E-mail: ContactUs@efa.org
Web: http://www.epilepsyfoundation.org

Intractable Childhood Epilepsy Alliance (ICE)
PO Box 365
250 Lewisville-Vienna Road
Lewisville, NC 27023
Telephone: (336) 918-9440
Web: http://www.icepilepsy.org

Tuberous Sclerosis Alliance
801 Roeder Road Suite 750
Silver Spring, MD 20910 US
Telephone: (301) 562-9890 or (800) 225-6872
E-mail: info@tsalliance.org
Web: http://www.tsalliance.org
American Academy of Neurology (AAN)
201 Chicago Avenue
Minneapolis, MN 55415
Telephone: (800) 879-1960
E-mail: memberservices@aan.com
Web: http://www.aan.com

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
Telephone: (203) 744-0100 or (800) 999-NORD
E-mail: orphan@rarediseases.org
Web: http://www.rarediseases.org

Clinical Centers and Medical Experts

View the Child Neurology Foundation’s Treatment Center Directory:

http://www.infantilespasmsinfo.org/Hospitals.php
Acknowledgements

Jacob Maren is a fourteen year old high school freshman. He is a musician -- he plays the piano, guitar, and ukelele, and sings in several rock bands. He is also a budding filmmaker, having made several short films, and scored them. He lives with his parents and two dogs in Litchfield County, Connecticut.

When Jacob was six months old, he was diagnosed with Infantile Spasms. Both he and his parents are enormously grateful that he received early treatment, and was left unscathed. When Jacob turned thirteen, he decided to try to raise money to promote awareness about Infantile Spasms. He contacted NORD. He and his father produced a music video, and he launched an online fundraising campaign to make possible the development of this guide.

NORD is grateful to Jacob, the American Academy of Neurology and the following physicians for making this guide possible:

**Cristina Y. Go, MD**
Paediatric Epilepsy Fellowship Training Co-director
The Hospital for Sick Children
Toronto, Canada

**O. Carter Snead III, MD, FAAN**
Division Head, Neurology
The Hospital for Sick Children
Toronto, Canada
NORD is grateful to the American Academy of Neurology and the following physicians for writing this guide:

Cristina Y. Go, MD
Paediatric Epilepsy Fellowship Training Co-director
The Hospital for Sick Children
Toronto, Canada

O. Carter Snead III, MD, FAAN
Division Head, Neurology
The Hospital for Sick Children
Toronto, Canada

This NORD Physician Guide was made possible by Jacob Maren and his family
These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from www.NORDPhysicianGuides.org.