

Overview of Treatment in Infantile Spasms

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ABSTRACT

Infantile Spasms is a rare disorder consisting of epileptic spasms that occur before the age of one year. This severe epilepsy affects about 0.31 in 1000 births with an average age at onset of 6 months. Treatment usually consists of hormonal therapies (adrenocorticotrophic hormone or corticosteroids) or vigabatrin. Decisions about choice of therapy are complicated because these first-line treatments can have significant side effects, are often expensive, and there are few randomized, controlled, blinded studies to guide therapy. Hormonal therapies are the most common first-line treatments and multiple trials suggest that they are the most effective. Vigabatrin may be more effective in treating infantile spasms in patients with tuberous sclerosis. Studies evaluating long-term cognitive outcomes in patients with infantile spasms have failed to show that any therapy produces superior long-term cognitive outcomes in all types of patients. However, there are some data suggesting that early treatment with hormonal therapies improves outcomes in patients for whom a cause of infantile spasms is never found. In this article, we review the evidence for available treatments for infantile spasms.

Key words: infantile spasms, ACTH, vigabatrin, prednisolone, prednisone, West Syndrome, Anschutz Medical Campus, Aurora, CO

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INTRODUCTION

Infantile Spasms (IS) is a rare disorder consisting of epileptic spasms that occur before the age of one year. Often, epileptic spasms are accompanied by an abnormal EEG background and developmental regression. Patients typically manifest a combination of seizures and developmental stagnation or regression and are then often found to have a highly abnormal EEG background called hypsarrhythmia (1). The seizures usually involve sudden bilateral flexion or extension of the neck, trunk, and extremities that are 1-2 seconds in duration. Typically, these spasms occur in clusters of 10 – 100 at a time, often when the affected individual wakes from sleep. These spasms are also often accompanied by a cry (2).

The incidence of this severe epilepsy is about 0.31 in 1000 births and the average age at onset is 6 months, with the vast majority of patients developing spasms before the age of 3 years. IS previously were classified two subgroups: symptomatic IS, so called when an underlying cause is known, and cryptogenic IS, when no such cause can be found (3,4). The most recent consensus diagnostic criteria recommend three designations for the etiology of IS: 1) Idiopathic infantile spasms, used to describe cases that occur without any identifiable underlying cause or associated neurologic symptoms; 2) Cryptogenic infantile

spasms, used to describe cases where IS are suspected of being caused by an underlying structural or biochemical cause, but for whom such a cause has not been identified; and 3) Symptomatic infantile spasms, used to describe cases where and identifiable cause has been found and where, very often, IS are preceded by other neurologic problems or clear developmental delay (5).

Few randomized controlled trials have evaluated the treatment of infantile spasms. Studies designed to answer questions related to treatment of IS are often limited by small sample size and retrospective design. In addition, broad variation in choice of first-line treatment, dose, and duration of therapy compound the problems introduced by small sample size, leading to a high number of small studies with a wide variety of aims, hypotheses, and outcome measures (6–8). Table 1 illustrates the small numbers of randomized trials designed to evaluate standard therapies for the treatment of IS, many of which are not blinded. However, a number of consensus statements point to a growing body of evidence in support of emerging standard therapies (8–10), including adrenocorticotrophic hormone (ACTH), corticosteroids (usually prednisolone), and vigabatrin. (See Table 2 for a complete list of all of the studies evaluating these therapies). However, there remains large variability in treatment among providers (7).

Drug	EEG Prospective Randomized Blinded	Prospective Randomized Blinded	EEG Prospective Randomized Open	EEG Prospective Open	Retrospective
ACTH	4	0	2	3	9
Corticosteroids	2	0	1	1	5
Vigabatrin	3	0	3	1	8
Hormonal	0	0	1	0	1

Table 1: Numbers of studies involving standard first-line therapies that meet the criteria contained in each column. Because studies often compare standard therapies, individual studies may be counted in multiple places. Some studies group ACTH and corticosteroids together as “hormonal therapies.”



Figure 1.

HISTORY

Infantile spasms were first formally described by W.J. West in a letter to *Lancet* in which he describes his experience with his own son (11). He stated, “I first observed slight bobbings of the head forward [that] were, in fact, the first indications of disease; for these bobbings increased in frequency, and at length became so frequent and powerful as to cause a complete heaving of the head forward toward his knees...” His report also includes a description of the intellectual disability he observed, which most often accompanies epileptic spasms in this disease.

The next major step in our understanding of IS came when the characteristic pattern seen on EEG, hypsarrhythmia, was described by Gibbs and Gibbs in 1952 (1,12). (Figure 1)

They described “a strikingly abnormal pattern consisting of very high voltage, random, slow waves and spikes in all cortical areas.” Although modern classification of epilepsy recognizes that epileptic spasms can occur without this characteristic EEG pattern (13), and that hypsarrhythmia can occur without accompanying epileptic spasms, this pattern is often present in patients with IS. The most recent consensus statement of definitions for the purposes of research proposes that the term West Syndrome be used “to describe the combination of spasms that occur in clusters and hypsarrhythmia on an EEG (5).”

An important development in IS occurred when Klein and Livingston described seizure reduction and EEG normalization in patients with epilepsy who received ACTH

(14), and Sorel and Dusaucy-Bauloye described a cohort of patients with IS in whom adrenocorticotrophic hormone (ACTH) controlled spasms in a number of patients (15). This was the first report of an agent effective in treating this disorder. Shortly after the report of response to ACTH, Low reported a similar response to cortisol (16). Subsequent studies confirmed the effectiveness of corticosteroids, including cortisone and prednisolone (17,18). In 1989 Livingston reported on the effectiveness of vigabatrin (gamma-vinyl GABA) in children with epilepsy (19) and in 1990 Chiron et al. reported for the first time on the effectiveness of this drug in treating IS (20). The history of these medications relative to the treatment of IS and a sampling of relevant studies is related in the section entitled "Treatment" below.

As efforts to study the effectiveness of various treatments have grown, so, too, has the need to standardize the classification of IS and quantify this disease both clinically and electrographically. With the advent of long-term video EEG, Frost et al. described a standardized approach to quantifying the clinical and electrographic features of IS, utilizing continuous video EEG and a number of other leads, such as EMG (21). This approach allowed clinicians to better quantify clinical and electrographic data before and after treatment. EEG is now a standard part of the pre-treatment diagnostic evaluation in patients with suspected IS. Despite this standardized approach, there is ongoing controversy about the precise definition of hypsarrhythmia and recent studies still demonstrate poor inter-rater reliability (22).

In general, clinical and cognitive outcomes are poor in patients with IS. A large proportion of patients go on to develop other seizure types and epilepsy, and many go on to have intellectual disability. An early retrospective analysis of patients who had been treated with cortisol for IS found no correlation between initial response to therapy and later cognitive ability (23). This lack of correlation continues in later analyses. A number of retrospective analyses support the finding that better cognitive outcomes are achieved in patients for whom an etiology is never found, so-called idiopathic IS (24–27). Nested analysis from the United Kingdom Infantile Spasms Study (UKISS) also suggested that, "better initial control of spasms by hormone treatment in those with no identified underlying aetiology may lead to improved developmental outcome (28)." Follow-up of 77/107 patients from the same UKISS cohort at 4 years of age confirmed the same result (29,30). An Israeli study reported excellent cognitive outcomes in a cohort of patients for whom no cause of IS could be found (idiopathic IS by the latest standard), with 22/22 patients who were treated within one month of onset having normal cognition on long-term follow-up. The treatment regimen employed in this study was unusual, with initial high-dose ACTH followed by a very long taper of oral prednisone (31). A consensus statement reviewed these and similar studies and echoed the same conclusion: patients with cryptogenic IS may have better cognitive outcomes when treated with hormonal therapies and decreasing time to treatment may improve cognitive outcome (9). A large retrospective cohort of 180 Serbian patients (32), all

treated with vigabatrin, reported much better cognitive outcomes than in another large follow-up study of Finnish patients where most patients were treated with ACTH (33). However, methods for measuring cognitive outcome differed and the threshold for categorizing "favorable" outcomes was lower in the Serbian cohort (34,35).

TREATMENT

ACTH

Mechanism

Adrenocorticotrophic hormone (ACTH) is available in two formulations. In the US, the form most commonly used is natural ACTH, isolated from animal sources. In the UK, Europe, and many other countries, synthetic ACTH, consisting of the first 24 amino acids of natural ACTH, is the predominant form. Both formulations are given as subcutaneous or intramuscular injections. ACTH works by stimulating the adrenal cortex to produce cortisol and aldosterone, though how this treats IS is still not understood. Many patients who receive ACTH experience side effects. In a review of 162 Finnish patients, 37% experienced clinically significant side effects, and 4.9% of patients died while receiving ACTH (36). This study reported "the most common complications were ... septic infections, pneumonias, and urinary and gastrointestinal infections." In addition to the significant side-effect profile, natural ACTH is an expensive therapy, leading many providers to opt for less expensive treatments (37,38). There is no standardized dose of ACTH and there is no universally-accepted equivalence between natural and synthetic ACTH. This wide variability in dosing makes it difficult to compare studies that do not use the same dose and formulation.

Studies and Effectiveness

Since the landmark report of Sorel and Dusaucy-Bauloye in 1958, ACTH has been the subject of a large number of retrospective studies designed to assess the effectiveness of this treatment. However, there have been few randomized controlled trials of this medication in infantile spasms, and there remains some uncertainty about the choice of first line therapy for patients with IS. The largest randomized controlled trial to assess effective treatment for IS grouped hormonal therapies (synthetic ACTH and corticosteroids) together and found hormonal treatment was more effective than vigabatrin (28). However, this trial was not large enough to detect a difference between the hormonal therapies. The ongoing uncertainty about optimal first-line treatment is reflected in the language used by the latest consensus reports. The 2012 joint evidence based guideline of the American Academy of Neurology and the Child Neurology Society states, "ACTH or VGB [vigabatrin] may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over VGB

First Author	Treatment	Year	PMID	EEG pre	EEG post	Prospective	Randomized	Blind
Low	ACTH and cortisol	1958	13613851	yes	yes	no	no	no
Harris	ACTH	1964	14230751	yes	yes	no	no	no
Seki	ACTH	1976	186371	no	no	no	no	no
Singer	ACTH	1980	6244378	yes	yes	no	no	no
Hrachovy	ACTH	1980	6254755	yes	yes	yes	no	no
Lerman	ACTH and corticosteroids	1982	6284904	yes	yes	no	no	no
Bachman	ACTH and valproic acid	1982	6275826	yes	yes	no	no	no
Hrachovy	ACTH and prednisone	1983	6312008	yes	yes	yes	yes	yes
Glaze	ACTH and prednisone	1988	2450190	yes	yes	yes	no	no
Nolte	hormonal vs non-hormonal	1988	3064626	yes	yes	no	no	no
Chiron	vigabatrin	1990	1967808	no	no	no	no	no
Chiron	vigabatrin	1991	1940125	yes	no	yes	no	no
Hrachovy	ACTH high and low dose	1994	8176573	yes	yes	yes	yes	yes
Aicardi	vigabatrin	1996	8681895	yes	no	no	no	no
Baram	ACTH and prednisone	1996	8604274	yes	yes	yes	yes	yes
Vigevano	ACTH and vigabatrin	1997	8208355	yes	yes	yes	yes	no
Chiron	vigabatrin and hydrocortisone	1997	9095401	yes	yes	yes	yes	no
Appleton	vigabatrin	1999	10565592	yes	yes	yes	yes	yes
Yanagaki	ACTH high and low dose	1999	10522523	yes	yes	yes	yes	no
Cossette	ACTH and vigabatrin	1999	10331702	yes	yes	no	no	no
Nabbout	vigabatrin	2001	11879370	yes	yes	no	no	no
Askalan	ACTH and vigabatrin	2003	12731640	yes	yes	yes	yes	yes
Lux	vigabatrin and hormone	2004	15541450	yes	yes	yes	yes	no
Kondo	ACTH	2004	16023546	yes	yes	no	no	no
Lux	vigabatrin and hormone	2005	16239177	yes	yes	yes	yes	no
Oguni	ACTH	2005	15925463	yes	yes	no	no	no
Karvelas	vigabatrin and corticosteroids	2009	18976934	yes	no	no	no	no
Shu	ACTH high and low dose	2009	19558807	yes	yes	yes	yes	unknown
Elterman	vigabatrin	2010	20404353	yes	yes	yes	yes	yes
Lagae	ACTH and vigabatrin	2010	20149693	yes	no	no	no	no
Bitton	ACTH and vigabatrin	2012	22889307	yes	yes	yes	no	no
Lee	vigabatrin and topiramate	2013	23856457	yes	yes	no	no	no
Thodeson	vigabatrin and hormone	2014	17201726	yes	yes	no	no	no

Table 2: List of the studies involving one of the three standard therapies for Infantile Spasms.

(9).” A recent Cochrane review of randomized controlled trials in the treatment of infantile spasms concluded that hormonal treatment, ACTH or corticosteroids, “resolves spasms faster than vigabatrin and in more infants, but it is not yet clear whether this will result in better long-term outcomes (6).”

Cossette et al. and Thodeson et al. performed separate retrospective analyses comparing ACTH and vigabatrin and found no significant difference in response (39,40). However, neither of these studies separated patients with TS, and neither was intended primarily to examine this difference. The UKISS trial did eliminate patients with TS and found significantly better response to ACTH (28,41). A multicenter prospective study also found better response with ACTH, but there was no randomization and the cohort may have been subject to treatment bias, because children with poor development less likely to receive ACTH (42).

The optimal dose of ACTH is unknown. In 1994 Hrachovy and coworkers performed a randomized single-blind trial comparing two doses of natural ACTH (20 – 30 IU/day and 150 IU/M²/day) and found no difference in response rate (43). In 1999 Yanagaki and coworkers reported an unblinded randomized trial comparing two doses of synthetic ACTH (0.2 IU/kg/day and 1 IU/kg/day) that also found no difference (44). Smaller retrospective analyses from a number of groups have reported good short-term and long-term remission in spasms with lower doses ACTH (45–47) and with a step-wise increase in ACTH in patients who did not respond to low starting doses (46,48).

Furthermore, as discussed above and reflected in consensus statements, it is not clear that any treatment imparts better long-term outcome overall. The United Kingdom Infantile Spasms Study (UKISS) showed that patients randomized to hormone treatment (corticosteroids or ACTH) showed better initial control of spasms than patients randomized to receive vigabatrin. However, there was no difference in seizure-freedom between either treatment on long term follow-up (28).

Corticosteroids

Mechanism

Corticosteroids exert broad anti-inflammatory and mineralocorticoid effects in a variety of tissues by binding to glucocorticoid receptors and recruiting histone deacetylase-2 to modify the activity of the transcription complex (49). The exact mechanism by which corticosteroids decrease epileptic spasms is not known. Use of steroids can lead to hypertension, cardiomyopathy, and an increased risk of severe infection.

Studies and Effectiveness

Shortly after the report of Sorel and Dusaucy-Bauloye on the effectiveness of ACTH, Low reported a similar response to cortisol (16). Subsequent studies confirmed the effectiveness of corticosteroids, including cortisone and prednisolone, in the treatment of IS (17,18). Studies

continue to show the effectiveness of corticosteroids as initial treatment for IS (50–52); however, it is not clear whether there is a difference in effectiveness between ACTH and corticosteroids.

It is not clear whether ACTH or corticosteroids are superior. In 1983 Hrachovy and coworkers reported a randomized, placebo-controlled, double-blind crossover study comparing patients who received high-dose ACTH to patients who received low-dose prednisone (2 mg/kg/day). Their study showed no difference between the two groups in cessation of spasms with initial therapy (53). In 1996 Baram et al. reported the results of a randomized controlled trial comparing ACTH to prednisone and showed a better short-term response to ACTH than to low-dose oral prednisone (2 mg/kg/day) (54). The reasons for these conflicting results are not clear. However, Hrachovy et al. reported a lower response rate to ACTH (42% before crossover) than did Baram et al. (86.6%). The response to prednisone was similar in both studies (33% in Hrachovy et al. and 29% in Baram et al.). As noted in the latest Cochrane review by Hancock et al., “It is now known that at birth, the newborn infant has poor capacity of HSD11B1 to reduce prednisone to prednisolone, and that this ability only slowly increases over the first six months of life. Hence, prednisone and prednisolone should not be considered equivalent treatments for infants, and it is likely that prednisone will not be as effective as prednisolone in the treatment of infantile spasms (6).” Lux and coworkers performed a nested analysis comparing ACTH to high-dose prednisolone (40 mg/day) and failed to show a statistically significant difference (41). This nested analysis was likely not powered to detect a difference between the two groups. A recent randomized, single-blind study comparing high-dose prednisolone to low- to moderate-dose ACTH actually showed a greater degree of decrease in hypsarrhythmia with prednisolone than with ACTH and no difference in cessation of clinical spasms between the two therapies (55).

The ambiguity in differing response rates between ACTH and corticosteroids has led many groups to use corticosteroids as first-line therapy, especially where cost or intolerability of side effects from ACTH are important factors. Kossoff and other members of his group adopted high-dose prednisolone as standard first-line therapy in 2007. Shortly afterward in a retrospective review, they reported that their recent patients treated with prednisolone did not show a statistically significant difference in rate of response when compared to the same number of their most recent patients treated with ACTH (56). Azam and coworkers reported trends in treatment in Pakistan, where the high cost and difficulty obtaining ACTH have led to a clear preference for prednisolone (57).

High dose corticosteroids may be more effective than lower dose corticosteroids. In 2014 a randomized unblinded study compared different doses of oral prednisolone (4 mg/kg/day versus 2 mg/kg/day) and found a significantly higher response rate in patients receiving the higher dose (58).

Vigabatrin

Mechanism

Vigabatrin increases levels of the inhibitory compound gamma amino butyric acid (GABA) by irreversibly inhibiting GABA transaminase. Vigabatrin has been associated with irreversible visual field loss (59). A recent review found that as many as 34% of all patients who receive vigabatrin develop visual field deficits (60). However, there appears to be a dose-related effect, with higher rates of this side effect in patients who take the medication for a longer period of time (60–62). However, some have commented that the risk of visual field defects is potentially small in light of the risks associated with hormonal therapies and the ultimate impact of continued IS on subsequent quality of life (63).

Studies and Effectiveness

Vigabatrin was initially studied in adults, but was soon studied as add-on therapy in children with intractable epilepsy (19). Shortly after the first reports of the effectiveness of vigabatrin in treating IS, work by Chiron, Dulac, and coworkers demonstrated that vigabatrin is particularly effective at treating patients with IS in the context of structural abnormalities, especially tuberous sclerosis (TS) (20,64). Review of a retrospective European cohort in 1996 by Aicardi et al., showed complete resolution of clinical spasms in nearly 69% of patients who received vigabatrin. This study again demonstrated that vigabatrin appears to be more effective in patients with tuberous sclerosis, with 96% of patients with TS showing complete clinical resolution of IS after initiation of vigabatrin (65).

Chiron et al. and Vigeveno and Cilio performed small prospective randomized trials comparing vigabatrin to corticosteroids or vigabatrin to synthetic ACTH. Both studies suggested that vigabatrin is more effective as a first-line agent in treatment of IS in patients with TS (66,67). A number of small trials, including one randomized placebo-controlled trial suggest that vigabatrin is an effective first-line treatment for (25,68). In 1999 Hancock and Osborne reviewed all studies that tracked response rates in patients with known TS and found that 73/77 (95%) of patients with TS had complete cessation of spasms with vigabatrin, while 170/313 (54%) of patients without TS had cessation of spasms with vigabatrin. Their conclusion was that vigabatrin should be considered as the first line treatment for IS in patients with TS (69). A recent retrospective analysis of vigabatrin in patients without TS showed that only 18/61 (30%) had short term response to vigabatrin, but the response rate was higher in patients with normal development prior to the onset of IS (70). Elterman and coworkers performed a large randomized trial comparing high and low-dose vigabatrin and found that a greater proportion of patients had cessation of spasms on short-term and long-term follow-up with high-dose vigabatrin (71).

OTHER TREATMENTS

The best-studied treatments for IS are hormonal therapies (ACTH and corticosteroids) and vigabatrin. A number of other therapies have been studied for the treatment of IS, including zonisamide (72), topiramate (73–75), sulthiame (76), nitrazepam (77), and valproic acid (78–80). Although there is no evidence that any of these agents are as effective as hormonal treatments or vigabatrin, these studies are nonetheless important because of the high numbers of patients who either fail to respond or experience intolerable side effects on standard first-line therapies. Recent data reported by Knupp et al. showed that 44/118 patients (37%) responded to a second medication after failing initial therapy for IS. Response was even better in patients who received standard medications (ACTH, corticosteroids, or vigabatrin) as first and second medications (27/49 (55%) vs 17/69 (25%), $p < 0.001$) (81).

Another alternative when first-line therapies have failed is the ketogenic diet. A 2013 report showed that the ketogenic diet helped some patients who failed vigabatrin or topiramate (82). Kosoff performed a retrospective analysis looking at ketogenic diet versus ACTH. This analysis showed a trend toward better initial response in ACTH, but fewer side effects and a lower rate of relapse with the ketogenic diet (83). There are also a few small studies suggesting benefit with combinations of medication, but large prospective studies have not yet been performed (84–86).

A subset of patients with IS have one or more focal features, focal seizures, hemiparesis, focal findings on imaging, asymmetric epileptic spasms, or hemihypsarrhythmia. These focal features may make a child a candidate for respective epilepsy surgery (87). A 1993 report by Chugani and coworkers showed that 15/23 patients who manifested focal features and in whom PET showed laterality consistent with findings on EEG became seizure free after surgery, with a further 4/23 having at least 75% reduction in seizures following surgery (88). Subsequent studies have shown similar benefits on seizure frequency, but not necessarily on developmental outcome (89). Patients who show improvement on developmental assessment after surgery are those who had normal development prior to the onset of IS (90); this finding is similar to findings about cognitive outcomes in patients who respond to medical therapy (28–30).

CONCLUSIONS

Infantile spasms are an important cause of intractable epilepsy and developmental delay in about 1 in 3000 births. There are few large, prospective, randomized controlled studies of treatments in IS. The best available evidence suggests that hormonal therapies (ACTH and corticosteroids) most often lead to remission of clinical spasms and resolution of hypsarrhythmia on EEG. The optimal dose of ACTH has not been determined, and a wide range of doses has been used. Evidence suggests that

high-dose corticosteroids may be more effective than low-dose corticosteroids. Vigabatrin may be the most effective first-line agent in patients with tuberous sclerosis. In the high proportion of patients who fail to respond or experience intolerable side effects on standard first-line therapy, alternative treatments include standard seizure medications, ketogenic diet, and, potentially, respective epilepsy surgery. There are few data to suggest the superiority of any treatment in leading to better long-term cognitive outcomes for patients with IS. However, there are some data to suggest that early diagnosis and treatment with ACTH can lead to better outcomes in patients for whom no etiology for IS can be found. Given the high degree of morbidity associated with this diagnosis, and the ongoing controversy regarding the best first-line treatment, continued efforts to conduct large prospective therapeutic trials are necessary.

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