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**Title**
Practice Parameter: Medical Treatment of Infantile Spasms

**Permalink**
https://escholarship.org/uc/item/5mt5c2df

**Journal**
Neurology, 62(10)

**ISSN**
0028-3878

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**Publication Date**
2004-05-25

**DOI**
10.1212/01.wnl.0000127773.72699.c8

Peer reviewed

# Practice Parameter: Medical Treatment of Infantile Spasms:

**Report of the American Academy of Neurology and the Child Neurology Society**

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## Abstract

**Objective**—To determine the current best practice for treatment of infantile spasms in children.

**Methods**—Database searches of MEDLINE from 1966 and EMBASE from 1980 and searches of reference lists of retrieved articles were performed. Inclusion criteria were the documented presence of infantile spasms and hypsarrhythmia. Outcome measures included complete cessation of spasms, resolution of hypsarrhythmia, relapse rate, developmental outcome, and presence or absence of epilepsy or an epileptiform EEG. One hundred fifty-nine articles were selected for detailed review. Recommendations were based on a four-tiered classification scheme.

**Results**—Adrenocorticotropic hormone (ACTH) is probably effective for the short-term treatment of infantile spasms, but there is insufficient evidence to recommend the optimum dosage and duration of treatment. There is insufficient evidence to determine whether oral corticosteroids are effective. Vigabatrin is possibly effective for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis. Concerns about retinal toxicity suggest that serial ophthalmologic screening is required in patients on vigabatrin; however, the data are insufficient to make recommendations regarding the frequency or type of screening. There is insufficient evidence to recommend any other treatment of infantile spasms. There is insufficient evidence to conclude that successful treatment of infantile spasms improves the long-term prognosis.

**Conclusions**—ACTH is probably an effective agent in the short-term treatment of infantile spasms. Vigabatrin is possibly effective.

West syndrome[1] is a unique, age-specific epilepsy of early infancy. Infantile spasms are distinct from myoclonic and tonic seizures.[2] They are characterized by an initial contraction phase followed by a more sustained tonic phase. They can be divided into three types (flexor, extensor, and mixed flexor-extensor spasms), and they can also be asymmetrical.[2] The EEG characteristically demonstrates hypsarrhythmia, and onset of spasms is frequently associated with neurodevelopmental regression. The incidence of infantile spasms is estimated at between 0.25 and 0.60 per 1,000 live births,[3-5] and the prevalence rate is 0.15 to 0.2 per 1,000 children age 10 or younger.[6]

Two large surveys were performed independently by the Child Neurology Societies in the United States and in Japan to determine the drug of choice for the treatment of infantile spasms. In the American survey, which primarily included US child neurologists, 88% of respondents used adrenocorticotropic hormone (ACTH) as initial therapy, the most frequently used regimen was a dosage of 40 IU/day for 1 to 2 months, and the choice of drug was not influenced by etiology.[7] In the Japanese survey, treatment was influenced by etiology, and the order of drug selection was pyridoxine, valproate, and then synthetic ACTH at much lower doses than used in the United States.[8] In a smaller survey of pediatric neurologists in the United Kingdom, the initial choice was influenced by etiology, and vigabatrin was the most frequently used first-line agent.[9]

Because of these different approaches to the treatment of children with infantile spasms, a practice parameter is warranted to develop evidence-based recommendations for the treatment of this disorder but is constrained by a number of factors. First, there is a paucity of prospective studies and even fewer randomized or controlled treatment trials in this disorder. In addition, published outcome measures are poorly described, are short term, vary from study to study, and are based on small numbers of patients because of the infrequent occurrence of the disorder. Finally, the agents used, dosage regimens, and treatment duration vary from study to study. Specific clinical questions include the following:

1. What are the most effective therapies for infantile spasms as determined by short-term outcome measures including complete cessation of spasms, resolution of hypsarrhythmia, and likelihood of relapse following initial response?

2. How safe are currently used treatments, and do they differ in their tolerability and frequency or severity of side effects?

3. Does successful treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcome or a decreased incidence of epilepsy?

## Description of process

The OVID interface was used to search both MEDLINE (1966 to May 2002) and EMBASE (1980 to May 2002) databases simultaneously. The search term "spasms, infantile" retrieved a total of 2,616 references. A text word search was also used to identify other potentially relevant studies. Terms used included the following: infant: spasm, hypsarrhythmia, hypsarrhythmi, cryptogen: infant: spasm, jackknife seizure, nodding spasm, salaam seizure, spasmus nutans, symptomatic infant: spasm, west syndrome:, lightning attack, salaam attack and blitznicksalaamkrampfe, petit mal quadrette, massive myoclon: spasm, and minor motor epilepsy. The wildcard symbol ":" was used to truncate words, allowing retrieval of articles that used variations in word endings. The combined MEDLINE and EMBASE text word searches identified 1,175 articles. All search titles and abstracts were analyzed for content. English language articles on therapy, prognosis, and side effects were selected, including original and review articles. There were 159 articles chosen for detailed review, and individual committee members reviewed, abstracted, and classified these articles to assess the quality of evidence-based data related to study design and treatment effect.

Articles included for analysis required the following: 1) A clearly stated diagnosis of infantile spasms. 2) An EEG demonstrating hypsarrhythmia or modified hypsarrhythmia. Hypsarrhythmia is defined as very high voltage random slow waves and spikes in all cortical areas. The spikes vary from moment to moment in duration and location.[10] Modified hypsarrhythmia includes variations such as hypsarrhythmia with increased synchronization, asymmetrical hypsarrhythmia, hypsarrhythmia with a consistent focus of abnormal discharge, hypsarrhythmia with episodes of attenuation, and hypsarrhythmia with little sharp wave activity or spike activity.[11] Articles using a routine EEG recording were acceptable for inclusion because very few articles used video-EEG monitoring. 3) Age of 1 month to 3 years. Infantile spasms were classified as either symptomatic or cryptogenic as defined by the International League Against Epilepsy.[12] The symptomatic group is characterized by "previous existence of brain damage signs (psychomotor retardation, neurologic signs, radiologic signs, or other types of seizures) or by a known etiology." The symptomatic group can be further divided into prenatal, perinatal, and postnatal groups. Prenatal causes include chromosomal abnormalities, inborn errors of metabolism, neurocutaneous syndromes, cortical malformations, and intrauterine infections. Perinatal causes include hypoxic ischemic encephalopathy and birth trauma. Postnatal causes include CNS trauma, infection, and intracranial hemorrhage.[3] The smaller cryptogenic group is characterized by "a lack of previous signs of brain damage or of known etiology." Cases described as idiopathic or "doubtful" and post immunization were included in the cryptogenic group for analysis.

Outcome measures included short- and long-term measures. Short-term outcome measures were defined as 1) complete cessation of spasms, 2) resolution of hypsarrhythmia and, where documented, normalization of EEG, and 3) relapse rate. Adverse effects and mortality were documented. In studies with a mean follow-up of >2 years, long-term outcome measures were 1) nonepileptiform EEG, 2) absence of seizures, and 3) normal development. Stringent criteria were not used in the analysis of the developmental outcome data because the results of developmental assessments were often based on clinical impression, developmental screening tools, and school placement rather than standardized, age-appropriate psychometric testing. There are very limited natural history data on infantile spasms. Thus, it is impossible to accurately quantify, but at least some children do spontaneously remit, approximately in the order of 10 to 25% according to older and uncontrolled reports.[13-15] Data recorded included description of the number of patients entering and completing the trial, age at onset of spasms, age at entry into the study, sex, etiology, drug dosage, duration of therapy, cointerventions, and duration of follow-up.

For the purposes of this practice parameter, we did not consider studies of children with Lennox-Gastaut syndrome, an epilepsy syndrome of early childhood that frequently follows infantile spasms. Studies were excluded if the patient's age was <1 or >36 months at the time of entry into the study or if an EEG was not performed to confirm the diagnosis of hypsarrhythmia or modified hypsarrhythmia. Retrospective studies were excluded if they were single case reports or case series with fewer than four infants. Studies on long-term prognosis that were uncontrolled for treatment, letters, abstracts, and unpublished data were also excluded.

A four-tiered classification scheme for diagnostic evidence recently approved by the Quality Standards Subcommittee was utilized as part of this assessment (Appendix 1). Depending on the strength of this evidence, it was decided whether specific recommendations could be made and, if so, the strength of these recommendations (Appendix 2). Evidence pertinent to each treatment together with the committee's evidence-based recommendations is presented.

## ACTH and oral corticosteroids

### Is ACTH effective in the treatment of infantile spasms?

**Evidence**—Fourteen studies met the inclusion criteria for analysis. Five were randomized controlled studies, one providing class I, one providing class II, and three providing class III evidence[16-20]; four were prospective open-label trials providing class III and class IV evidence[21-24] (table 1); and five were retrospective case series, also providing class IV evidence[25-29] (table 2). Only one class II study was placebo controlled,[17] and two were crossover studies using prednisone (class II)[17] or vigabatrin (class III).[19] Age at onset of spasms ranged from 1 week to 24 months, and age at entry into the study ranged from 1 to 34 months. All trials used video-EEG monitoring to document a treatment response. Two studies used synthetic ACTH,[19,20] and one used ACTH fragments.[22] ACTH dosage varied from 0.2 IU/kg up to 150 IU/m$^2$, and duration of treatment at the highest dose ranged from 1 to 6 weeks, with total treatment time varying from 4 to 12 weeks. All studies but one involved small numbers (5 to 59) of patients, and only two were stratified at entry into cryptogenic and symptomatic groups.

In the randomized controlled trials, cessation of spasms was reported in 87% of patients in one class I study,[16] 42% of patients in one class II study,[17] and 54 to 80% of patients in three class III studies.[18-20] Time from initiation of treatment to cessation of spasms as stated in three studies was 7 to 12 days. In all randomized controlled trials except one,[16] a greater percentage of cryptogenic patients responded to ACTH. The class I study[16] reported a response rate of 87% using high-dose ACTH therapy, whereas the class II study[17] achieved a response rate of 42% using low-dose and short-duration ACTH therapy. Two class III studies found no dose-related difference in the response rate of infantile spasms to ACTH therapy.[18,20] The relapse rate was 15% in the class I study,[16] 33% in the class II study,[17] and 19 to 24% in class III studies.[18-20]

There were four open-label prospective studies of ACTH treatment of infantile spasms: Two were class III cohort studies,[21,23] and two others were class IV.[22,24] All 5 children responded to low-dose ACTH in one class III study,[21] whereas one class IV study reported a 93% response rate in 15 children treated with high-dose therapy. Relapse rates were 20[21] and 36%, respectively.[24] One class III study compared the efficacy of synthetic ACTH with oral corticosteroids and benzodiazepines.[23] This study was stratified for symptomatic/cryptogenic etiology. In the 69 symptomatic patients treated with ACTH, 39% had cessation of spasms, and EEG normalized in 29%. Analysis of comparative efficacy between ACTH and prednisone was not possible in the cryptogenic group because the short-term responses to ACTH and to ACTH followed by prednisolone were combined into one treatment group. Use of ACTH fragments resulted in cessation of spasms in 33% of patients.[22]

The majority of studies on the use of ACTH in infantile spasms are retrospective. Five studies meeting selection criteria were analyzed, providing class IV evidence with numbers ranging from 25 to 166 children[25-29] (see table 2). Response rates for cessation of spasms ranged from 59 to 100% and resolution of hypsarrhythmia from 57 to 97%, but relapse rates ranged from 9 to 62%.

### Are oral corticosteroids effective in the treatment trials of infantile spasms?

**Evidence**—Five studies were analyzed, with numbers ranging from 12 to 39 children: two randomized controlled studies providing class II and III evidence,[16,17] two prospective open-label trials (one was a cohort study, the other with patients acting as their own controls) provided class III evidence,[23,30] and one retrospective case series provided class IV evidence[28] (table 3). Both randomized controlled trials used 2 mg/kg of prednisone for 4 to 7 weeks, and the

response rate was 29 to 33%. In a class III open prospective study, 39 symptomatic and 38 cryptogenic patients who were treated with prednisolone 2 mg/kg, had cessation of spasms in 36 and 39% of cases, respectively.[23] The EEG normalized in 28% of symptomatic patients and 42% of cryptogenic patients. In these three studies, the response rate using oral prednisone was not different from that which might be expected with no treatment based on limited natural history data, and in none of the studies were the effects of oral steroids compared with those of a placebo group. The class IV study reported cessation of spasms and resolution of hypsarrhythmia in 59% of children treated with 3 mg/kg/day of prednisone.[28] None of the controlled trials compared differing doses of oral corticosteroids.

### Is ACTH more effective than oral corticosteroids in the treatment of infantile spasms?

**Evidence—**Two class I and II randomized controlled trials,[16,17] one class III prospective open-label trial,[23] and one class IV retrospective case study[28] compared ACTH and prednisone (see tables 1 to 3). The class I randomized controlled trial demonstrated superior efficacy of high-dose ACTH therapy,[16] and the class II study showed no difference in efficacy between low-dose ACTH and prednisone.[17] High-dose ACTH therapy was superior to prednisone in the class IV study, with cessation of spasms in 100% of patients treated with ACTH vs 59% resolution of spasms in the prednisone group. The EEG normalized in 97% of ACTH-treated patients vs 50% in the prednisone group.[28]

### What are the side effects of ACTH and oral corticosteroids?

**Evidence—**In the five randomized controlled trials, hypertension was reported in 0 to 37% of patients,[17-20] irritability in 37 to 100%,[18-20] infection in 14%,[18] and cerebral atrophy in 62% of patients in one study.[20] ACTH was discontinued in 1 of 19 (5%) patients in one study because of side effects.[19] There were no deaths. In the two studies comparing high-dose vs low-dose ACTH, hypertension[18] and "cerebral shrinkage"[20] were more common in patients on high-dose ACTH. In the four prospective open-label studies, hypertension was reported in 7 to 40% of patients,[21-24] irritability in 85 to 100%,[23,24] and infection in 6%[22]; ACTH was discontinued in two of five (40%) patients in one study because of side effects.[21] There were 5 deaths in 304 cases[22,23]; in one study, two of three deaths from sepsis were directly attributable to ACTH.[23]

**Conclusions—**One class I, one class II, and five prospective class III studies demonstrate that ACTH is probably effective in the short-term treatment of infantile spasms and in the resolution of hypsarrhythmia. Time to response is usually within 2 weeks, and an "all-or-none" response has been reported in a number of studies.[17,24] The data are insufficient to determine the optimum dosage and duration of therapy. One class II and several class III studies showed limited efficacy for the use of oral corticosteroids in infantile spasms (<40% resolved) that did not differ substantially from the spontaneous rate of remission based on limited natural history data. ACTH is more effective than oral corticosteroids in causing the cessation of seizures. Side effects reported for ACTH were common and included hypertension, irritability, infection, reversible cerebral shrinkage, and rarely death due to sepsis.

### Recommendations

1. ACTH is probably effective for the short-term treatment of infantile spasms and in resolution of hypsarrhythmia (level B).

2. There is insufficient evidence to recommend the optimum dosage and duration of treatment with ACTH for the treatment of infantile spasms (level U).

3. There is insufficient evidence that oral corticosteroids are effective in the treatment of infantile spasms (level U).

## Vigabatrin

### Is vigabatrin effective in the treatment trials of infantile spasms?

**Evidence**—Fourteen studies met the inclusion criteria for analysis: one randomized placebo controlled study providing class I evidence,[31] two randomized controlled studies providing class III evidence,[19,32] six prospective uncontrolled open-label trials,[33-38] and five retrospective case series,[25,39-42] providing class IV evidence (table 4). Age at onset ranged from 1 week to 18 months, and age at treatment ranged from 2 to 28 months.

The class I randomized placebo-controlled trial (n = 20 in each group) showed that at the end of the 5-day double-blind phase, seven (35%) patients treated with vigabatrin were spasm-free and five (25%) had resolution of hypsarrhythmia compared with two (10%) and one (5%), respectively, in the placebo group (*p* = 0.063). Relapse was seen in four (20%) of vigabatrin-treated patients. Forty-two percent of those who entered the open-label phase were spasm-free. [31] In one of the larger class III studies (n = 179), 23% of patients were spasm-free 2 weeks after commencement of treatment, and this increased to 65% at the end of a 3-month open-label period.[32] In the other class III study (n = 23), 48% of patients were spasm-free and had resolution of hypsarrhythmia. Twenty-one to 44% of symptomatic patients responded compared with 27 to 57% of cryptogenic patients.[19,31,32] The relapse rate ranged from 8 to 20% across the three randomized controlled studies.[19,31,32]

In the six class IV open-label uncontrolled prospective studies (n = 6 to 116 patients), the response rate ranged from 0 to 59% for children with symptomatic infantile spasms and from 50 to 100% for cryptogenic infantile spasms; children with cryptogenic infantile spasms had a higher response rate to vigabatrin than those with symptomatic spasms across all prospective studies.[33-38]

In the nine prospective studies reviewed, vigabatrin dosages ranged from 18 to 200 mg/kg/day. The numbers were not large enough to determine if the efficacy of vigabatrin in infantile spasms was dose dependent. The time from initiation of therapy to cessation of spasms ranged from 12 to 35 days. In the class I study, 20 children who initially received placebo for 5 days before crossing over to vigabatrin had a similar outcome when compared with the 20 children who received vigabatrin at the beginning of the spasms. The time to EEG response was 7 to 35 days, and 11 to 83% of children had resolution of hypsarrhythmia. The relapse rate of infantile spasm after initial control ranged from 0% in one study with seven children with tuberous sclerosis to 29%; however, it is difficult to compare these data because the period of follow-up was widely variable, ranging from 3 months to 6.5 years.

### Is vigabatrin effective in the treatment of infantile spasms in children with tuberous sclerosis?

**Evidence**—Seven studies (total n = 45) were identified, providing class III and class IV evidence. Only those prospective studies of children with tuberous sclerosis and infantile spasms who were evaluated under 3 years of age were included.[19,32,33,35,36,38,42] The response of the infantile spasms to vigabatrin in infants with tuberous sclerosis was uniformly good, with a high percentage of responders whose spasms remitted. Overall cessation of spasms was seen in 41 of 45 (91%) of children treated with vigabatrin, with a 100% response rate seen in five studies.[19,32,35,36,38]

### What are the side effects of vigabatrin?

**Evidence**—In the three randomized controlled studies, sedation was noted in 9 to 24% of patients,[19,31,32] irritability in 4 to 9%,[19,31,32] and insomnia[32] and hypotonia[19] in 9%; vigabatrin was discontinued in 0 to 6% of patients because of side effects.[19,31,32] There were

two deaths unrelated to vigabatrin and one death in which the cause was not known across the three studies.[19,32] In the six class IV open-label uncontrolled prospective studies, sedation was noted in 14 to 16% of patients,[33,35,37] irritability in 13 to 33%,[33-36] and hypotonia in 33%.[34] None of the patients discontinued treatment, and there were no reported deaths in 244 patients across six studies.

The most significant side effect of vigabatrin is the development of concentric visual field defects, which has been reported in 10 to 40% of adult patients on vigabatrin treatment in uncontrolled case series.[44,45] This side effect also has been recently reported in children.[46, 47] In one study, 6 of 12 children receiving vigabatrin had visual field defects. Visual field assessment could not be performed in 141 additional children because of age or developmental delay.[43] Currently, the incidence of visual field deficits in infants under 1 year of age treated with vigabatrin is unknown. However, there is emerging evidence that abnormalities in the electroretinogram may occur in children as a result of vigabatrin therapy.[48]

### Is vigabatrin more effective than hormonal agents in the treatment of infantile spasms?

**Evidence**—Two studies that compared vigabatrin with steroids in the treatment of infantile spasms were analyzed: a randomized controlled trial providing class III evidence[19] and a retrospective case series providing class IV evidence.[25]

Although the vigabatrin doses were similar (100 to 150 mg/kg/day), either ACTH or hydrocortisone was used in varying doses. In the class III randomized controlled trial, the efficacy, defined as total resolution of spasms at 20 days, was not significantly different ($p = 0.12$).[19] In the class IV retrospective study, the drugs were of similar efficacy, but the outcome measure was 12 months spasm-free. In both studies, the rate of EEG improvement was superior for ACTH as compared with vigabatrin, but the relapse rate was higher for ACTH-treated children ($p$ values not stated).[25] Side effects were more common in patients treated with corticosteroids (27 to 37%) compared with 6 to 13% of patients treated with vigabatrin.

**Conclusions**—Two class III randomized controlled trials and the majority of class IV studies demonstrated that vigabatrin reduced the occurrence of infantile spasms and was associated with resolution of hypsarrhythmia, but less than half of those treated responded. One small class I study showed the same trend, but the difference was not statistically significant when compared with placebo. Vigabatrin appears to be effective within 14 days of initiation of therapy. A consensus of class III and class IV studies indicated that vigabatrin reduced the occurrence of infantile spasms in the great majority of children with tuberous sclerosis. Vigabatrin is considered by the Food and Drug Administration to be "experimental and unproven" for all indications, and it is not licensed for use in the United States. The potential of vigabatrin for retinal toxicity in children receiving the drug for infantile spasms is a concern, but the magnitude of risk is unknown and therefore cannot be factored into a risk-benefit equation.

### Recommendations

1. Vigabatrin is possibly effective for the short-term treatment of infantile spasms (level C, class III and IV evidence).

2. Vigabatrin is also possibly effective for the short-term treatment of infantile spasms in the majority of children with tuberous sclerosis (level C, class III and IV evidence).

3. Serious concerns about retinal toxicity in adults suggest that serial ophthalmologic screening is required in patients on vigabatrin. However, data are insufficient to make recommendations regarding the frequency or type of screening that would be of value in reducing the prevalence of this complication in children (level U, class IV studies).

## Other agents

### What other agents have been evaluated for the treatment of infantile spasms?

**Valproic acid**—Two studies met the inclusion criteria for analysis; both were class IV uncontrolled prospective open-label studies.[49,50] Valproate dose ranged from 25 to 100 mg/kg/day. One study reported cessation of spasms in 73% and resolution of hypsarrhythmia in 91% of 22 children at 6 months' follow-up.[50] The majority responded within 2 weeks, but 23% relapsed. Thrombocytopenia occurred in one-third of patients, requiring discontinuation of valproate in four patients. The other study reported cessation of spasms in 72% of children at 3 months' follow-up.[49]

**Nitrazepam**—Two class IV retrospective case series met the inclusion criteria for analysis. [51,52] Dose ranged from 0.5 to 3.5 mg/kg/day. Cessation of spasms was reported in 3 of 10 (30%)[51] and 13 of 24 (54%)[52] of children. Resolution of hypsarrhythmia occurred in 11 of 24 (46%) and relapse in 2 of 13 (15%) of children in one study.[52]

**Pyridoxine**—Pyridoxine has been reported to be the treatment of first choice for infantile spasms in Japan, but there are no randomized controlled trials of this drug. Two uncontrolled prospective open-label trials providing class IV evidence were analyzed.[53,54] The response rate ranged from 13 to 29% in these studies. There is no evidence to suggest that the response rate of infantile spasms to pyridoxine therapy exceeds the spontaneous remission rate that would be predicted from limited natural history data.

**Newer antiepileptic drugs and novel therapies**—Zonisamide,[55] IV immunoglobulin (IVIG),[56] liposteroid,[57] the ketogenic diet,[58] thyrotropin-releasing hormone (TRH),[59] and topiramate[60,61] all have been administered for the treatment of infantile spasms. All except one class III study[57] provided class IV evidence, either in small uncontrolled prospective open-label studies or in retrospective case series.

**Combination therapies**—Two small uncontrolled prospective open-label studies used a combination of ACTH and vigabatrin[62] and hydrocortisone and valproate,[63] providing class IV evidence. A short-term (1-week) response to ACTH plus vigabatrin was seen in all nine patients, with one child relapsing after 9 months. Cessation of spasms was seen in 77% of 94 children treated with sodium valproate and hydrocortisone within 2 weeks; 81% of 59 followed to at least age 2 years were seizure-free.

**Conclusions**—There are insufficient or inadequate data to determine whether valproic acid, nitrazepam, pyridoxine, zonisamide, topiramate, novel therapies (IVIG, liposteroid, ketogenic diet, TRH) or combination therapies are effective in the treatment of infantile spasms.

### Recommendations

1. There is insufficient evidence to recommend other treatments (valproic acid, benzodiazepines, pyridoxine, newer antiepileptic drugs, or other or novel therapies) for the treatment of infantile spasms (level U, class III and IV evidence).

## Long-term outcome

### Natural history studies

The only available information on the natural history of infantile spasms comes from an evaluation of the pre-ACTH literature, but comparison of treatment studies to natural history controls is constrained by a number of factors. Interpretation of natural history outcomes in infantile spasms that were stratified into cryptogenic and symptomatic patients proved difficult

because of limited diagnostic testing in the 1950s and 1960s, particularly in regard to the neuroimaging techniques used at that time. In addition, there were inconsistencies in the literature concerning use of the terms "cryptogenic" and "symptomatic," as previously reviewed.[1,12,64] Also, inclusion criteria differed across studies, and assessment of cognitive outcome was based on qualitative assessments including school placement rather than on formal psychometric testing. With these caveats, it is instructive to examine outcome studies of children with infantile spasms in the presteroid era.

Gibbs et al.[10] in 1954 reported long-term follow-up in 103 survivors over 3 years of age from an original cohort of 237 patients with infantile spasms. Detailed clinical and EEG data were available in 69 children. This cohort can be considered untreated as none received steroids and all drugs used at that time are known to be ineffective against infantile spasms. At age 5 or older, 11% of the children still had infantile spasms, 45% had other seizure types, and 55% were seizure-free. Hypsarrhythmia persisted in 31%, focal EEG abnormalities were noted in 52%, and the EEG was normal in 17%. Only 13% of children over 1 year of age had normal intellectual development, but the method of assessment was not stated and there was no stratification for cryptogenic and symptomatic groups. Mortality was 11% before age 2, but the cause of death was not given.

There also are reports of early, spontaneous remission of infantile spasms.[14,65] One retrospective study reported spontaneous remission in 11% of 44 patients treated with metharbital or phenytoin, but not steroids, within 6 months of the onset of spasms and in 25% by 12 months of onset.[14] However, it was not stated what percentage of children in this group developed other seizure types. This is an important omission, given the fact that approximately 20% of children with infantile spasms develop complex conditions such as the Lennox-Gastaut syndrome. The developmental outcome of children in this group was poor, with only 9% being defined as normal. This outcome was not significantly different when compared with a separate cohort treated with either low-dose ACTH or prednisone.[66]

### What is the effect of short-term treatment of infantile spasms on long-term outcome?

**Evidence—**Seven studies provided class III and IV evidence for the long-term outcome of infantile spasms. None was randomized or controlled, five were prospective open-label studies,[23,34,38,63,66] and two were retrospective case series[67,68] (table 5).

One prospective class III study reported long-term follow-up in 64 patients,[66] 48 of whom had previously been entered in randomized crossover treatment protocols.[17] The other 16 children in this cohort were treated in a prospective open-label protocol of either ACTH or prednisone.[21,30] Low-dose ACTH (20 IU) and 2 mg/kg of prednisone were used across the studies, and outcome was analyzed by treatment and etiology. The majority of children (87%) had symptomatic spasms. Mean duration of follow-up was 50 months, with a range of 9 months to 10 years. There was a 5% mortality rate in symptomatic patients, but cause of death was not stated. Cryptogenic patients had a better outcome, with 2 of 8 cryptogenic patients being cognitively normal, compared with 1 of the 56 symptomatic patients ($p < 0.05$). Infantile spasms persisted in 42% of children, whereas 53% of patients developed other seizure types and 47% were seizure-free. There was no significant difference in outcome for ACTH treatment compared with prednisone. Delay in initiation of treatment of >5 weeks from onset of the spasms had no influence on long-term cognitive outcome or on the development of epilepsy.

In the second prospective class III study, follow-up beyond 6 years was reported in 102 children from an original cohort of 121 cryptogenic cases.[23] Fifty percent of ACTH-treated patients were developmentally normal, 62% were seizure-free, and 39% had a normal EEG. When ACTH was compared with other therapies such as oral steroids, benzodiazepines, or conventional anticonvulsants, there was a significant difference in favor of ACTH for

psychometric development and achieving a seizure-free state ($p < 0.05$). An improved neurodevelopmental outcome also was associated with early commencement of therapy of <1 month.

One retrospective class IV study compared outcome in children treated with ACTH, vitamin $B_6$, and sodium valproate. Twenty-one percent of ACTH-treated and 57% of $B_6$-responsive patients had normal cognitive outcome. Fifty-six percent of ACTH-treated and 86% of $B_6$-responsive patients were seizure-free. None of the valproate-treated patients had normal IQ, but all were seizure-free.[67] As previously observed in other studies, cryptogenic patients had a better outcome. In contrast, outcome was uniformly poor in another study comparing ACTH and valproate; only 8% of patients had an IQ over 70, and 26% were seizure-free with no significant difference between cryptogenic and symptomatic or ACTH- and valproate-treated patients. Delay in initiation of treatment had no influence on long-term outcome.[68]

Two prospective open-label class IV studies reporting long-term outcome in infants treated with vigabatrin in addition to other medications were identified.[34,38] In one study, 17% of children were normal or slightly developmentally delayed, and 72% were seizure-free for at least 1 year.[34] In the other study, 36% of children were seizure-free and developmentally normal. Nine (90%) of cryptogenic patients had a good developmental outcome compared with one (3%) symptomatic patient after follow-up from 10 months to 3.5 years.[38]

These studies support that a cryptogenic etiology of infantile spasms is associated with a better long-term outcome. Other factors independent of treatment reported to be associated with a good prognosis include normal development prior to onset of spasms, with no prior neurologic deficit and absence of other seizure types in association with spasms.[23,66]

**Conclusions**—The evidence is conflicting and limited to class III and IV that treatment of infantile spasms with agents including ACTH, oral corticosteroids, vigabatrin, valproic acid, and pyridoxine improves the long-term prognosis for cognitive outcome or decreases the later incidence of epilepsy.

### Recommendations

1. The data are insufficient to make any recommendations regarding the use of ACTH, corticosteroids, vigabatrin, valproic acid, and pyridoxine to improve the long-term outcomes (seizure freedom and normal development) of children with infantile spasms (level U, class III and IV evidence).

2. The data are insufficient to conclude that early initiation of treatment should be used to improve the long-term outcome of children with infantile spasms (level U, class III and IV evidence).

**Future research**

1. Further prospective randomized masked controlled studies are required to determine the optimal treatment of children with infantile spasms, with the following features included:

   a. Studies should be stratified at entry for etiology, and inclusion criteria should include infantile spasms and the presence of either classic or modified hypsarrhythmia. The infantile spasms and EEG should be confirmed by video-EEG monitoring.

   b. A standardized pretreatment developmental assessment is necessary to enable longitudinal evaluation of cognitive outcome.

> c. A standard dose and duration of treatment are essential to allow statistical comparison of short- and long-term outcomes across centers.
>
> d. Short-term measures should be precisely defined and should include complete cessation of spasms as well as a grading of the EEG response to include resolution of hypsarrhythmia, residual epileptiform activity, or complete normalization.
>
> e. Long-term measures also should be well defined and should include cognitive outcomes using standardized psychometric assessments. The long-term incidence of epilepsy should also be determined.
>
> 2. There is a need for the development of an animal model to investigate mechanisms of epileptogenesis in infantile spasms and identify novel targets for therapeutic development
>
> 3. Efficacy of newer anticonvulsants should specifically be assessed, based on a knowledge of their mechanisms of action.

## Acknowledgments

## Appendix 1: American Academy of Neurology evidence classification scheme for a therapeutic article

Class I: evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) Primary outcome(s) is/are clearly defined; (b) exclusion/inclusion criteria are clearly defined; (c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; and (d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above *or* a randomized control trial in a representative population that lacks one criteria of a–d.

Class III: all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: evidence from uncontrolled studies, case series, case reports, or expert opinion.

## Appendix 2: American Academy of Neurology system for translation of evidence to recommendations

| Translation of evidence to recommendations | Rating of recommendation |
| --- | --- |
| Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies. | A = established as effective, ineffective, or harmful for the given condition in the specified population. |
| Level B rating requires at least one convincing class II study or at least three consistent class III studies. | B = probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. |
| Level C rating requires at least two convincing and consistent class III studies. | C = possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. |
| | U = data inadequate or conflicting. Given current knowledge, treatment is unproven. |

## Appendix 3: Quality Standards Subcommittee Members

Gary Franklin, MD, MPH (co-chair); Gary Gronseth, MD (co-chair); Charles E. Argoff, MD; Stephen Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD; Michael Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; Samuel Wiebe, MD; and William J. Weiner, MD, Catherine Zahn, MD (ex-officio).

## Appendix 4: Child Neurology Society Practice Committee

Carmela Tardo, MD (chair); Bruce Cohen, MD (vice-chair); Elias Chalhub, MD; Roy Elterman, MD; Murray Engel, MD; Bhuwan Garg, MD; Brian Grabert, MD; Annette Grefe, MD; Michael Goldstein, MD; David Griesemer, MD; Betty Koo, MD; Edward Kovnar, MD; Leslie Ann Morrison, MD; Colette Parker, MD; Ben Renfroe, MD; Michael Shevell, MD; Shlomo Shinnar, MD; Gerald Silverboard, MD; Russell Snyder, MD; Dean Timmons, MD; and Greg Yim, MD.

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**Table 1**

**Prospective ACTH studies: Short-term results**

| Ref. | n | Class | Type of ACTH (dose) | No. wk of full dose | Total Rx, wk | Other Rx | Mean (range) F/U, mo | % Spasms stopped | SIS vs CIS, % | Resolution of hypsarrhythmia, % | Relapse, % | Side effects, % | Time to improved |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 59 | I/III* | N* | 3 | 12 | No | NS | 54 | 49 vs 78 | 22 RH | 19 | 18% HPT, 42% Irrit[†] | NS |
| High dose | | | N (150 IU/m²) | 3 | 12 | No | NS | 50 | 45 vs 75 | 23 | 15 | 31% HPT, 46% Irrit | NS |
| Low dose | | | N (20 IU/m²) | 3 | 12 | No | NS | 58 | 52 vs 80 | 21 | 21 | 4% HPT, 37% Irrit | NS |
| 16 | 15 | I/III* | N (150 IU/m²) | 2 | 4 | No | 15 | 87[#] | 92 vs 67 | 87 RH | 15 | NS | 1 wk |
| | 14 | | Prednisone (2 mg/kg/d) | 2 | 4 | No | 16.9 | 29 | 30 vs 25 | 29 RH | NS | NS | 75% in 2 wk |
| 17[‡] | 12 | II | N (20 IU/m²) | 6 | 7 | No | NS | 42 | NS | 42 RH | 33 | 24% HPT | |
| | 12 | | Prednisone (2 mg/kg/d) | | | No | NS | 33 | NS | 33 RH | 29 | 25% HPT, 63% Atrophy | 33% in 2 wk |
| 20 | 25 | III | S§ | 6 | 6 | Yes | 12 | 80 | 75 vs 88 | 75 SIS/88 CIS | 45 SIS/16 CIS | | NS |
| Low dose | 12 | | (0.2 IU/kg) | 2–4 | 4–6 | Yes | | 75 | 75 vs 75 | 75 SIS/75 CIS[||] | 50 SIS/0 CIS | 7% Atrophy, 92% Sed, 100% Irrit | NS |
| High dose | 13 | | (1.0 IU/kg) | 4–6 | 4–6 | Yes | | 85 | 75 vs 100 | 75 SIS/100 CIS[||] | 40 SIS/33 CIS | 12% Atrophy, 83% Sed, 100% Irrit | NS |
| 19[‡] | 19 | III | S (10 IU/d) | 5.7 | 5.7 | No | (9–44) | 74 | 64 vs 88 | 78 CN/100 RH | 24[¶] | 37% HPT, 5% Irrit | 12 d |
| | 23 | | VGB (100–150 mg/kg/d) | 5.7 | 5.7 | No | (9–44) | 48 | 44 vs 57 | 36 CN/48 RH | 8 | 13% Drowsy, Hypotonia, Irrit | 14 d |
| 21 | 5 | III | N (20–40 IU) | NS | 6–10 | No | 10 | 100 | NS | 100 CN | 20 | 40% HPT | 1 wk |
| 23** | | III | N | Var | Var | NS | 6 y | | | | | 19% HPT, 12% Hypo-$K^+$, 3 died | NS |
| SIS | 69 | | N (110 IU/m²) | 3 | 8 | NS | 10 | 39 | | 29 CN | NS | | NS |
| CIS | 36 | | N (110 IU/m²) | 3 | 8 | NS | 10 | 58[††] | | 59 CN | NS | | NS |
| CIS | 37 | | ACTH, prednisolone | 8, 14–20 | Var | NS | 10 | 58[††] | | 59 CN | NS | | NS |
| 24 | 15 | IV | N (150 IU/m²) | 1 | 12 | Yes | 43.3 | 93 | NR | 93 | 36 | 100% Irrit, 13% serious side effects | 3 wk |
| 22 | 18 | IV | ACTH, 1–24 (0.8 mg/kg) | 4 | 6 | Yes | 6 | 33 | 21 vs 75 | 33 | NS | 11% HPT, 6% Pneum, 11% died | |

*The studies by Hrachovy et al [18] and Baram et al [16] are considered class I studies when one is comparing high-dose vs low-dose ACTH or ACTH vs prednisone but class III studies when considering whether either medication was effective in decreasing the number of infantile spasms because neither study contained a placebo-controlled group.

[†]Total of 42 adverse events.

[‡]Results prior to crossover (phase I).

§Progressive dosage regimen starting at 0.2 IU/kg and increasing to 1.0 IU/kg.

||No statistically significant difference between etiologic subgroups.

¶After crossover (at the end of phase II).

#$p \leq 0.02$ compared to prednisone group.

**Short-term outcome at 10 mo. Numbers of patients differ in Methods and Results.

††Results combined for ACTH alone and ACTH plus PNL treatment groups in CIS patients.

ACTH = adrenocorticotropic hormone; Rx = treatments; F/U = follow-up; SIS = symptomatic infantile spasm; CIS = cryptogenic infantile spasm; N = natural; NS = not stated; RH = reversal of hypsarrhythmia; HPT = hypertension; Irrit = irritability; S = synthetic; Sed = sedation; VGB = vigabatrin; CN = completely normal; Var = variable; Hypo-K+ = hypokalemia; Pneum = pneumonia.

**Table 2**

**Retrospective ACTH studies: Short-term results**

| Ref. | n | Class | Type of ACTH (dose) | No. wk of full dose | Total Rx, wk | Other Rx | Mean F/U, mo | Cessation of spasms, no. (%) | SIS vs CIS, no. (%) | Resolution of hypsarrhythmia, no. (%) | Relapse, % | Side effects, % | D/C* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | 25 | IV | N (110 IU) | 2.1 | NS | No | 26.5 | 14 (67) | 8 (89) vs 10 (83) | 12 (57) | 4(27) | 27 | 3 |
| 26 | 22 TS | IV | N (20–140 IU) or S (0.2–1.2 mg) | 6 | 6 | NS | 98 | 16 (73) | NR | NS | 10(62) | HPT 45, CM 9 | |
| | 25 CIS | | | NS | NS | NS | | 20 (80) | | NS | 6(30) | | |
| | 119 SIS | | | NS | NS | NS | | 71 (59) | | NS | 22(31) | | |
| 27 | 26 | IV | N (40–129 IU/m²) | 2–25 | 4.5–44 | NS | 36 | 17 (65) | NR | 17 (65) | 2(12) | NS | NS |
| 28 | 30 | IV | N (150 IU/m²) | 1 | 12 | NS | 25 | 30(100) | NS | 29 (97) CN | 14(47) | NS | |
| 29 | 55 | IV | N (80 IU alt) | 2 | 6–14 | Yes | 53 | 41 (75) | NS | NS | 5 (9) | Pneum 2 | 0 |
| Early, <1 mo | 31 | | | | | | | 27 (87)† | | | | | |
| Late | 24 | | | | | | | 14 (58) | | | | | |

*
Discontinued because of side effects.

†
$p < 0.002$.

ACTH = adrenocorticotropic hormone; Rx = treatments; F/U = follow-up; SIS = symptomatic infantile spasm; CIS = cryptogenic infantile spasm; N = natural; NS = not stated; TS = tuberous sclerosis; S = synthetic; NR = not relevant; HPT = hypertension; CM = cardiomyopathy; CN = completely normal; alt = alternate days; Pneum = pneumonia.

**Table 3**

**Treatment with oral steroids: Short-term treatment**

| Ref. | n | Class | Type of steroid (dose) | Duration of full dose, wk | Total treatment duration, wk | Other Rx | Mean F/U, mo | Cessation of spasms, no. (%) | SIS vs CIS, no. (%) | Resolution of hypsarrhythmia, no. (%) | Relapse, no. (%) | Side effects, no. (%) | Time to improved |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | 14 | I/III* | Prednisone (2 mg/kg) | 2 | 4 | No | 16.9 | 4(29) | 3 (30) vs 1 (25) | 4 (29) RH | NS | Nil ceased Rx | 1 wk |
|  | 15 |  | ACTH (150 IU/m²) | 2 | 4 | No | 15 | 13(87) | (92) vs (67) | 13 (87) RH | (15) | Nil ceased Rx | 1 wk |
| 17† | 12 | II | Prednisone (2 mg/kg) | Variable | Variable | No | NS | 4(33) | NS | 4 (33) RH | 2 (29) | HPT 6 (25), 10 (63) atrophy | 33% w/in 2/52 |
|  | 12 |  | ACTH (20 IU/m²) | 6 | 7 | No | NS | 5(42) | NS | 5 (42) RH | (33) |  | 75% w/in 2/52 |
| 23‡ |  | III | Prednisolone (2 mg/kg) | 8 | 20–32 | NS | 10 |  |  |  |  | HPT (10) | NS |
| CIS | 38 |  | Prednisolone (2 mg/kg) | 8 | 20–32 | NS | 10 | 15(39) | NS | 16 (42) CN | NS |  | NS |
| SIS | 39 |  | Prednisolone (2 mg/kg) | 8 | 20–32 | NS | 10 | 14(36) | NS | 11 (28) CN | NS |  | NS |
| 30 | 12 | III | Prednisone (2 mg/kg) | 6 | 20 | NS | NS | 3(25) | NS | 3 (25) | 0 (0) | NS | NS |
| 28 | 22 | IV | Prednisone (3 mg/kg) | 4 | 16 | NS | 47 | 13(59) | NS | 11 (50) CN | 8 (62) | NS | Mean 7 d |

The study by Baram et al.[16] is considered a class I when comparing ACTH vs prednisone but class III study when considering whether either medication was effective in decreasing the number of infantile spasms because it did not contain a placebo-controlled group.

*Results prior to crossover (phase I).

†Short-term outcome at 10 mo.

‡Rx = treatment; F/U = follow-up; SIS = symptomatic infantile spasms; CIS = cryptogenic infantile spasms; RH = reversal of hypsarrhythmia; NS = not stated; ACTH = adrenocorticotropic hormone; HPT = hypertension; CN = completely normal.

**Table 4**

**Vigabatrin studies: Short-term results**

| Ref. | n | Class | Dose, mg/kg | Other Rx | Mean (range) F/U, mo | Cessation of spasms, no. (%) | Cessation at later F/U, no. (%) | SIS vs. CIS, no. (%) | Resolution of hypsarrhythmia, no. (%) | Relapse, no. (%) | Side effects, no. (%) | D/C, no. (%) | Time to improved, d |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 | 40 | I | 150 | Yes | 5 | 15 (42)* | | 9 (32) vs 6 (50) | | | 1 (2) died | Nil | 12 |
| Placebo | 20 | | | | | 2 (10)† | | | 1 (5) | 2 (10) | 6 (30) | Nil | |
| VGB | 20 | | | | | 7 (35)† | | | 5 (25) | 4 (20) | 12 (60) | Nil | |
| 32 | 179 | III | | Yes | (3–24) | 32 (23)‡ | 87 (65)‡ | 20 (21) vs 45 (27) | 32 (23)‡ | 14 (16) | Sed 42 (25), Insom 15 (9), Irrit 15 (9) | 9 (6) | NS |
| LD | 90 | | 18–36 | | | 8 (11) | NS | | 8 (11) | NS | | | |
| HD | 89 | | 100–148 | | | 24 (36) | NS | | 24 (36) | NS | | | |
| 19§ | 23 | III | 100–150 | No | (9–24) | 11 (48) | 11 (48) | 7 (44) vs 4 (57) | 11 (48)// | 1 (8)¶ | 2 (13), 1 (5) died** | I(4) | 14 |
| 33 | 116 | IV | 50–200 | No | 23 | 45 (39) | 45 (39) | 24 (29) vs 21 (62) | 45 (39) | 20 (17) | Sed 19 (16), Irrit 15 (13) | Nil | 30 |
| 34 | 23 | IV | 50–150 | Yes | 65 | 11 (48) | 13 (72)†† | 7 (37) vs 4 (100) | NS | 3 (14) | 2 (10) 2 died‡‡ | Nil | 35 |
| 35 | 29 | IV | 50–125 | No | 18 | 17 (59) | | 13 (59) vs 4 (66) | NS | 5 (29) | Weight gain, Irrit, Sed 4 (14) | Nil | NS |
| 36 | 6 | IV | 50–100 | No | 13 | 4 (75) | | 1 (33) vs 3 (100) | 5 (83) | 1 (25) | Hypotonia, Irrit 2 (33) | Nil | NS |
| 37 | 28 | IV | 75–150 | No | 20 | 18 (57) | | 8 (47) vs 6 (55) | 14 (50) | 0 (0) | Sed 4 (14) | Nil | 14 |
| 38 | 42 | IV | 40–150 | Yes | 10 | 11 (26) | | 6 (19) vs 5 (50) | NS | 3 (27) | Mild | Nil | 17 |
| 25 | 21 | IV | 100–150 | NS | 21 | 14 (67) | 11 (69) | 8 (72) vs 8 (80) | 8 (39) | 1 (6) | 3 (14) | Nil | NS |

| Ref. | n | Class | Dose, mg/kg | Other Rx | Mean (range) F/U, mo | Cessation of spasms, no. (%) | Cessation at later F/U, no. (%) | SIS vs. CIS, no. (%) | Resolution of hypsarrhythmia, no. (%) | Relapse, no. (%) | Side effects, no. (%) | D/C, no. (%) | Time to improved, d |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 39 | 18 | IV | 50–150 | No | 25 | 9 (50) | | 4 (36) vs 5 (71) | NS | 5 (56) | Irrit, Sed 2 (11) | Nil | NS |
| 40 | 25 | IV | 60–80 | NS | 19 | 16 (64) | | 13 (68) vs 3 (50) | 19 (76) | 4 (25) | 3 (12) Irrit 2, Sed 1 | Nil | 12 |
| 41 | 7 | IV | 50–100 | Yes | NS | 4 (57) | | 3 (75) vs 1 (50) | 1 (14) CN | 0 (0) | NS | NS | 21 |
| 42 | 250 | IV | 25–400 | Yes | 8 | 131 (68) | | 97 (75) vs 43 (69) | 132 (69) | 28 (21) | 33 (13) | 2 (1) | 7 |

*
Following entry to open-label phase.

†
At end of double-blind phase.

‡
Fifty-two percent of tuberous sclerosis patients were spasm-free and had no hypsarrhythmia 2 wk after starting treatment. The number of patients seizure-free increased to 87 (65%) at 3 mo.

§
Results describe outcome at end of phase I (prior to crossover).

‖
Four (36%) have completely normal EEG.

¶
At end of phase II (after crossover).

**
Cause of death unrelated to treatment.

††
Outcome at 3 mo.

‡‡
Cause of death not stated.

Rx = treatments; F/U = follow-up; SIS = symptomatic infantile spasm; CIS = cryptogenic spasm; D/C = discontinued because of side effects; VGB = vigabatrin; Sed = sedation; Insom = insomnia; Irrit = irritability/agitation; LD = low dose; NS = not stated; HD = high dose; CN = completely normal.

**Table 5**

**Results of treatment of infantile spasms on long-term outcome**

| Ref. | Class | n | Dose | Duration of full dose, wk | Total Rx duration, wk | Other Rx | Mean (range) F/U | Normal development, no. (%) | Normal EEG, no. (%) | Seizure-free, no. (%) | Deaths, no. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 66 | III | 64 | | 6 | 6 | No | 50 mo | 3 (5)* | NS | 30 (47) | 3 (5)† |
| | | 8 | CIS | | | | 44 mo | 2 (25)‡ | | | |
| | | 56 | SIS | | | | 51 mo | 1 (2) | | | |
| | | 28 | ACTH 20–30 IU | 6 | 6 | No | | 1 (4) | | | |
| | | 36 | PNL 2 mg/kg/d | 6 | 6 | No | | 2 (6) | | | |
| 23 | III | 102 | | Var | Var | NS | >6 y | | | | 3, 2§ |
| | | 36 | ACTH 110 IU/m² | 3 | 8 | NS | | 18 (50) | 14 (39) | 23 (62) | |
| | | 37 | ACTH 110 IU/m², PNL 2 mg/kg/d | 14–20 | 22–28 | NS | | 22 (59) | 15 (41) | 24 (65) | |
| | | 17 | PNL 2 mg/kg/d | 8 | 20–32 | NS | | 2 (12) | 7 (41) | 5 (29) | |
| | | 12 | AED | NS | NS | NS | | 2 (17) | 4 (33) | 3 (25) | |
| 67 | IV | 109 | | NS | NS | NS | 11.5 y | 26 (24)∥ | NS | 64 (59) | 0 (0) |
| | | 14 | CIS | | | | | 10 (71) | NS | 13 (93) | |
| | | 95 | SIS | | | | | 16 (17) | NS | 51 (54) | |
| | | 14¶ | B₆ 30–400 mg/d | NS | NS | NS | | 8 (57) | NS | 12 (86) | |
| | | 77 | ACTH 10 IU | 2.4 | NS | NS | | 16 (21) | NS | 43 (56) | |
| | | 4 | VPA 21–42 mg/kg/d | NS | NS | NS | | 0 (0) | NS | 4 (100) | |
| 68 | IV | 28 | | NS | NS | NS | NS (23–88) mo | 2 (8)** | NS | 7 (26) | |
| | | | CIS | | | | | 0 (0) | NS | 2 (20) | |
| | | | SIS | | | | | 4 (23) | NS | 4 (23) | |
| | | | ACTH 80 IU | | | | | 0 (0) | NS | 2 (20) | 2 (18) |
| | | | VPA 60 mg | | | | | 4 (25) | NS | 4 (25) | 5 (31) |
| 34 | IV | 18 | VGB 50–150 mg/kg/d | | | Yes | 5.35 y | 3 (17)†† | 4 (22) | 13 (72) | 2 (10) |
| 38 | IV | 42 | VGB 40–150 mg/kg/d | | | Yes | 10–42 mo | 10 (26) 1 (3) SIS vs 9 (90) CIS | NS | 23 (59) 13 (45) SIS vs 10 (100) CIS | 3 (7) |
| 63 | IV | 94 | VPA 40 mg/kg/d, H/C 15 mg/kg/d | | | No | 3.1 y | 26 (37) 6 (18) SIS vs 20 (74) CIS** | NS | 48 (81) 28 (85) SIS vs 20 (74) CIS | NS |

\*
$IQ > 80$.

†All symptomatic patients.

‡$p < 0.025$ for CIS $vs$ SIS patients.

§Two deaths secondary to complications of ACTH.

‖Developmental quotient > 75.

¶Only reported long-term outcome in $B_6$-responsive cases.

\*\*
$IQ > 70$.

††Normal or slightly delayed.

Rx = treatment; F/U = follow-up; CIS = cryptogenic infantile spasm; SIS = symptomatic infantile spasm; ACTH = adrenocorticotrophic hormone; PNL = prednisone; VGB = vigabatrin; VPA/HC = combination of sodium valproate and hydrocortisone; $B_6$ = vitamin $B_6$; AED = antiepileptic drug; NS = not stated; Var = variable.