PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Infantile Spasms.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Infantile Spasms

Developed by Dr. Talia Lenton-Brym, Dr. Laura Betcherman and Dr. Robyn Whitney for PedsCases.com.
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Introduction

Hello, my name is Talia, and my name is Laura, and we are second year pediatrics residents at SickKids in Toronto. This podcast was developed under the guidance of Dr. Robyn Whitney, a Pediatric Neurologist at The Hospital for Sick Children. Today, we will be discussing infantile spasms.

One night in the Emergency Department, I saw a 10-month-old boy, whose parents were concerned about abnormal movements. He had been born at term to a healthy, first-time mom. He could crawl and pull to stand. He babbled and could say 'dada'. He was described as an easy baby who was social and interactive. Over the last month, however, he had had progressive difficulty with sitting and standing, and was not grabbing objects as well as previously. He was preferentially using his right hand. He had multiple clusters each day of a series of brief, jerking movements after which he would burst into tears.

The **objectives** of this PedsCases podcast are to:

1. Explain how to identify Infantile Spasms and differentiate it from mimickers
2. Describe the clinical presentation of infantile spasms
3. Explore possible causes of infantile spasms, and to
4. Discuss diagnosis and management of infantile spasms.

Let's get started with defining infantile spasms. You may have heard of West syndrome. West syndrome was actually first described by Dr. William West in 1841 in his son, in a letter to the Lancet! Although often used synonymously with infantile spasms, West syndrome actually refers to the triad of (1) infantile spasms, (2) hypsarrhythmia on EEG, and (3) neurodevelopmental arrest or regression. Infantile spasm should be used only to describe the spasms themselves. Infantile spasms have an incidence of 1/2000-4000 live births. There is a positive family history in 3-6% of cases of infantile spasms and some studies report a male predominance. West Syndrome is an example of an infantile epileptic encephalopathy. The term epileptic

encephalopathy is used when the epileptic activity itself contributes to cognitive stagnation or deterioration of the child.

Clinical presentation

Over 90% of cases of infantile spasms appear in the first year of life, with a usual onset between 4-12 months of age and a peak at 6 months. Infants who present with spasms may have previously been developmentally normal or delayed. They may have begun to experience developmental regression, in particular axial hypotonia, loss of hand grasp, and visual and social inattention, such as lack of eye contact, decreased social engagement, and less smiling. The spasms themselves consist of muscular contractions lasting 1-2 seconds. There are 3 main types of spasms: flexor, extensor, and mixed extensor-flexor. The spasms vary in intensity, from massive contraction of multiple muscle groups, resulting in the classic 'jackknifing' at the waist, to more subtle, mild contractions of isolated muscle groups, such as ocular spasms or head drops. They are usually, but not always, symmetric. Asymmetric spasms may indicate cortical brain pathology such as a stroke or a focal cortical malformation. Many infants have more than 1 type of spasm, and they can evolve with time. They may rarely experience autonomic symptoms with the spasms, including flushing, sweating, or increased heart rate or respiratory rate.

The spasms typically occur in clusters, with each cluster lasting a couple of minutes, and many clusters occurring each day. They do not usually occur during sleep, but often occur on arousal from sleep. Remember this point, which we will come back to later.

Afterwards, children may have increased irritability or crying.

There are no clear triggers of spasms. Precipitating factors, such as handling, loud noises, fever, or excitement, have been described, however these reports are mostly anecdotal and have not been confirmed in studies using video EEG.

Classification

The classification of infantile spasms has been historically divided into 3 categories: symptomatic, cryptogenic, or idiopathic. The majority are classified as symptomatic, meaning that an etiology has been identified. Symptomatic infantile spasms are diagnosed in a child with a pre-existing neurologic abnormality, such as when the spasms occur due to either a structural brain abnormality like stroke, hypoxic ischemic encephalopathy, or due to an underlying genetic or metabolic cause, such as an inborn error of metabolism.

Cryptogenic infantile spasms are diagnosed when no apparent cause is identified, but is suspected because the child has pre-existing delay or neurological impairment prior to the onset of spasms. This category represents 10-15% of cases.

Finally, the idiopathic classification refers to spasms with no identifiable cause, in a previously developmentally normal child with a normal neurologic exam before the onset of spasms.

Q: Dr. Whitney, does the etiology of infantile spasms impact outcomes?
A: Generally, infants with idiopathic infantile spasms who are developmentally appropriate before the onset of spasms have a better prognosis compared to symptomatic and cryptogenic cases. Idiopathic has the best prognosis, followed by cryptogenic, and then symptomatic. However, all children who develop spasms are at risk of developmental delay and developing other types of seizures regardless of the etiology.

Etiology

There are several different causes of infantile spasms and these include genetic etiologies including down syndrome and tuberous sclerosis, structural etiologies such as stroke, malformations of cortical development, tumors, and trauma, metabolic etiologies particularly neonatal hypoglycemia and inborn errors of metabolism, infectious etiologies such as post-meningitis, congenital infections or encephalitis and unknown etiologies.

The association of infantile spasms with tuberous sclerosis is important to be aware of, because up to half of patients with tuberous sclerosis will present with infantile spasms.

Although many hypotheses have been put forward, the underlying pathophysiology of infantile spasms is still largely unknown.

Diagnosis

When you are concerned about a child having infantile spasms, an urgent and comprehensive evaluation is required. Spasms can be subtle and easy to miss or attribute to gastroesophageal reflux or an exaggerated Moro reflex, and a high degree of suspicion is needed.

The first step is a detailed history and physical exam, with close attention to the neurological exam. On history, it is important to ask for a detailed description of the spasms, including the onset, duration, timing (particularly if they occur upon wakening), symmetry, semiology and level of consciousness. It is important to clarify if the events happen while sleeping, while awake, or on transition from sleep to wake cycle. Don't forget to ask about any post-ictal changes such as crying and irritability, drowsiness, confusion, or disorientation. It is important also to assess for the presence of other possible seizure types. Assess the child's development and make note of any regression or stagnation, which is a red flag. Ask about concerns for visual changes by asking about decreased eye contact or decreased social engagement.

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As always, ask about birth history, including any prenatal screening and perinatal and postnatal insults such as neonatal meningitis or hypoxic ischemic encephalopathy. Ask about a family history of seizures, neurologic abnormalities, or genetic syndromes such as tuberous sclerosis, which can be inherited in an autosomal dominant fashion. Ask about medications, allergies, immunizations and social history.

Make sure to do a full neurologic exam, including a skin exam with a Wood's lamp for ash-leaf spots associated with tuberous sclerosis.

After a thorough clinical evaluation, an urgent referral to a pediatrician or neurologist is needed for assessment and urgent initial electroencephalograph (or EEG).

Q: When we order or refer for an EEG, what type should we request? Is an awake EEG sufficient?
A: It is essential to have a sleep recording on EEG, because the finding of hypsarrythmia is enhanced in non-REM sleep and may be missed with only an awake EEG.

On EEG, the classic finding in the interictal period, that is, between seizures, is called hypsarrhythmia. This refers to a "chaotic rhythm" - a continuously abnormal, very high amplitude pattern with random high voltage slow waves and multi-focal spikes. The spasm (the ictal event) is characterized by an electrodecrement on EEG which is characterized by a high voltage sharp wave/slow wave followed by generalized attenuation and lasts > 1 second. An electromyography (or EMG) recording is also an essential component of the EEG. It measures the electrical activity produced by skeletal muscles and can therefore help to identify subtle spasms. Check out the PedCases.com website for an example of hypsarrhythmia on EEG.

Once a diagnosis of infantile spasms is made, a search for the cause needs to be initiated. Structural brain abnormalities should be ruled out with an MRI. Some cases, as we mentioned, are associated with chromosomal abnormalities like Down syndrome, and if there are other suggestive features, a chromosomal microarray analysis and karyotype should be sent. A basic metabolic work-up to look for inborn errors of metabolism is generally recommended. Other targeted genetic testing may be sent, depending on the clinical scenario, and is usually guided by a pediatric neurologist. Depending on what you find during your history and physical exam, consultation to ophthalmology, cardiology, or genetics may be required.

Differential diagnosis

The differential diagnosis for infantile spasms includes gastroesophageal reflux and Sandifer Syndrome, which refers to dystonic posturing of the trunk and head, described as back arching, that can occur with severe gastroesophageal reflux, and is not a true seizure. It is important to take a detailed feeding history to differentiate reflux from infantile spasms.

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Non-epileptic phenomenon can mimic infantile spasms. Benign neonatal sleep myoclonus refers to abnormal jerky movements, that generally occurs in the first month of life, only during sleep. Tonic reflex seizures of early infancy present at 1-3 months of age with generalized tonic contraction and extension of all limbs, associated with apnea and cyanosis lasting 3-10 seconds. It can be distinguished from infantile spasms by the normal EEG. The Moro reflex, stereotypies and self-stimulatory behaviours may also be confused with infantile spasms.

Q: Dr. Whitney, I sometimes find it difficult to differentiate spasms from sleep myoclonus. Do you have any tips to help with this?
A: There are a few ways to differentiate a spasm from sleep myoclonus. As you mentioned, consider the age of the child, because benign sleep myoclonus usually occurs in the first couple of months of age whereas spasms occur later on. In terms of clinical clues, sleep myoclonus may be synchronuous or asynchronous and usually affects the distal limbs/extremities. Spasms are usually bilateral and symmetric. Myoclonus occurs in the early stages of sleep and is sensitive to stimuli (like noise) and waking up the infant will make the myoclonus stop, compared to spasms that usually occur while awake and cannot be stopped.

Also on the differential are other epileptic encephalopathies, including early infantile epileptic encephalopathy, or Otahara Syndrome, and early myoclonic encephalopathy. Otahara presents with tonic spasm that occur in sleep or awake states, unlike infantile spasms which does not usually occur during sleep. Early myoclonic epilepsy presents as erratic myoclonus. These epilepsy syndromes generally also present much earlier than infantile spasms, in the first month of life and are associated with a characteristic EEG pattern called burst suppression.

Benign myoclonus of infancy and benign myoclonic epilepsy of infancy are disorders that are sometimes confused with infantile spasms. The age of onset in both disorders is also similar to infantile spasms and the best way to differentiate the two from infantile spasms is with an EEG. In benign myoclonus of infancy, the events look very similar to infantile spasms and occur in clusters but the EEG is normal. Benign myoclonus of infancy is considered a movement disorder. In benign myoclonic epilepsy of infancy, the events can also mimic infantile spasms and most often involve myoclonus of the upper extremities. However, the EEG shows generalized poly-spike and wave and not hypsarrythmia. The prognosis in both conditions is generally favorable when compared to infantile spasms.

An EEG with sleep is often required to differentiate between these disorders, as infantile spasms can be subtle and its presentation can overlap with those mentioned in the differential diagnosis.

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Treatment

The first line treatment for infantile spasms is generally Vigabatrin, a GABA-transaminase inhibitor. It prevents the breakdown of the inhibitory neurotransmitter GABA. This is typically used for two weeks and the child is monitored to see if spasms abort clinically and if the EEG pattern of hypsarrythmia disappears. Cessation of spasms occurs in approximately 48-54% of cases. It is especially effective in patients with tuberous sclerosis. If effective, treatment is generally continued for 6 months and then weaned over the subsequent 1-2 months.

Q: How do we determine if treatment has been effective or not?
A: To say that a treatment has been effective, we are looking for both the resolution of spasms and the disappearance of the hysparrhythmia pattern on EEG. Eliminating spasms alone is insufficient.

Of note, there is a potential for retinal toxicity with Vigabatrin, so infants on this medication require close monitoring with an electroretinogram by a pediatric ophthalmologist.

If first-line treatment is ineffective, adrenocorticotropic hormone (or ACTH) or prednisolone is started. ACTH has been shown to be more effective than oral prednisone or prednisolone, and hormonal therapy overall is more effective than Vigabatrin. However, ACTH is expensive, can only be administered intramuscularly and has a significant side effect profile. Side effects with steroids are common and include hypertension, irritability, susceptibility to infections, increased body weight, reversible cerebral atrophy, and sleep disturbances. It should therefore be used only for short periods of time, usually for 2-6 weeks. Relapse occurs in 1/4-1/3 of patients. To date, it is not clear which treatment modality (hormonal vs. Vigabatrin) results in better long-term neurodevelopmental outcomes. However, in the case of cryptogenic infantile spasms, hormonal therapy with either ACTH or prednisolone may be considered over VGB to possibly improve development.

If ACTH is not effective after 1-2 weeks of treatment, alternative options are explored. These include the ketogenic diet or initiation of another anti-epileptic drug. However, the evidence supporting the use of other anti-epileptic medications in infantile spasms is lacking. Epilepsy surgery may be an option, when spasms are the result of a focal brain malformation/insult, such as with tuberous sclerosis. Video EEG should be used in conjunction with parental report to assess response to therapy. The goal of treatment is resolution of both clinical seizures and normalization of EEG.

Prognosis

Infantile spasms remain a challenge for pediatric neurologists. Infantile spasms are a time-limited condition, with spasms and the EEG pattern of hypsarrythmia stopping by 3-5 years of age irrespective of treatment. But there is a high risk of cognitive impairment, learning difficulties, autism, and chronic epilepsy, including evolution into

Lennox-Gastaut syndrome. Over 90% of kids with infantile spasms have epilepsy at 10 years of age, and 30-40% evolve to Lennox-Gastaut syndrome.

Poor prognostic factors include developmental delay preceding onset of spasms, onset of spasms in the first few months of life, and delayed recognition and treatment. As mentioned before, prompt assessment and work-up is important.

Coming back to our case, the infant from our ER had multiple spasms during the clinical evaluation. They were characteristic of infantile spasms, with sudden flexion of the trunk, and abduction of the arms. The family was referred to Neurology for an urgent EEG, which showed hemi-hypsarrhythmia on the left. MRI revealed a stroke in the left middle cerebral artery. He was started on Vigabatrin but was ultimately treated with ACTH, to which he responded well.

That concludes our PedsCases podcast on Infantile Spasm. We will now review some of the key points discussed in this podcast:

- Infantile spasms are a seizure type, which generally occurs in the first year of life. The spasms can be flexor, extensor or mixed type and often occur in clusters
- West syndrome is diagnosed when infantile spasms occur in combination with hypsarrhythmia and developmental stagnation or regression
- Spasms can be subtle, and detecting them requires a high degree of suspicion
- Suspected infantile spasms should be evaluated with a complete history and physical, EEG with non-REM sleep, MRI for structural brain lesions, and metabolic and genetic testing, which is usually guided by a pediatric neurologist
- Treatment options for infantile spasms include Vigabatrin, Prednisolone, or ACTH
- In selected cases, epilepsy surgery may be a treatment option
- Prognosis is guarded, with the majority of children developing epilepsy and some evolving into Lennox-Gastaut syndrome
- Early recognition and management can improve patient outcomes and quality of life, however more research is needed to better understand the long-term outcomes with different treatment modalities

That concludes our PedsCases podcast on infantile spasms. Thank you to Dr. Whitney for helping us with this podcast. Stay tuned for more PedsCases podcasts!

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