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Topical Review

Infantile Spasms: Outcome in Clinical Studies

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ABSTRACT

Children with infantile spasms are likely to have a poor outcome. Outcome measures for infantile spasms include primary response to treatment, relapse of spasms, neurological development, death, and progression to another type of epilepsy (Consensus Statements of the WEST Delphi Group 2004). This review is based mainly on prospective studies and emphasizes data about the current first-line drugs, adrenocorticotropic hormone, vigabatrin, and prednisolone, taking into account the proportion of patients with known and unknown etiology, which has a very strong effect on seizure outcome. In most studies, hormonal treatment (adrenocorticotropic hormone or prednisolone) is the optimal monotherapy, except for patients with tuberous sclerosis complex, in whom vigabatrin appears superior. Combination therapy (hormones plus vigabatrin) may well be more effective than either agent alone. The underlying etiology is the most important prognostic factor. In studies with a long follow-up (up to 50 years), a favorable cognitive outcome has been observed in approximately one quarter of patients and complete seizure freedom in one-third. Autism is relatively frequent, and premature mortality is high throughout life. Modifiable prognostic factors include early recognition of the spasms with prompt treatment, short duration of hypsarrhythmia, prompt treatment of relapses of spasms and multifocal epileptic discharges, and early treatment of adverse effects. It is hoped that eventually advanced genetics and molecular data will allow an understanding of the pathogenetic mechanisms of many specific etiologies to allow disease-specific treatment such as is emerging for tuberous sclerosis.

Introduction

An important goal for the treatment of children with infantile spasms is good cognitive outcome, but unfortunately, most of them have significant neurodevelopmental deficits. Good cognitive outcome seems to be dependent on prompt cessation of spasms and resolution of hypsarrhythmia. A number of well-designed clinical trials have compared current treatment options, although most studies have evaluated only short-term outcome. There are only a few prospective studies—most have short follow-ups and long-term outcome studies are scarce.

Outcome measures for infantile spasms have been outlined by the West Delphi Group using a Delphi methodology with 46 invited clinicians from 15 countries.[1] Consensus was reached for the importance of the following outcomes: primary clinical response, primary electroclinical response, relapse-free primary response (clinical and electroclinical), continuing subtle spasms without clinical spasms, distribution of time to relapse, proportion of relapse-free remission over time, development at age two years, death and other serious events, presence of seizures and progression to other seizure types, and nonserious adverse events. Most of these outcome measures apply both to study design and clinical practice. The group failed to reach a consensus on the definition of hypsarrhythmia.[1]

Outcome

This review emphasizes several key issues about infantile spasms—the relationship between etiology and outcome, the results of short-term treatment, adverse effects of treatment, long-

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term outcome, and the changes that could be made to therapeutic protocols to improve the outcome.

Does the etiology influence the outcome?

Etiology appears to be the most important predictor of outcome. In the past, etiology of infantile spasms was charcterized as symptomatic and cryptogenic, terms that have been used inconsistently in the literature by various authors. A small number of patients was said to have an idiopathic etiology. The updated classification refers simply to known (symptomatic) and unknown (cryptogenic) etiologies.[5,6] In symptomatic spasms, there is often a pre-existing encephalopathy, abnormal neurological signs, and/or significant abnormalities on brain imaging. Individuals with no known cause ("cryptogenic") for their infantile spasms typically have normal prior development, symmetric spasms, and no atypical features (such as asymmetric, asynchronous, focal, subtle spasms, or spasms associated with partial seizures). They also tend to exhibit typical findings on electroencephalography (EEG).[2] Some patients have no known cause for their infantile spasms ("cryptogenic") even after undergoing a thorough evaluation, including state-of-the-art brain imaging and any relevant metabolic and genetic studies.

Idiopathic spasms are attributed to a known or presumed genetic predisposition and have a favorable outcome.[3] Idiopathic spasms cannot be confirmed with certainty at the time of diagnosis, and the terms idiopathic and cryptogenic spasms are often synonymous in the older literature.[4] Over time, the evaluation of spasms has become more sophisticated, with genetic and metabolic studies and more comprehensive magnetic resonance imaging (MRI) investigations. Consequently, some children with a previously unknown etiology would now be classified as having symptomatic spasms. The most recent classification of the etiology of infantile spasms groups the causes as structural-metabolic, genetic, infectious-immune, and unknown groups.[5,6]

Thus symptomatic and cryptogenic are not very satisfactory descriptive terms. However, the literature that defines most of what we know about infantile spasms uses the old classification and consistently has found that "cryptogenic" group has the best response to treatment and best long-term outcome. In this review these older, established terms are often used[7] because they cannot be easily translated into the newer classification. Where possible the newer classification will be applied.

MRI appears to be the most important tool to categorize patients as having cryptogenic (unknown cause) or symptomatic etiology (known cause), and brain structural abnormalities markedly influence the prognosis. MRI may be repeated between age 18 months and two years, because subtle focal cortical dysplasia may be undetectable at onset of infantile spasms but become visible as myelination progresses. According to Wirrell et al., cost-effective evaluation for those without an obvious cause after initial clinical evaluation and MRI includes an array comparative genomic hybridization followed by an epilepsy gene panel if the microarray is not definitive, serum lactate, serum amino acids, and urine organic acids.[8] In this multicentered study (the National Infantile Spasms Consortium) 251 patients were investigated. An obvious cause was found after initial examinations (clinical assessment and/or MRI) in 138 (58%). For those without an identified cause after the initial examination, genetic testing showed a causal abnormality in 23.5% and a variant of unknown significance in 14.8%. Only three children underwent whole-exome sequencing, all with normal results.[8] In the multicenter, Epilepsy/Genome Project database, 100 of 126 patients with infantile spasms of unknown etiology underwent whole-exome sequencing. Pathogenetic *de novo* variants were identified in 15 individuals (15%). If no cause is identified, whole-exome sequencing should be strongly considered.[9]

At the first clinical evaluation the doctor may be able to offer the prognosis to parents, if it looks favorable. If the etiology remains unknown and development was normal before spasm onset, the patient will become free of spasms and have normal or nearly normal psychomotor development in about 80% cases.[10-13] Some symptomatic cases may also have a favorable prognosis; spasms may also cease in 50% patients, and the development will be roughly normal in about 20% cases.[14-16]

Patients with symptomatic etiology may have a favorable seizure outcome if the etiology is neonatal hypoglycemia (N = 9 of 147),[14] Down syndrome (N = 17 of 43),[17,18] stroke or infarct (N = 12 of 377),[19] periventricular leukomalacia (PVL) (N = 8 of 32),[20] and neurofibromatosis (N = 4 of 5).[18] The outcome is almost always poor in children with severe brain malformations,[14] postinfectious etiology,[14] and tuberous sclerosis complex (TSC) (N = 53 of 53).[21,22] Individuals with primarily genetic causes, such as SCN2A, are more likely to have poor developmental outcomes.[23,24]

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

Most studies report the results of short-term treatment, usually after two to three weeks of treatment. The proportion of patients with known versus unknown etiology should be noted in every study, because the response to therapy is consistently better in the unknown etiology group.[11,12]

The methodology of reported studies has been very variable including the choice of drugs and their formulations, lead time from spasm onset to therapy, and dose and duration of therapies.

Prospective studies of children treated with hormonal and vigabatrin (VGB) therapies are shown in Tables 1 and 2. Based on these studies, hormonal therapy with adrenocorticotropic hormone (ACTH), tetracosactide, or prednisolone or VGB treatment are currently the preferred first-line treatments for infantile spasms. The proportion of patients with resolution of their spasms varies in prospective studies. For ACTH, response rates vary from 36.7% to 87% (mean 61%, 10 studies); for prednisolone, from 11% to 70% (mean 46%, four studies), and for VGB, from 11% to 58% (mean 36%, eight studies) (Tables 1 and 2).

There are two large prospective studies from the United States and United Kingdom.

US study

Knupp et al.[31] reported the results of the multicenter, prospective National Infantile Spasms Cohort study. A total of 230 consecutive children with infantile spasms had their treatment selected by the attending physician, and cases included both those with unknown and known etiology. The overall response rate was lower than reported in studies focusing on low-risk patients. The clinical and electrographic treatment response was evaluated three months after the onset of treatment. A good response occurred in 53 of 97 (55%) of those who received ACTH, 21 of 54 (39%) of those who received prednisolone, and 17 of 47 (36%) who received VGB. Surprisingly, neither the etiology nor the pretreatment developmental status substantially modified the treatment response.

UK study

The large, multicenter, randomized, United Kingdom Infantile Spasm Study (UKISS) compared hormonal (prednisolone or tetracosactide) therapy and VGB in the short-term treatment (14 days) of infantile spasms in 107 children. The response rates at 14 days

TABLE 1.
Short-Term Outcome of Patients With Infantile Spasms Treated With Steroids or ACTH in Prospective Studies

Class of Evidence	No. of Patients	CIS (% of Patients)	ACTH Dose	Duration at Full Dose (Weeks)	Total Treatment Duration (Weeks)	Spasms Stopped (%)	EEG Resolution	Time Point to Evaluate the Response	References
III	105	39	110 IU/m^2	3	8	49	39	10 mo	Lombroso[25]
I	26	ND	150 IU/m^2	3	12	54	23	23 mo	Hrachovy et al.[26]
	24		20 IU/m^2	3	12	58	21	21 mo	
I	15	25	150 IU/m^2	2	4	87	87	16 mo	Baram et al.[27]
	12	40	Prednisolone 2 mg/kg/d	2	4	33	33	16.9 mo	
III	19	48	10 IU	3-5; 5	5-6	74	78	9-44 mo	Vigevano and Cilio[28]
III	25	48	Tetracosactide 0.5 mg every second day	2	ND	76	70	2 wk	Lux et al.; UKISS[29]
	30	43	Prednisolone 40 mg/d	2	10	70	70	10 wk	
III	97	14	20-40 IU/d	3	5-6	64	77	3 wk	Riikonen[30]
	54	13	120 IU/d	3	5	54	74	3 wk	
I	97	25	ACTH	2	4	55	N.D.	3 mo	Knupp et al.[31]
	54	13	Prednisolone	2	4	23			
1	49	ND	40-60 IU/d	2	5	36,7	18	4 wk	Wanigashinghe et al.[32]
	48	ND	Prednisolone	2	5	58,3	44	4 wk	
1	186	45	Hormonal therapy with VGB, combination therapy	42 d	3 mo	72	66	42 d	O'Callaghan et al.; ICISS study[33]
1	191 ACTH N = 60 Prednisolone N = 130	46	ACTH 0.5 mg every second day, prednisolone 40-60 mg/d, hormonal therapy	42 d	1 mo	57	55	42 d	O'Callaghan et al.; ICISS study[33]
III	66	48	Prednisolone after VGB	VGB 3 mo prednisolone 42 d	6	72	ND	7 mo	Ko et al.[34]

Abbreviations:
ACTH = Adrenocorticotropic hormone
CIS = Cryptogenic infantile spasms
EEG = Electroencephalography
IU= International units
ND = No data
VGB = Vigabatrin

were 40 of 55 (73%) for infants assigned to hormonal treatments (prednisolone 21 of 30 [70%], tetracosactide 19 of 25 [76%]) and 28 of 52 (54%) for infants assigned to VGB. Cessation of spasms was statistically more likely in infants receiving hormonal treatment than in those given VGB. TSC was excluded.[29] However, with further follow-up to 14 months, there was no difference in spasm control between treatments.[38] Better initial control of spasms by hormonal treatment in those with no identified underlying etiology was considered to lead to improved developmental outcome.[38]

The International Collaborative Infantile Spasms Study

O'Callaghan et al. presented a multicenter, open-label, randomized trial, the International Collaborative Infantile Spasms Study (ICISS), carried out in 102 hospitals in five countries. This study with 377 patients is the largest randomized trial of treatment of infantile spasms and found that a combination of hormonal (tetracosactide or high-dose prednisolone) and VGB was more effective at stopping the spasms between days 14 and 42 than hormonal (ACTH or prednisolone) therapy alone. The spasm resolution response rate was 133 of 186 (72%) patients on hormonal therapy combined with VGB, versus 108 of 191 (57%) patients on hormonal therapy alone.[33] Details of specific diseases and their response to treatment were given in a further ICISS report by Osborne et al. One hundred fifty-seven (42%) had no identified etiology and 219 (58%) had a proven etiology, of whom 128 responded, 58 of 108 (54%) were allocated hormonal treatment, and 70 of 111 (63%) were allocated combination treatment. Stroke and infarct had a better average response to treatment than other underlying etiologies.[19] TSC was excluded from the study.

TABLE 2.
Short-Term Outcome of Patients With Infantile Spasms Treated With Vigabatrin in Seven Prospective Studies

Class of Evidence	No of Patients	CIS (% of Patients)	Vigabatrin mg/kg/d	Duration at Full Dose	Spasms Stopped (%)	EEG Resolution %	Time Point to Response Evaluation	References
I	20	30	50-150	5 d	35	23	12 d	Appleton et al.[35]
III	75	28	18-36	12 wk	11	ND	14 d	Elterman et al.[36]
	67	33	100-150	12 wk	23	ND	14 d	
III	23	39	150	ND	48	36	20 d	Vigevano and Cilio[28]
III	52	38	100-150	14 wk	54	50	14 d	Lux et al.[29]
I	47	2	100-150	Variable	36	ND	3 mo	Knupp et al.[31]
III	180	25	50-150	17 d	58	56	14 d	Djuric et al.[37]
III	42	23	50-150	7-20 d	26	26	20 d	Granström et al.[10]

Abbreviations:
CIS = Cryptogenic infantile spasms
EEG = Electroencephalography
ND = No data

A few other, small, less rigorous studies[10,31,34] have suggested that polytherapy may be more effective than monotherapy; however, these studies used different medications with different mechanisms of action and are not considered definitive. It seems clear that when the first treatment has failed, an alternative should be given. Increasing evidence suggests that combination of steroid and VGB, either successively or simultaneously, is more effective than one drug alone.

Nonetheless, it may be important to emphasize that simultaneous administration of the two drugs exposes the patients to the adverse effects of both drugs.

ACTH

ACTH has been in use for treatment for infantile spasms since 1952 and remains the first-line drug for treatment, as shown in the current therapeutic algorithm (Table 3).

In 2004 and 2012, the American Academy of Neurology and Child Neurology Society reported guidelines for the treatment of infantile spasms.[4,42] The aim was to determine the overall strength of evidence and formulate recommendations. Relevant studies during the period 2002 to 2011 were separated from a collection of studies published before 2002. These systematic reviews identified 1935 possibly relevant publications, but based on methodology, only 68 were selected for detailed review and only 26 contributed to the final analysis. In 2015, the International League Against Epilepsy Commission on Pediatrics also provided a summary of recommendations for management of infantile seizures.[43] All three of these summary statements were published before the ICISS combination study.

Dose and duration of therapy

Doses of ACTH vary in different countries: Japan, 0.1 mg/day,[44] and more recently, 0.0125 mg/kg/day[45]; Finland, 0.5 mg on alternate days[46,47]; United Kingdom, 0.5 mg on alternate days[29]; and the United States, 60 to 80 IU/day (=0.6 to 0.8 mg/day).[48] Considerably higher doses per kilogram are used for infants in the United States than in Japan. The reason for this difference is unknown.

In the analysis by the American Academy of Neurology and Child Neurology Society, it was concluded that there are insufficient data to recommend an optimal dose of ACTH or duration of treatment for infantile spasms.[4] In 2012, the evidence-based guidelines update[42] suggested that low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms (Class I and II evidence). Therefore, the following recommendation was given: low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B moderate research-based evidence).

Still, in 2012 high-dose ACTH continued to be the most commonly used first-line drug for infantile spasms in the United States.[49] Large doses were recommended by Snead et al.,[50] Baram et al.,[27] and Stafström et al.[48] It has been strongly suggested that effective treatment should result in both cessation of the spasms and resolution of hypsarrhythmia in the EEG and is thought to be an "all or none response."[51] Timely EEG to observe the effect of the treatment and prompt treatment modification, if needed, are important.[51] Only short courses of hormonal therapy (two weeks followed by a taper) are recommended by many authors[48,51] because a short course, in many patients, results in a permanent response.[52]

Unfortunately, there are no studies comparing the effects of "natural" (porcine or bovine) ACTH, the corticotropin used in the United States, and synthetic ACTH (tetracosactide) used in other parts of the world.

TABLE 3.
Seizure-Free Patients at Three to Four Months After Hormonal or Vigabatrin Treatments

Number of Patients	Drug	Seizure-free Patients (%)	References
200	ACTH	44	Matsumoto et al.[39]
147	ACTH	42	Riikonen[30,40]
19	ACTH	42	Vigevano and Cilio[28]
23	VGB	43	
28	VGB	43	Wohlrab et al.[41]
20	VGB	42	Appleton et al.[35]
97	ACTH	55	Knupp et al.[31]
54	Prednisolone	39	Knupp et al.[31]

Abbreviations:
ACTH = Adrenocorticotropic hormone
EEG = Electroencephalography
VGB = Vigabatrin

Oral steroids

In the UKISS trial by Lux et al.[29] oral steroids (prednisolone 40 to 60 mg/day) had a similar response as ACTH (0.5 mg on alternative days). In contrast, in another randomized prospective study from Sri Lanka[53] ACTH was statistically inferior to oral steroids at five weeks (response 18 of 49 = 40% and 28 of 48 = 58%, respectively). An electroclinical response was obtained more slowly with ACTH than with prednisolone when measured at 28 days. In the Sri Lankan study the response rate (cessation of spasms) with ACTH was exceptionally low compared with the UKISS (19 of 25 patients, 76%).[29] The reason for this difference is unknown but may be related to a longer lead time to treatment in the Sri Lankan study or the different ACTH formulas used (Acton Prolongatum, Himachal Pradesh, India, and Synacthen Depot, respectively). In four prospective studies (Table 1) the mean response rate to prednisolone was 46%.

A recent systematic review concluded that it is possible to offer only a Level C recommendation to support the efficacy of oral corticosteroids for the acute clinical control of epileptic spasms and EEG resolution based on Class III evidence.[54]

The use of prednisolone in high doses is preferred by some authors, particularly in economically less developed countries because of its low cost. More studies, however, are needed comparing ACTH and prednisolone in prospective randomized trials. The long-term developmental outcome of patients treated by prednisolone needs to be evaluated.

Vigabatrin

The results of seven prospective studies of VGB in infantile spasms are shown in Table 2. In the study of 179 infants by Elterman et al.[55] patients were randomized to low- or high-dose VGB, and the seizure outcome was confirmed by video-EEG. The response rate with VGB at day 14 was 23% but 60% at three months. The time to response was shorter in those receiving high-dose versus low-dose VGB.[36] The response to VGB seems to come later and in fewer infants than with ACTH, a finding also noted in a Finnish study.[10]

In this Finnish prospective, crossover study by Granström et al., VGB (50 to 100 mg/kg/day) was effective in 26% of 42 patients with a variety of etiologies. Total cessation of the spasms and resolution of hypsarrhythmia was monitored by video-EEG. VGB was given as the first-line drug. ACTH was then offered in combination with VGB. The total response rate was 60%.[10] As shown in the UKISS study, the combination of hormonal and VGB treatment may give better results.[10,33,38,56]

Lux et al.[29] and Bitton et al.[57] reported higher response rates to VGB, 52% and 62%, respectively (infants with TSC were excluded in both studies). VGB nonresponders may respond to steroids, and vice versa. More than one-third of children with infantile spasms respond to a second medication.[56]

VGB treatment may alter the semiology of spasms so that they become more minor or subtle and are accompanied by multifocal spikes on EEG.[58] When multifocal spikes or hypsarrhythmia persist, there are always spasms on video-EEG,[58] and recovery is likely to be incomplete with a poor prognosis. "Little seizures have big consequences."[59]

Tuberous sclerosis complex and infantile spasms

TSC represents an important cause of infantile spasms, up to 10% cases. There are several peer-reviewed publications that report convincing evidence of the effectiveness of VGB in treating children with infantile spasms, especially those with TSC. The consensus is that VGB is the drug of choice to treat infantile spasms in children with TSC.[60,61]

TSC results from mutations in the *TSC1* and *TSC2* genes. These are tumor suppressor genes that influence the mammalian target of rapamycin (mTOR) signaling pathway. Mutations of these genes cause hyperactivation of the mTOR system and result in cell growth and hamartomatous tumors in multiple organs. VGB blocks the breakdown of γ-aminobutyric acid (GABA) transaminase, which is responsible for the metabolism of GABA, a major inhibitory neurotransmitter. VGB has also been shown to inhibit activation of the mTOR pathway and seizures in a mouse model of TSC complex[62]; however, in the future, mTOR inhibitors (e.g., rapamycin) may challenge the role of VGB as the preferred drug for infantile spasms.[63]

The first small prospective study[64] of children with infantile spasms and TSC found VGB to be more effective than hydrocortisone in stopping the spasms. In a large, single-blind multicenter three-year study by Elterman et al. published in 2001, there was a significantly higher response rate to VGB for children who had TSC (13 of 15) than for children with other etiologies (19 of 117).[55] A Finnish study noted that the response rate to ACTH in patients with TSC was also high (73%) (16 of 22 infants),[21] but because of the need for prolonged therapy, VGB is likely a better choice.

Other therapies for infantile spasms

Some patients with medically refractory spasms have causative, localized brain lesions; resective surgery yields improvement in both seizure control and cognitive development.[65] Ketogenic diet is also a reasonable treatment alternative for infantile spasms, especially for children refractory to antiepileptic drugs. Ketogenic diet may be better tolerated than steroids.[66,67]

Relapses of infantile spasms after initial treatment

The proportion of patients who are seizure-free three to four months following ACTH or VGB are very similar, 44%, on average (Table 4). Unfortunately, relapses of spasms occur relatively frequently after an initial response to all current therapies. The overall relapse rate after ACTH treatment has been estimated to be 15% to 34%, 15% to 24% in Class I to III studies, 33% in the Class II study, and 19% to 24% in Class III studies.[4]

After initial therapy, these relapses occur after a few days up to 18 months, with a mean of 4.6 months.[30] In the ICISS, 57 of 298 (19%) relapses occurred by day 42. Of these, 33 occurred after combination therapy (VGB + hormones), and 24 occurred after hormonal therapy.[34]

Relapses occurred after all treatments but were more common with oral steroids than with ACTH or VGB in the study by Knupp et al.[31] Relapse rates after small or large doses of ACTH were similar in the Finnish study.[30] In the Sri Lankan study, the risk of relapse following ACTH or prednisolone therapy was similar.[32] Nabbout et al.[70] reported that children with TSC not only had the best response rate but also the highest relapse rate after VGB therapy. The prediction of relapses is often inaccurate, but EEG spike discharges during "remission" may have value in identifying patients whose spasms will reappear or in whom other seizure types emerge.[71]

Unfortunately, no pharmacologic treatment exists to prevent relapses. Other drugs, such as topiramate and zonisamide have been unsuccessful.[72]

Side effects of therapy

The common side effects of both drugs (steroids and VGB) are irritability, sleep disturbances, and drowsiness. Both also have severe side effects. The risk-benefit ratio should always be considered.

ACTH

Contraindications for ACTH treatment include acute infections, a history of clinically apparent infection with herpes or cytomegalovirus, and severe heart failure. The main side effects of ACTH are hypertension, suppression of the immune system with infections, electrolyte imbalances, gastrointestinal problems, hypertrophic cardiomyopathy, and adrenal hypofunction after therapy.[73-75] Infections were significantly more common (in 21 of 54, 39%) with large doses (120 IU/day) than with smaller doses (40 IU/day) (22 of 97, 23%) in the Finnish cohort of 162 patients.[74-76] Five had proven bacterial sepsis during treatment with ACTH, with three deaths. Adverse effects were more frequent with synthetic derivates than with natural corticotropins[75,76] probably due to the prolonged effect of the synthetic derivates. In a recent study from the Netherlands, patients were treated with high-dose tetracosactrin (0.8 mg/day = 80 IU/day) for four weeks and then tapered off over four weeks for a total treatment of eight weeks. Mortality was high; 37 of 162 patients died by age three years, although late deaths were unlikely related to hormonal treatment.[77]

ACTH-induced severe side effects are avoidable by careful vigilance, use of low ACTH doses with individualized therapy according to the response, and slow tapering of ACTH followed, if needed, by substitution of cortisol with careful monitoring of the hypothalamic-pituitary-adrenal (HPA) axis. Severe side effects from ACTH were not seen in the later years of an ACTH spasms study from Finland.[52] It would seem safest to give ACTH at the minimal effective dose for the minimal effective time.[76,78]

Prednisolone

A retrospective study of 87 children treated with high-dose oral corticosteroids for infantile spasms reported that 52% had side effects. There were four with severe side effects and one case of death.[79] In the UKISS[38] one child died of *Staphylococcus aureus* septicemia on day 15 of treatment with prednisolone. Of course, high-dose prednisolone for long periods of time can lead to suppression of the HPA axis.

Adrenal insufficiency

Withdrawal of ACTH or prednisolone at the end of treatment can expose HPA dysfunction with the risk of adrenal insufficiency. Higher doses and longer use are associated with the highest risk.[80]

TABLE 4.
Where Does ACTH Sit in the Therapeutic Algorithm?

Hormonal treatment is the best single treatment of the spasms (Cochrane Review[68])
ACTH might be more effective than prednisolone (Go et al.[42])
ACTH might be more effective than vigabatrin in other etiologic categories except tuberous sclerosis (Cochrane review[68])
Hormonal therapy (ACTH or prednisolone) as the first-line drug might be connected with better cognitive outcome in the group of infantile spasms with unidentified etiology (Darke et al.[69]; Go et al.[42])
Both drugs, either ACTH or vigabatrin, may be the second-line drug for children who do not respond to the first-line drug in 2-3 weeks (Knupp et al.[56])
Combination treatment (vigabatrin and hormones) may have a better short-term response rate (ICISS) than ACTH alone[33]

Abbreviations:
ACTH = Adrenocorticotropic hormone
ICISS = International Collaborative Infantile Spasms Study

ACTH preparations with more prolonged action such as tetracosactrin probably cause more pronounced post-treatment suppression and involution of adrenal cortex than corticotropin.

Signs of mild adrenal insufficiency in infants are nonspecific (nausea, fatigue, poor feeding) and not clinically evident without stress (e.g., a febrile illness).[81] Even minor degrees of adrenal insufficiency can be fatal in a stressed child. Given the seriousness of adrenal crisis, the Finnish protocol[73] calls for direct testing for hypocortisolism in patients with prolonged ACTH and cortisone treatment with the provision of appropriate cortisol substitution until full recovery is confirmed.

There have been only four small infantile spasm studies with a total of 35 patients who underwent post-treatment assessment of adrenal function.[81] In one study, two-thirds of the patients had abnormal stimulation tests up to 2 weeks after stopping corticotropin.[73] Mytinger and Bowden[81] found a relatively low incidence of abnormal adrenal function (two of 14 patients) tested two to 18 weeks after the last day of hormone therapy. The authors recommend that clinicians should be vigilant in monitoring for signs of adrenal insufficiency for at least three months after withdrawal of hormone therapy. Prophylactic hydrocortisone was not routinely recommended, except if there were concerns about adrenal insufficiency, especially in stress situations. The nonspecific and subtle nature of the signs of adrenal insufficiency make this recommendation somewhat questionable, unless there is a direct assessment of adrenal function.

The incidence of abnormal HPA function and time to full recovery after ACTH and prednisolone therapy should be more carefully studied.

Vigabatrin side effects

VGB-specific adverse effects include peripheral visual field defects (VFDs), the most feared adverse effect, and structural changes in the brain MRI scan. The VFDs seem to be irreversible. Sustained retinal damage, assessed by electroretinogram (ERG), can be detected at two to three months of VGB treatment.[82] In the United States, VGB is available only under a special restricted, distribution program (the Support, Help and Resources for Epilepsy (SHARE) program (http://www.lundbeckshare.com; FDA, 2009)). "While taking VGB, patients should have periodic ophthalmologic evaluations beginning at the baseline evaluation at initiation of therapy as well as three to six months after cessation of treatment." This is a very challenging task for infants because ERG or measurements of the loss of retinal nerve fiber layer using optical coherence tomography may require general anesthesia and specialized ophthalmologists to interpret the results. At present, there are no reliable methods to judge whether VFDs emerge during VGB therapy in infancy.

Visual field defects occur in 30% to 40% adults treated with VGB sometimes severe enough to hamper driving a motor vehicle. VFDs are an additional complication for disabled children, who may already have impaired vision for other reasons. A recent study showed that after six and 12 months of VGB treatment 5.5% and 13.3% children, respectively, developed VGB retinal defects as measured by ERG.[83] The cohort included 146 participants with infantile spasms treated with VGB, and more than 500 assessments were collected at multiple visits. There is, however, uncertainty about how ERG deficits correlate with VFDs.[84]

Gaily et al.[85] studied 15 children, aged six to seven years, who were started on VGB treatment during the first year of life. The risk of VFDs was considered low. A larger, more recent multicenter study on VFDs in 35 school-aged children treated with VGB during infancy for infantile spasms[86] showed that VGB causes VFDs in children at rates comparable to adults (34%). The rate increased from 9% to 63% as the duration of treatment increased. Three of 10 children (30%) who received VGB for 12 to 24 months had VFDs. Patients with TSC who underwent longer VGB treatment were the most likely to have VFDs. It appears that retinal toxicity starts to increase after six months of therapy.[83]

An important goal of future studies should be identification of both patients who are less susceptible to VGB-induced retinal toxicity and those who are at especially high risk.

Several theories have been proposed to explain the cause of VGB-associated VFDs. These include toxic reactions, idiosyncratic reactions, polypharmacy, pharmacogenetic differences, elevated levels of retinal ornithine, taurine deficiency, GABA accumulation in the retina, dysfunction in GABA-innervated horizontal and amacrine cells in the inner plexiform layer of the retina, and the infantile spasms themselves.[86]

Unexpected movement disorders were relatively frequent (14 of 186 patients) in the ICISS when large doses of VGB were combined with hormonal therapy.[33,87] The relationship of these movement disorders to VGB remains unclear because they were not related to the MRI changes that are associated with VGB therapy.

Many studies have reported that VGB may produce transient MRI abnormalities consistent with intramyelinic edema.[88-90] MRI abnormalities may appear in a third of patients as early as after three months of treatment and seem to be restricted to infancy. The MRI abnormalities resolve following withdrawal of VGB in almost all patients. MRI abnormalities occur in the thalami, basal ganglia, brainstem tegmentum, and cerebellar dentate nuclei. The abnormalities may rarely be accompanied by dystonia, but the majority of affected children are asymptomatic. For infants receiving VGB who develop a new neurological abnormality such as dystonic movements, an MRI is likely appropriate.

Intramyelinic edema has not been detected in adult VGB-treated patients with neuropathological examinations at autopsy or with surgical brain samples. However, a recently reported 27-month-old boy with infantile spasms died of sudden unexpected death in epilepsy. At autopsy, his brain showed white matter spongiosis, identical to lesions previously demonstrated in animal models of VGB therapy.[91]

TABLE 5.
Long-Term Outcome of Patients With Infantile Spasms

Number of Patients	Follow-up Time, years	Therapy	Duration of Therapy	Normal Percent	Mortality Percent	Author
150	3-13	ACTH 40-60 IU/d, prednisolone 2 mg/kg/d, dexamethasone 0.3 mg/kg/d	3 wk-3 mo	16	22	Jeavons et al.[92]
100	>5	ACTH 20-40 IU/d, prednisolone 2 mg/kg/d, dexamethasone 0.3 mg/kg/d	3-5 wk-3 mo	21*	19	O'Donohoe et al.[93]
200	>5	N.D.	N.D.	23	19	Matsumoto et al.[39]
214	20-35 mean 25.6	ACTH 20-40 IU/d, ACTH 120 IU/d	5-6 wk	25*	31	Riikonen[14,30]
138	>2	ACTH 0.2-1.28 IU/kg	1-5 wk	6†	2	Ito et al.[94]
180	2.4-18.9 mean 10.64	50-150 mg/kg	2-6 mo	33*	5.5	Djuric et al.[37]
207	24-54 mean 39.5	ACTH 20-40 IU/d, ACTH 120 IU/d	5-6 wk	25*	49	Sillanpää et al.[95]

Abbreviations:
ACTH = Adrenocorticotropic hormone
IQ = Intelligence quotient
IU = International units
N.D. = No data
* Mildly impaired included IQ > 70-75.
† Relatively short follow-up, young age of the patients.

Long-term outcome

Table 5 shows studies of patients with infantile spasms and long follow-up.

The Finnish study (Riikonen)

The only population-based study with long-term follow-up is from Finland. This study began in the 1960s and was prospective and longitudinal. Overall, 214 children with infantile spams were followed for 20 to 35 years or until death,[14] and follow-up data were obtained from 100% patients. As outlined below, the study documented intellectual outcome, academic achievement, social success, psychiatric disorders, and later epilepsy.

All patients had epileptic spasms and either hypsarrhythmia or "modified hypsarrhythmia." The spasms were classified as "cryptogenic" (cause unknown) in 29 patients and "symptomatic" (cause known or neurological abnormality) in 185 patients. The diagnosis was made at a mean age of six months. Large doses of ACTH (80 to 120 IU [0.8 to 0.12 mg/day]) were given to 54 patients and lower doses (20 to 40 IU [0.02 to 0.04 mg]) to 97 patients. The response rates were 64% (60 of 97 patients) and 54%, (29 of 54 patients), respectively. The duration of the treatment was relatively short, five to six weeks. All adults with favorable outcome had a short lead time to treatment.[14] Patients who responded to ACTH had a better cognitive outcome than the other groups[14]; this applied to both the cryptogenic group (70%) and, interestingly, the symptomatic group (23%). Long-term cognitive outcome was better with the low-dose (20 to 40 IU/day) regimen than the high-dose (80 to 120 IU/day) regimen.[14]

Intellectual outcome of the 147 surviving patients was classified either by conventional psychological tests or based on educational status[14] in the following way: normal school (intelligence quotient [IQ] greater than 85), 25 patients; school for the educationally handicapped (slightly impaired, IQ 68 to 85), 11 patients; training school (mild learning disability, IQ 40 to 60), 36 patients; and the rest uneducable (IQ less than 40), 75 patients. Thirty six (24%) had a favorable outcome with IQ greater than 68. The developmental state was evaluated for 114 children aged six years by conventional psychological tests (Cattel, Vineland, Bender, Terman-Merrill, Bayley, and Wechsler Intelligence Scale for Children). Seven of the 25 children with normal intelligence had some difficulty with fine motor tasks in writing, reading, and mathematics. Similar specific deficits were described by Gaily et al.[96] and Lagae et al.[16] in individuals without a known cause of infantile spasms.

Academic achievements, marital status, children, driving license, and military service

At the end of follow-up, 25% were employed at jobs ranging from professional to manual labor. Occupations of the patients with normal (25) or slightly impaired intelligence (11) were the following: professionals (7): physician (1), engineer (1), professional in forestry at the university level (1), elementary school teacher (1), special teacher for educationally impaired children (1), illustrator (1), and university student (mathematics) (1). Other occupations were manual worker (1), office worker (1) retail/sales (8), housewife (1), retired (3), and other (6), altogether 36 different occupations. All except two had a full-time job, and all had the usual level of income.

Ten were married or living with an adult partner. Five had children, and all nine children were healthy. Eleven had a driving license. Eight of the 13 men had completed compulsory military service.

Psychiatric outcome

In the complete Finnish cohort (n = 214), autism was diagnosed in 33 (13%) patients, and hyperkinetic behavior, in 29 (14%).Two patients had a psychosis.[97] Altogether a quarter had psychiatric disorders. Temporal focal abnormalities in the EEG were found in 70% patients with autism,[97] a similar finding to the results of positron emission tomographic (PET) studies by Chugani et al.[98] These PET studies showed that of 110 children with infantile spasms, 18 showed bitemporal hypometabolism, of whom 10 had diagnostic features of autism.

Later epilepsy and EEG

Infantile spasms usually disappear at age three to four years. The transition from infantile spasms to Lennox-Gastaut syndrome occurred in 18%.[14] At 20 to 35 years after the onset of infantile spasms, a third of the 147 surviving patients were seizure-free (in remission for at least two years), another third had daily to monthly seizures, and the remaining third had seizures less frequently.[14,40]

Most often seizures were focal, often with secondary generalization.

The EEG at last examination was normal or only slightly abnormal in a fifth of the cases.[14] In patients with normal intelligence EEG was normal in 60%, but it was normal only in 13% of the others.

Mortality

At the end of 20 to 35 years of follow-up of the 214 patients with infantile spasms, a third (67 patients) had died.[14] One-third of the 67 deaths (23 patients) occurred before age three years. The most common immediate cause was infection, and eight patients (12% of all deaths) died during ACTH treatment (all demonstrated adrenal enlargement and hypertrophic cardiomyopathy).[14,40,75] Five of these eight deaths occurred when the patients were receiving daily synthetic ACTH or very large ACTH doses.[40] Neuropathological examinations performed in 38 (57%) cases showed a wide range of lesions including brain malformations in 26 (66%) autopsied patients.[14,98]

With even longer follow-up of the same patients, nearly one half had died by age 50 years with a mean age of death of 19 years.[95] One-fourth had died by age 17.2 years. The mean annual mortality was 15.3 per 1000 patients-years.[95] Autopsy reports were available in 73% of 102 patients and indicated that in the vast majority, pneumonia was the immediate cause of death, presumably related to the underlying neurological disorder. Ten percent deaths were classified as sudden unexpected death in epilepsy, and 7% were thought to be the direct result of a seizure.[95] Patients with a known etiology compared with those with an unknown etiology had a five-fold higher risk of death.[95]

Other long-term studies

UKISS and ICISS

In the UKISS, patients were followed for four years. In patients with no identified etiology, intelligence at the end of follow-up was significantly higher when the initial treatment was hormonal therapy than with VGB.[69]

In the ICISS, combination therapy (VGB plus hormones) had a more rapid response in a higher proportion of patients than hormonal therapy alone. Disappointingly, combination therapy did not result in improved developmental or epilepsy outcomes at 18 months compared with hormonal therapy alone.[87] Further studies of combination treatment will be welcome.

Vigabatrin

Djuric et al.[37] reported their experience with 180 children treated with VGB and followed for an average of 10 years. At the end of follow-up 33% had normal intelligence (IQ greater than 70) and 58% were seizure-free. These results compare favorably with the Finnish study of 147 ACTH-treated patients wherein 36% were seizure-free and 24% had a favorable cognitive outcome: IQ greater than 85 in 25 patients and IQ 68 to 85 in 11 patients and seizure freedom in 36%.[14,30]

Autistic spectrum disorder

Patients with infantile spasms are at increased risk of autistic spectrum disorders. A meta-analysis showed that about 20% children with infantile spasms have autistic spectrum disorder compared with about 6% of overall childhood-onset epilepsy.[99] Patients with infantile spasms who have TSC seem to be at a particularly high risk of autism. Autistic behavior was observed in 37 of 69 (57%) children with TSC and infantile spasms in the study by Hunt and Dennis[100] as opposed to 13% in a Finnish study of children who had infantile spasms from all causes.[97]

Epilepsy and EEG

Development of Lennox-Gastaut syndrome after infantile spasms occurred in 23% of 105 patients in the prospective follow-up study by Lombroso.[25] Based on a review of 15 studies that evaluated the long-term prognosis of infantile spasms, an average of 17% (range 0 to 54%) eventually developed Lennox-Gastaut syndrome.[101] Investigators have failed to find any correlation between various EEG features associated with infantile spasms and long-term outcome, except for asymmetrical EEG patterns due to underlying structural abnormalities of the brain, which were associated with an unfavorable outcome. Gaily et al.[58] reported that persistence of multifocal spikes was always associated with continuing spasms after VGB therapy. The transition from motor spasms to subtle spasms has been observed in a few (four of 44) infants when serial video-EEG was used.[58] Persistent spasms at age one year may predict long-term intellectual disability.[15,58] Persistence or worsening of epileptic discharges in EEG, especially multifocal discharges, are highly predictive of spasms, a warning sign.[58] The appearance of epileptic discharges after ACTH therapy has been related to seizure relapse.[102]

Quality of life

One hundred twenty Japanese patients with a previous diagnosis of infantile spasms were assessed at an average age of 25 years with a questionnaire to measure social outcome.[103] Most patients had attended school in a special education setting, but at follow-up 20% still had very limited independence for activities of daily living. Only 9% had full-time work as adults. Sixty per cent were judged to have a reasonable quality of life (such as being able to walk, communicate, eat, dress, and use the toilet) and could enjoy daily life. Very few could lead an independent life. Another Japanese study addressed 117 patients by questionnaires, completed by primary care givers 20 years after the onset of spasms. The response rate was only 45%.[94] Two patients were deceased, 40% still had daily or weekly seizures, and 25% were seizure-free. Only half of the patients were able to walk by age three years. By age six years, 41 were able to communicate. Most adult patients needed assistance in their everyday life.

Mortality

Mortality rates in different long-term studies are summarized in Table 5. In the 10-year follow-up of a cohort of patients born from 1994 to 1999 from the University Hospital of Helsinki, Finland, the mortality rate was 13% by age three years (seven of 55 patients, 13%),[15] which is similar to the mortality at three years in the study by Riikonen.[14,30] It is to be noted that all patients with newly diagnosed infantile spasms had first received VGB treatment in the Helsinki study.

However, in a recent study from the Netherlands[77] the cumulative mortality at age three years was 31%, even higher than in the Finnish study. Freedom from seizures was an independent predictor of survival.

Can we improve the outcome? Lead time to treatment, response to treatment, duration of hypsarrhythmia, and correlation to outcome

Lead time to treatment

Several studies have found a relationship between short time to treatment and improved mental outcome.[11,12,25,92,104-106] Furthermore, Kivity et al.[12] documented normal cognitive outcome in all 22 patients with an unknown cause for infantile spasms when they received ACTH within one month of onset. Fifteen other patients had a longer lead time before ACTH, and normal cognition was seen

in only 40%. The UKISS showed a stepwise decline in intellectual outcome with longer lead time to treatment in the group of unknown etiology at age four years.[105] Intellectual outcome was assessed using the Vineland Adaptive Behavioral Scores.

Furthermore, in a recent multicenter prospective study[56] of 118 patients who had failed their first treatment for infantile spasms, the response to a second treatment was better when the initial treatment lead time was less than four weeks.

Response to treatment

Important information came from the UKISS. Patients with unknown cause who were primarily allocated to hormonal therapy had a better cognitive outcome at age four years than those allocated to VGB.[69] The authors concluded that ACTH should be given as the first-choice drug for patients with an "unidentified" etiology. Prompt control of spasms and improvement in the concomitant EEG appear to be important in achieving optimal long-term cognitive development.

Duration of hypsarrhythmia

It seems highly likely that the duration of hypsarrhythmia is responsible, at least in part, for the cognitive decline, irrespective of other seizure types. In a retrospective study of 48 patients, Primec et al.[106] showed that the risk of intellectual disability increases after three weeks of hypsarrhythmia.

Prevention of infantile spasms

Some causes of infantile spasms may be preventable. It is likely that reduction of the numbers of babies born small for gestational age, prompt treatment of hypoglycemia, and early treatment of herpes encephalitis will reduce the number of cases of infantile spasms. Furthermore, some metabolic disorders that cause infantile spasms may be preventable or cured by early detection.

A study of infants with TSC by Jozwiack et al.[107] suggested that the severity of cognitive impairment and epilepsy might be reduced by starting VGB when spike discharges appear on the EEG before the onset of clinical seizures. There were 10 infants in this early "prevention" group who were compared with 31 retrospective controls who had received conventional treatment only after clinical seizures had developed. At age 24 months "psychomotor retardation" and drug-resistant epilepsy was significantly less frequent and less severe in the "prevention" group. This original report has led to ongoing large clinical trials in the United States (Clinical Trials Gov.) and the EPISTOP (http://epistop.eu) study in Europe.

Curatolo et al.[61] concluded that administration of VGB may be considered in children with TSC with subclinical epileptiform discharges, but recommendations for clinical practice should await the results of the US and European randomized trials. Repeated monitoring of EEG during the first months of life before onset of seizures may be crucial for early preventive treatment.

About 10% patients with TSC are diagnosed prenatally with the finding of cardiac rhabdomyomas. When repeated EEGs have been recorded in these babies, spikes and sharp waves have indicated a high risk of subsequent seizures. The time between detection of abnormalities on EEG and the onset of clinical seizures varied from one to eight days in five patients who were diagnosed with TSC pre- or perinatally and had regular EEG monitoring every four to six weeks.[108]

Another high-risk group for infantile spasms is preterm babies with PVL.[109] Japanese authors propose that the preterm infants with PVL who show epileptic discharges before corrected age three months should be treated by antiepileptic drugs to prevent the onset of West syndrome, although it is not easy to identify patients for prevention of West syndrome with sufficient antecedence.[109]

Improving cognitive and seizure outcome in infantile spasms remains a demanding task. Widjaja et al.[110] noted no improvement in neurodevelopmental outcome in studies published before, during, and after 2004. In general, the outcome remained poor even for the unknown cause group. Most of the reviewed studies had relatively short follow-ups and were retrospective.

There are certain things that can be done to prevent infantile spasms or improve the patients' outcome: good maternal care (avoiding infections, toxemia, hypoxia, and small for gestational age babies); early recognition of spasms and prompt treatment; timely EEG evaluation of response to therapy and change to other antiepileptic drugs when necessary, or use of combination therapy; avoidance of side effects of therapy including consideration of the risks and benefits of some treatments, especially with combination therapy[111]; early treatment of relapses and epileptic discharges in EEG (especially multifocal spikes); treatment of pre-hypsarrhythmic EEG in high-risk infants like those with TSC; use of ACTH for patients without known etiology; and considering ketogenic diet, brain stimulation, or surgery in refractory patients.

Conclusions

Numerous factors have been shown to influence the short- or long-term outcomes of children with infantile spasms. A majority of the studies have been retrospective and have included different populations and different treatment regimens. It is difficult to know if the prognosis has changed over time.

The most important prognostic factors are the underlying etiology and presence or absence of developmental abnormalities at spasm onset. Improved etiologic diagnostics should allow more accurate prognostic counseling.

Early cessation of the spasms is important for cognitive outcome. A short duration of hypsarrhythmia is important regardless of etiology but may be especially important in the unknown cause group. ACTH still seems to be the most effective single treatment, but combination of the hormonal treatment with VGB either simultaneously or sequentially shows promise. The role of prednisolone requires further study. Recurrence of the spasms does not seem to be heavily dependent on the type of medication used. Smaller ACTH doses might bring better cognitive outcome than large doses. EEG findings at cessation of epileptic spasms are of prognostic importance for recurrence.

The adverse effects of treatments are now well known, as are the means to avoid or treat them. Risk-benefit considerations are important for the choice of treatment. An important principle is to use drugs at their lowest effective dose for the shortest duration, although defining the best treatment regime requires more study.

There are only few long-term outcome studies, and they show that at most, a quarter of patients have a favorable long-term cognitive outcome and a third remain seizure-free. Many comorbidities are associated with infantile spasms (autism, cerebral palsy, sensory defects), and mortality is high throughout life. Early treatment may be the most important way to improve neurodevelopmental outcome.

In the long run it will be necessary to learn more about brain maturation, neural networks, cellular pathomechanisms, genetic etiologies and mechanisms, and genetics. This knowledge may facilitate development of novel pharmacologic interventions with the ultimate goal of improving the cognitive outcome. With advancing genetic and molecular data, it should be possible to directly target pathogenetic mechanisms as in specific disorders such as TSC. Follow-up studies of interventions in specific etiologic

subclasses will be important. Novel treatments such as melanocortin receptor agonists, neuroprotective treatment, rapamycin, and medical cannabinoids should be addressed in further studies.

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