INFANTILE SPASMS AND TSC

It is very important for parents and health care providers to recognize infantile spasms, an age-specific seizure type often associated with tuberous sclerosis complex (TSC). Infantile spasms occur in 1 in 2,000 children from many different causes, and in an estimated 40% of children with TSC. Onset of infantile spasms peaks between four and six months of age, although these seizures can begin anytime in the first two years and, rarely, even later in the first decade (when these seizures are referred to as juvenile spasms). Infantile spasms are often initially mistaken for other conditions. However, prompt diagnosis and appropriate treatment of infantile spasms are critical. Soon after the spasms begin, children may stop making developmental progress or even lose skills they had previously acquired. This type of seizure can be associated with significant intellectual disabilities if left untreated. Swift and effective treatment may provide the best developmental outcome possible for a child with TSC having infantile spasms.

What are Infantile Spasms?

The first description of infantile spasms was by English Physician, Dr. W. J. West, more than 170 years ago. His description is as accurate today as it was then and is very poignant since he was describing his son.

“The child is now near a year old; was a remarkably fine, healthy child when born, and continued to thrive till he was four months old. It was at this time that I first observed slight bobblings of the head forward, which I then regarded as a trick, but were, in fact, the first indications of disease; for these bobblings increased in frequency, and at length became so frequent and powerful, as to cause a complete heaving of the head forward toward 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 ten to twenty or more times at each attack, which attack would not continue more than two or three minutes; he sometimes has two, three, or more attacks in the day; they come on whether sitting or lying; just before they come on he is all alive and in motion, making a strange noise, and then all of a sudden down goes his head and upwards his knees; he then appears frightened and screams out; at one time, he lost flesh, looked pale and exhausted, but latterly he has regained his good looks, and, independent of this affection, is a fine grown child”

Dr. West described the subtle head bobblings that are often confused with other normal baby behaviors. The crying out may be confused with colic. However, as time went on, Dr. West noted that the spasms became more and more apparent. Dr. West described what are called “flexor spasms” or jackknife seizures. However, the opposite type of spasm, called an extensor spasm, which is described as a cheerleader motion, with an arching of the head and back, and a straightening of the legs. In either case, one or both arms may fling out in a motion that mimics a startle response (Moro reflex). Clusters of spasms may happen
repeatedly throughout the day but most commonly occur upon awakening in the morning or after a nap.

When infantile spasms occur in conjunction with TSC, they may not be typical in presentation; the spasms are very often a mixed type, with characteristics of both flexion and extension. Lateralizing features such as head turning or eye deviation (turning away) may be present. The seizures may affect the two sides of the body unequally; in some cases, only one side of the body may be affected at all. Such lateralizing features and asymmetry, though common in infantile spasms associated with TSC, may further delay diagnosis because the seizures may not look like classic, textbook infantile spasms.

The health care provider may refer to the seizures as infantile spasms or West Syndrome. West Syndrome is actually a combination of epileptic spasm combined with a particular EEG pattern called hypsarrhythmia (see below). Therefore, West Syndrome is a subgroup of infantile spasms. Children with TSC (and who have other causes of infantile spasms) have been documented to have infantile spasms without the presence of hypsarrhythmia.

**Psychomotor Regression and Behavioral Changes**

Once children begin to have infantile spasms, they often fail to meet new milestones and may even regress, losing intellectual and/or physical skills previously learned. Dr. West clearly described the consequences of IS in his son:

“...he neither possesses the intellectual vivacity or the power of moving his limbs, of a child of his age; he never cries at the time of the attacks, or smiles or takes any notice, but looks placid and pitiful, yet his hearing and vision are good; he has no power of holding himself upright or using his limbs, and his head falls without support.”

When infantile spasms begin, parents may notice a loss of interest in people and objects in the child’s environment. Social interaction may diminish, smiling may cease, sleep may become disrupted, and the child may seem irritable or indifferent to the surroundings. A child who had learned to sit may stop sitting or even lose the ability to roll over; a child who had been babbling happily may become silent or fussy. Regression in children with TSC should always be thoroughly investigated and, when infantile spasms are a possible explanation, they should certainly be ruled out.

**Electroencephalogram (EEG) Patterns**

Some infants with infantile spasms and TSC exhibit clinical and EEG characteristics that are different from typical infantile spasms. Seizures at the onset of infantile spasms may be mainly characterized by partial motor seizures. Infantile spasms are often asymmetrical and preceded by lateralizing features (movements on only one side of the body). Visual recording techniques have led to significant progress in the classification of seizures associated with TSC, demonstrating that they have a focal or multifocal origin in the vast majority of cases. In most cases, an awake interictal EEG shows focal or independent multifocal spike and slow-wave activity at onset, and later a pseudo-hypsarrhythmic pattern.

Focal (in one brain area) or multifocal (in several brain areas) abnormalities may be found when the EEG is performed between the neonatal period and the development of infantile spasms. Infants with infantile spasms due to TSC exhibit a particular EEG characterized by a multifocal asynchronous pattern of spike discharges and irregular slow activity of 2-3 Hz
Reducing the amplification and increasing the number of electrodes make it easier to recognize focal abnormalities (Curatolo, 1994). Although the EEG foci can be located in any part of the brain, the most common location for infantile spasms is the posterior temporal and occipital regions. Drowsiness increases slow-wave activity and an increase in the amount of epileptiform activity may be observed during REM sleep. Multifocal and focal abnormalities tend to generalize, and bursts of more synchronous polyspikes and waves separated by sudden voltage attenuation become evident resembling hypsarrhythmia (Dulac et al., 1984). Severe sleep problems are frequent after the onset of infantile spasms and are mainly due to sleep-related epileptic events. All-night sleep studies in children with infantile spasms have shown an increased number and duration of awakenings after sleep onset, and a marked reduction in total sleep time and in REM sleep time (Curatolo, 1994).

Overcoming Obstacles to Diagnosis
There may be a delay in the diagnosis of infantile spasms if the primary care providers are not familiar with this type of seizure. The unusual seizure can easily be overlooked by parents and health care providers who are unaware of its significance. Thus, getting a timely and accurate diagnosis may sometimes call for active advocacy on the part of the parents who suspect that there is something wrong with their child, or they think the child may be having infantile spasms. A diagnosis of infantile spasms may be dismissed out of hand because (a) the child’s EEG does not show hypsarrhythmia; (b) the child is considered too old for spasm onset; (c) the spasms are asymmetrical or atypical in appearance; (d) spasms evolve from or into another seizure type; or (e) the spasm occurs singly rather than in a more typical cluster. None of these conditions is sufficient to rule out a diagnosis of infantile spasms in children with TSC.

If, as a parent, you become concerned that a diagnosis of infantile spasms may have been overlooked, begin by broaching the subject directly with your child’s health care provider. If you remain dissatisfied, consider the following options: (a) video recording your child’s episodes and showing them to your child’s health care providers; (b) pursuing a second opinion at a TSC Clinic, a Comprehensive Pediatric Epilepsy Center, or with a neurologist with expertise in treating TSC; or (c) checking into the emergency room of a children’s hospital, stating you believe your child is having infantile spasms.

Treatment of Infantile Spasms
There are two treatments for infantile spasms approved by the Federal Drug Administration (FDA) in the USA. Vigabatrin was approved in 2009 and ACTHar Gel was approved in 2010. These two treatments, as well as other treatment options, are described below.

Vigabatrin
Vigabatrin is a medication that blocks the breakdown of GABA (gamma aminobutyric acid) transaminase, which is responsible for the metabolism of GABA, a major inhibitory neurotransmitter in the brain. The consensus developed at the NIH Tuberous Sclerosis Complex Consensus Conference in 2000 was that vigabatrin is the drug of choice to treat infantile spasms in children with TSC (Hyman and Whittemore, 2000). There are several peer-reviewed publications that report convincing evidence of the effectiveness of vigabatrin in treating children with infantile spasms, especially those with TSC (Chiron et al., 1991, 1997; Elterman et al., 2001, 2010; Lux et al., 2002; Mackay et al., 2002; Mikati et al., 2002; Westmoreland, 1988; Curatolo, 1991).
2002; Mackay et al., 2004; Thiele, 2004). The major advantages of vigabatrin are the ability to rapidly escalate the dosage at the initiation of treatment with vigabatrin, rapid efficacy, suitability for outpatient treatment and particularly good tolerability with generally only minor adverse effects, with exception of possible visual field loss (see below) (Nabbout, 2001).

Vigabatrin (Sabril®) was approved for use in the USA by the Food and Drug Administration (FDA) in 2009 (see www.sabril.net). For information and assistance with obtaining vigabatrin, go to www.LundbeckShare.com or call toll-free: 1-888-45-SHARE (1-888-457-4273).

Visual Field Loss Associated with Vigabatrin

Visual field loss associated with use of vigabatrin was first reported in 1997 in adults (Eke et al, 1997; Russell-Eggit et al, 2000; Besch et al, 2002) and later in some children (Harding et al., 2002). A recent study indicates that loss of peripheral visual fields may be more common in adults than in children, with 44% and 34% exhibiting loss of visual fields, respectively (Macquire et al., 2010).

The safety of vigabatrin in children with infantile spasms is of particular concern because pre-existing vision problems have been described in this group (linuma K et al. 1994; Castano G et al. 2000; Brooks BP et al. 2002; Hammoudi DS et al. 2005). Because of the possibility of peripheral vision loss, the FDA requires that any physician who prescribes vigabatrin for their patients must be registered, and there are visual testing and reporting requirements for all individuals who use vigabatrin. Health care providers may indicate that an individual is not able to perform the visual field testing on the form when they prescribe vigabatrin if testing will not be feasible for a specific individual.

In many cases, the patient may not be aware that they have the visual field loss because it develops slowly and does not affect central vision. The visual problem is confirmed by perimetric testing, a special type of vision testing that measures the portion of space in which objects are visible at the same moment during steady fixation of gaze in one direction. The current problem is determining the risk-benefit ratio of vigabatrin in children with infantile spasms and to specify the groups where their use could be optimal. In children, especially in the young or disabled, it is difficult if not impossible to detect the visual field loss and it is not yet known if children are at higher or lower risk for this adverse effect compared to adults. Children younger than age 9 years usually are unable to cooperate for perimetry studies. The Department of Ophthalmology at The Hospital for Sick Children in Toronto has been monitoring for possible vigabatrin visual toxicity since about 1999 by doing a baseline electroretinogram (ERG) in infants and young children and bi-annual follow-up exam(s). They repeat the ERG within three months if there is a decreased amplitude in the 30 Hz flicker response (Westall CA et al. 2003; Buncic JR et al. 2004; Hammoudi DS et al. 2005).

In 2009, MRI abnormalities were reported in very young children taking vigabatrin (Pearl, et al, 2009). The changes were in the central structures of the brain. It was not clear that there were any clinical consequence, and, when the vigabatrin was discontinued, all of the changes resolved. A similar MRI abnormality was seen in a TS patient treated for IS, and, when the vigabatrin was stopped, the abnormality disappeared. (Hsieh, 2010)
Because of the risk of vision loss, and the MRI abnormalities, vigabatrin is used in babies (1 month to 2 years of age) with infantile spasms only when you and your doctor decide that the possible benefits of vigabatrin are more important than the possible risks. However, it is very important to understand the developmental consequences of continued IS when making these decisions. Children who are first treated with vigabatrin, but who do not achieve a good response, may consider using ACTH.

**Adrenocorticotropic Hormone (ACTH; marketed as Acthar® Gel)**

ACTH has been used for many years as a treatment for infantile spasms. The clinical benefits of ACTH in infantile spasms could partially relate to its stimulatory effects on the release of adrenocorticosteroids and neurosteroids. For some children with TSC, ACTH is effective in treating infantile spasms when vigabatrin is not, and the reverse is also true. There are side effects related to use of ACTH in infants, including increased intraocular pressure (Friling et al., 2003), immunosuppression and possible increase in the size of cardiac rhabdomyomata, the heart tumors associated with TSC (Hishitani et al., 1997; Hiraishi et al., 2000). Careful consideration of treatment for your child should be discussed with the child’s health care provider to discuss the benefits and risks of each treatment option.

Acthar® Gel was approved by the FDA in October 2010 for the treatment of infantile spasms. For more information about Acthar® Gel and the ACTHar Support and Access Program (A.S.A.P.) go to [www.acthar.com](http://www.acthar.com) or call 1-888-435-2284, Monday-Friday from 8:00 am-8:00 pm ET.

**Other Treatment Options**

One of the ongoing questions is whether orally administered steroids rather than Acthar® Gel, which must be given by injection, might be effective in treating IS. There are no comparative studies that answer the question definitively but, some clinicians are using oral prednisone or prednisolone instead of ACTH (Lux, 2002, Hussain, in press). Most clinicians use vigabatrin as the first drug but, if it is not successful then a trial of ACTH or prednisolone is warranted. However, it should be noted that ACTHar gel has been approved by the FDA for treatment of IS but presnisolone has not.

Clinical trials reporting the efficacy of other medications (zonisamide, topiramate) for the treatment of infantile spasms have shown some promise in initial small studies, but failed to effectively treat infantile spasms in larger, multi-center clinical trials. It is likely that the reported initial success with these medications reflects the spontaneous remission rate of 20-25% of all individuals with infantile spasms. These new antiepileptic drugs represent a potential nonhormonal approach for infantile spasms, but additional studies are needed to verify their efficacy and tolerability. Future studies will hopefully identify rational anti-epileptic drugs that not only control infantile spasms but also minimize its risk on the development of the brain.

Another therapy, the ketogenic diet has been reported to be a safe, well-tolerated and possibly effective alternative epilepsy treatment in some children with infantile spasms (Kossoff et al. 2002; Hong et al., 2010) who are refractory to standard antiepileptic medications. Children to be placed on the diet must be carefully selected, monitored, and
followed. The diet is to be regarded as a strict medical regimen and requires a comprehensive medical team approach in concert with intensive parental involvement. The ketogenic diet generally provides sufficient nutrition to maintain growth within normal parameters over a defined period. Kosoff and colleagues (2002) reported 50% of the children with hypsarrhythmia and follow-up EEGs had EEG improvement. Diet-related adverse reactions (nephrolithiasis, gastroesophageal reflux) should be monitored.

Despite the efficacy of vigabatrin, hormonal therapy (ACTH or Prednisolone) and other medical therapies, some children with TSC continue to have spasms and experience psychomotor regression. These children with drug-resistant seizures may be candidates for surgery and should be evaluated by an epilepsy team that is experienced in doing surgery for epilepsy in children with TSC (Chugani et al., 2010).

In summary, infantile spasms should be treated as soon as the diagnosis is made. The drug of choice for treatment of infantile spasms in children with TSC is vigabatrin. If the seizures are not controlled with vigabatrin utilizing a high enough dose, then the use of ACTH or prednisolone should be considered. Children with TSC may also be candidates for surgical treatment and the child should be considered for surgery as outlined below.

It is important to avoid treating children with TSC with medications that may induce or make infantile spasms worse. Medications such as phenobarbital, phenytoin, carbamazepine and tiagabine should not be used in children and especially in infants with TSC (Dulac, 2001).

Treatment with valproate or one of the newer antiepileptic medications, such as topiramate, rather than with phenobarbital, carbamazepine or phenytoin, is recommended when the diagnosis of infantile spasms has not yet been made (Dulac, 2001), even in small children and infants.

Surgery
Recent progress in surgical treatment of epilepsy has proven to be helpful for some children with TSC and infantile spasms (Asarnow et al., 1997; Asano et al., 2001; Curatolo et al., 2001; Chugani et al., 2010). Recent advances have improved the outcome for children treated surgically for IS. (Wu, 2010)

It is becoming increasingly clear that, in carefully selected cases of infantile spasms, surgical resection of the epileptogenic cortex can result in seizure control and improved developmental outcome (Chugani & Pinard, 1999; Jonas et al, 2005). It is recommended that selection criteria for surgical treatment include:

- **Intractability of seizures.** The infant’s seizures should be refractory to appropriate trials of medical management (one cannot use “all” because it is not possible to try “all” of the medications).

- **Focal features on EEG.** Focal abnormalities should be present on interictal and/or ictal EEGs of potential surgical candidates.
• **Focal abnormalities on neuroimaging.** All infants should show either an anatomical (CT/MRI/MEG) or functional (PET/SPECT) lesion.

However, the most appropriate time to consider cortical resection to treat medically intractable infantile spasms has not been clearly defined. The risks that need to be reconciled to make this decision are: What is the risk of loss of developmental potential if surgery is delayed too long versus what is the risk of unnecessary surgery if it is done too soon. Shields and coworkers (1999) proposed that, in addition to evaluation of seizures, developmental assessment be a key factor in the surgical decision. If a child with infantile spasms has met developmental milestones even though he or she has infantile spasms, the potential benefits of surgery should be carefully weighed with the potential risks. [For additional information, see Information Sheet on Epilepsy Surgery for Individuals with Tuberous Sclerosis]

**Prognosis**
Vigabatrin has demonstrated high efficacy in treating infantile spasms due to TSC. In a study by Jambaque and coworkers (2000), they found that the cessation of spasms with vigabatrin was associated with significant improvement of cognition and behavior in children with TSC. Controlling secondary generalization induced by infantile spasms also seems to be a key factor for intellectual development in children with TSC.

A study by Joinson et al. (2003) examined the intellectual abilities in individuals with TSC ages 4 to 75 years. They found that 55.5% had an IQ in the normal range, 14% had mild to severe impairments, and 30.5% had profound disability (IQ < 21). Forty-four per cent of the individuals with TSC had an IQ < 70. The likelihood of impairment was associated with a history of seizures, particularly infantile spasms. All individuals with learning disability had a history of seizures that usually started before 12 months of age and that often presented as infantile spasms. This study showed that a history of seizures, as well as a history of infantile spasms, was predictive of the degree of intellectual impairment, reinforcing the importance of early diagnosis and rapid treatment of infantile spasms in children with TSC.

**References**


Hussain, et al. Treatment of infantile spasms with very high dose prednisolone before high dose ACTH. Epilepsia, In Press


Resources and Links

Infantile Spasms and TSC: A Devastating Diagnosis (Online Video)

http://www.eurekalert.org/pub_releases/2010-09/w-una090110.php

NINDS Infantile Spasms Information Page – Provided by the National Institutes of Health
http://www.ninds.nih.gov/health_and_medical/disorders/infantilespasms.htm

WebRing – provides information, stories about other individuals with infantile spasms, and links to other sites
http://j.webring.com/hub?ring=infantilespasms&list

Medline Plus – Provided by the National Library of Medicine and National Institutes of Health (Drugs and Supplements)


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