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Original Article

Prognostic factors of infantile spasms: Role of treatment options including a ketogenic diet ☆

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Abstract

Objectives: The aim of this study was to provide additional evidences on prognostic factors for infantile spasms and the possible role of a ketogenic diet. *Methods:* A retrospective analysis was performed for patients with infantile spasms who had been followed up for more than 6 months between January 2000 and July 2012 at Samsung Medical Center (Seoul, Republic of Korea). We analyzed the association between possible prognostic factors and seizure/developmental outcomes. *Results:* Sixty-nine patients were included in this study and their mean follow-up duration was 52.5 (9–147) months. In the patients who had been followed up for more than 2 years, 53.6% ($n = 30/57$) remained seizure-free at the last visit. Sixty patients (86.9%) showed developmental delay at last follow-up. Forty-two patients (60.9%) became spasm-free with one or two antiepileptic drugs, one patient with epilepsy surgery for a tumor, and seven patients with a ketogenic diet after the failure of two or more antiepileptic drugs. The etiology and age of seizure onset were the significant prognostic factors. *Conclusions:* In this study, about 60% of the patients became spasm-free with vigabatrin and topiramate. Ketogenic diet increased the rate by 10% in the remaining antiepileptic drug resistant patients. However, 86.9% of the patients showed developmental delay, mostly a severe degree. Early diagnosis and prompt application of treatment options such as antiepileptic drugs, a ketogenic diet or epilepsy surgery can improve outcomes in patients with infantile spasms.

Keywords: Infantile spasms; Outcome; Vigabatrin; Ketogenic diet; Development; Levetiracetam; Topiramate; Valproate

1. Introduction

Infantile spasms are also known as West syndrome, in recognition of Dr. William James West, who first described them in 1841 [1]. His description of infantile spasms included mode of onset, character of the spasms, status of spasm clusters, and association with mental or developmental retardation [1,2]. Long-term outcome of infantile spasms is very grave. A prospective study reported that one-third of the patients with infantile spasms died in early age. Additionally only about 25% of patients maintain normal or mildly abnormal intelligence, and only one-third become seizure free [3–5].

There have been many studies about the prognostic factors of infantile spasms, which included various aspects of its etiology, electroencephalography (EEG), and treatment [4,6–12]. The prognostic factors reported as favorable include cryptogenic etiology, age at onset over 4 months, absence of atypical spasms and partial seizures, nonexistence of asymmetrical EEG abnormalities, short treatment lag, and an early and sustained response to treatment [4].

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Among the various prognostic factors, the potential utility of initial EEG in reflecting the etiology and forecasting outcomes has drawn interest. To date a few studies have reported an association of the severity of hypsarrhythmia or the presence of asymmetry with poor prognosis [4,13,14]. However, there is still insufficient evidence about the prognostic value of initial EEG.

Treatment options have been a matter of great interest as a manageable prognostic factor. In 2012, the American Academy of Neurology reported an evidence-based guideline update for the medical treatment of infantile spasms [15]. According to the guideline, low-dose of adrenocorticotropic hormone (ACTH) is probably as effective as high-dose ACTH, and ACTH is superior to vigabatrin. The guideline noted there is insufficient evidence on the efficacy of other agents such as levetiracetam, topiramate, or valproate, as well as ketogenic diet [15]. A ketogenic diet has been useful in managing infantile spasms and other refractory epilepsies in infancy [7,16]. However, definitive evidence is lacking [15,17].

We performed this study to provide additional evidences about the prognostic factors of infantile spasms placing an emphasis on initial EEG and treatment options including ketogenic diet.

2. Patients and methods

Sixty-nine patients (38 males, 31 females) with infantile spasms were included in this retrospective study. They had been followed-up for more than 6 months at Samsung Medical Center (Seoul, Republic of Korea) between January 2000 and July 2012. The inclusion criteria were clinical diagnosis with epileptic spasms, age <2 years at onset, and availability of initial EEG.

We reviewed the electronic medical records, brain imaging, and EEGs to identify the patients' etiology, treatment, clinical course, developmental progress, and outcomes of the seizures. The treatment strategy in our institution generally begins with vigabatrin if the parents agree to the possible side effects, especially visual field constriction. If not, topiramate is used. The second-line is the alternatives of the first-line drugs. Levetiracetam has been used as the first- or second-line drug in some patients. Ketogenic diet is usually tried when there is no response to at least two antiepileptic drugs. Outcomes were divided into short- and long-term. The definition of short-term outcome followed that of the West Delphi Group in 2004 [18], with primary clinical outcome being the cessation of clinical spasms within 14 days of treatment and for $\geqslant$28 consecutive days from the time of the last witnessed spasm. The long-term outcome was estimated in patients who were followed-up for more than 2 years ($n = 57$) and was assessed as freedom from seizures, presence of focal or generalized seizures, or Lennox-Gastaut syndrome (LGS) evaluated for 4 weeks before the last follow-up. Developmental outcomes were divided into three categories using Korean Development Test for Infant (The Korean Pediatric Society, 2002): normal, mildly delayed (<6 month delay), and delayed (more than 6 month delay). For patients whose developmental quotient data were not available, we evaluated developmental milestones based on their medical records.

We reviewed the initial EEGs at the time of diagnosis and analyzed them according to the presence of hypsarrhythmia (typical or variations in typical hypsarrhythmia and not hypsarrhythmia), preservation of normal background activities (<10%, 10–50%, >50%), presence of generalized attenuation (<10%, 10–50%, >50%), and evidence of a focal epileptic locus (presence or absence).

The definitions of typical hypsarrhythmia and variations in typical hypsarrhythmia were adapted from those of Hrachovy and Frost [2]. Additionally, we classified the low-amplitude variant (<50 μV) into variations in typical hypsarrhythmia group. The normal background activity was defined as having normal organized background activities and normal sleep parameters such as sleep spindles and vertex sharp transients. The proportion of normal background activities and generalized attenuation patterns was calculated by measuring the duration on the initial EEG (sampling 10-min duration from a non-REM sleep EEG). The presence of a focal epileptic locus was defined as a persistent focal spike or sharp waves, focal slowing, and focal depression. The EEG was reviewed and scored by two epileptologists. When the scoring differed between the two readers, the result was discussed and agreed on before being applied for analysis.

We analyzed the association between factors and seizure/developmental outcomes using the χ^2 test or Fisher's exact test. The covariates considered were the age at seizure onset, time interval between the seizure onset and the diagnosis, etiology, presence of hypsarrhythmia/normal background activity, and evidence of a focal epileptic focus in the initial EEG. For analyzing the interaction between the variables, we used the multiple linear regression model. The data were analyzed with SPSS® statistics version 19 (SPSS, Chicago, IL, USA).

3. Results

3.1. Clinical characteristic of the patients

The mean onset-age of infantile spasms was 5.4 months (range, 0.5–13 months) with a mean follow-up of 52.5 months (range, 9–147 months). The mean time between the onset and the diagnosis of spasms was 1.1 months (range, 0–6 months), and the semiology of spasms varied (Table 1). Forty-four patients (63.8%) displayed identifiable etiologies; the most frequent causes

Table 1
Clinical features of the patients.

Features	Number of patients (%)
Follow-up duration	
6–24 months	12 (17.4%)
>24 months	57 (82.6%)
Semiology of spasms	
Flexor spasm	39 (56.5%)
Tonic spasm	19 (27.5%)
Extensor spasm	5 (7.2%)
Mixed spasm	1 (1.4%)
Asymmetric spasm	4 (5.8%)
Hemi-spasm	1 (1.4%)
Etiology	
Cryptogenic	25 (36.2%)
Symptomatic	44 (63.8%)
Malformations of cortical development	10 (14.5%)
Periventricular leukomalacia	10 (14.5%)
Brain atrophy	6 (8.7%)
Tuberous sclerosis	5 (7.2%)
Hemorrhagic/ischemic stroke	4 (5.8%)
Metabolic disorders	3 (4.3%)
Hypoxic ischemic encephalopathy	3 (4.3%)
Microcephaly	1 (1.4%)
Genetic disorder	1 (1.4%)
Tumor	1 (1.4%)
Seizure outcome	
Short-term outcome	$N = 69$
Spasm free	49 (71%)
Persistent spasms	3 (4.3%)
Appearance of other type of seizure	17 (24.6%)
Long-term outcome	$N = 57$
Seizure-free	30 (52.6%)
Lennox-Gastaut syndrome	6 (10.5%)
Partial seizure	6 (10.5%)
Generalized seizure	9 (15.8%)
Partial and generalized seizure	3 (5.3%)
Infantile spasms	3 (5.3%)

were malformations of cortical development and periventricular leukomalacia (Table 1).

3.2. Treatment, outcomes of the seizures, and developmental results

Twelve patients (17.4%) had a history of seizures before the onset of the infantile spasms: neonatal seizures ($n = 4$) and focal or generalized seizures ($n = 8$). Ten patients were being treated with antiepileptic drugs at the onset of infantile spasms. Vigabatrin (84.1%) was the most frequently used first-line antiepileptic drug, followed by topiramate (13.0%) and levetiracetam (2.9%). The second-line drugs were topiramate ($n = 17$), vigabatrin ($n = 9$), valproate ($n = 5$), and levetiracetam ($n = 4$). The seizure-free rate with vigabatrin was 35.8% (24/67) and 26.9% (7/26) with topiramate.

Oral prednisolone was prescribed in 13 patients as a second-line drug. Two patients became spasm-free. The ketogenic diet was prescribed in 14 patients (20.3%) after they failed to get seizure freedom with two or more antiepileptic drugs. One patient had epilepsy surgery as an initial treatment for a right parieto-occipital tumor. After the surgery, he became seizure free, and EEG normalized. The pathologic result was desmoplastic infantile astrocytoma.

Twenty-two patients (31.9%) became seizure-free with the first-line antiepileptic drug, and the overall short-term seizure outcome (spasm-free) was 71% (Fig. 1). Long-term seizure-free rate over 2 years was 53.6% (Table 1). Twenty-nine patients (42%) were normal in development before the onset of infantile spasms. At the last follow-up, 35 (50.7%) patients showed severe

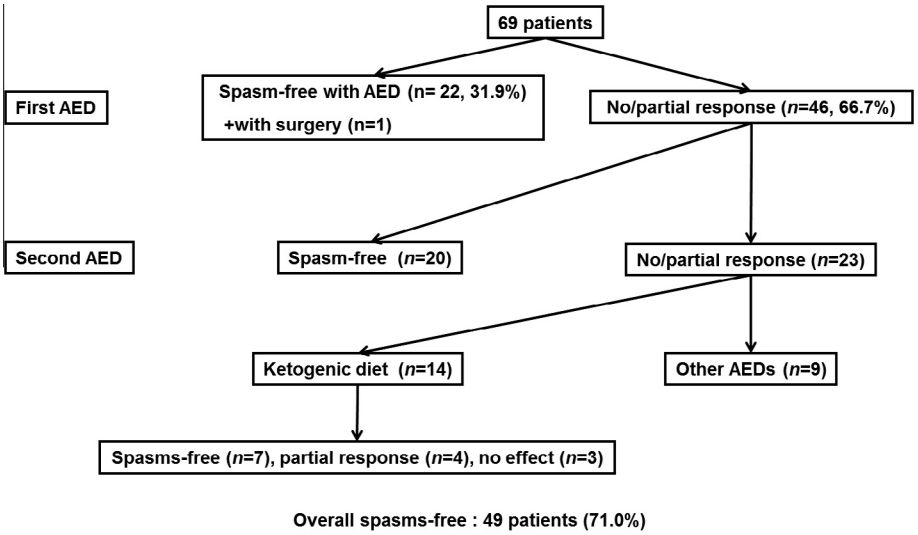

Figure 1. Outcomes of infantile spasms in patients with subsequent antiepileptic drugs and ketogenic diet. Twenty-three patients became free of spasms with the first antiepileptic drug or surgery, and another 20 became spasm-free following the addition of a second antiepileptic drug. The ketogenic diet was prescribed to 14 of the patients after failure of two or more antiepileptic drugs, and seven of these patients became spasm-free. AED: antiepileptic drugs.

developmental delay and 24 (34.8%) showed mild developmental delay.

3.3. Analysis of the initial EEG

Thirty-eight patients had typical hypsarrhythmia, and 22 did not (Table 2). There was evidence of focal epileptic loci in 16 patients (23.2%). Among 63 patients who had follow-up EEGs after the onset of the infantile spasms, 21 children (33.3%) had normalized EEG.

3.4. Prognostic factors

Among the various covariates, the etiology was significantly associated with developmental outcomes and final long-term seizure outcomes, but not with the short-term results of spasms (Table 3). The characteristics of initial EEG did not have a significant influence on the outcomes. Early seizure onset was associated with poor control of spasms ($p = 0.05$). Further analysis with using multiple linear regression model revealed the same results. Patients who became spasm-free following initial treatment displayed favorable developmental outcomes ($p < 0.01$).

Table 2
Analysis of initial EEG.

Features	Number of patients (%)
Presence of hypsarrhythmia	47 (68.1%)
Typical hypsarrhythmia	38 (55.1%)
Variations in typical hypsarrhythmia*	9 (13.0%)
Non-hypsarrhythmia	22 (31.9%)
Preservation of normal background activities	
<10%	34 (49.3%)
10–50%	21 (30.4%)
>50%	14 (20.3%)
Presence of generalized attenuation	
<10%	38 (55.1%)
10–50%	23 (33.3%)
>50%	8 (11.6%)
Evidence of focal epileptic locus	
Presence	16 (23.2%)
Absence	53 (76.8%)

* It includes increased interhemispheric synchronization, asymmetry, a consistent focus of abnormal discharge, episodes of attenuation, high-voltage bilaterally asynchronous slow activity, and increased periodicity.

4. Discussion

This study was performed to determine the prognostic factors in infantile spasms by analyzing initial EEGs and treatment options. Most of the patients had been treated using a relatively homogenous treatment protocol and were followed-up for over 2 years. The findings on the initial EEG did not represent a significant prognostic factor. Etiology and the time of spasm-onset were significant prognostic factors influencing subsequent seizures and developmental outcomes. Patients who became spasm-free with the first treatment and, therefore, experienced short duration of infantile spasms had better developmental outcomes.

Previous studies have shown that 80–90% of patients with infantile spasms have profound developmental delays [3,4]. The underlying etiology is likely a significant influencing factor for developmental outcomes [9]. The factors reported to be associated with a favorable prognosis include cryptogenic etiology, early onset, absence of atypical spasms and partial seizures, no seizure history before the spasms, early treatment, and good initial response [4,9]. Similarly, in this study, etiology and time of spasm-onset were the significant prognostic factors; cryptogenic etiology was associated with a good prognosis in terms of long-term seizure outcomes and developmental outcomes, and early seizure onset was associated with poor outcomes in terms of short-term control of spasms.

The overall spasm-free rate was 71% ($n = 49$). Most of the patients ($n = 42/49$, 85.7%) became spasm-free with only antiepileptic drugs other than ACTH. ACTH is regarded as the most effective agent for infantile spasms. However, it is not available in most Asian countries [15,17]. Therefore, the efficacy of antiepileptic drugs other than ACTH in infantile spasms requires validation. The results of this study provide additional evidences for the use of vigabatrin or topiramate in patients with infantile spasms.

Reported spasm-free rate with vigabatrin ranges from 1% to 60% [9,19–21]. The same result was found in this study (35.8%). According to a previous multicenter randomized controlled study, the seizure-free outcome with vigabatrin was 54% (76% with ACTH) at 14 days, and the long-term maintenance of remaining seizure freedom

Table 3
Prognostic factors for seizures and developmental outcomes.

Variable	p value (χ^2)		
	Short-term spasms' outcome	Long-term seizure outcome	Developmental outcomes
Etiology	0.07	0.01	0.02
Seizure onset	0.05	0.10	0.28
Interval between onset and diagnosis	0.77	0.62	0.38
Presence of hypsarrhythmia	0.27	0.31	0.86
Presence of normal background activity	1.00	0.68	0.95
Evidence of focal epileptic locus	0.39	0.49	0.35

was similar between ACTH and vigabatrin [22]. Vigabatrin has also been shown to be highly effective for patients with tuberous sclerosis–associated spasms [23,24].

In this study, topiramate was the second most frequently used antiepileptic drug (as first-line drugs, $n = 9$; as second-line drugs, $n = 17$), and the response rate was 26.9% when it was mostly used as an adjunctive therapy to vigabatrin. The reported spasm-free rates with topiramate ranged from 20% to 30% when it was used as a first-line therapy and 18–45% when it was used as an adjunct therapy [9], similar to this study.

A Ketogenic diet was adopted in 14 patients who were intractable to two or more antiepileptic drugs and it was successful in half of the patients. The first large study about the efficacy of ketogenic diet in 2001 reported the similar result that it was effective in 70% of the patients [25]. In another study of intractable infantile spasms, 72% of patients showed long-term efficacy after 6 months of a ketogenic diet [26]. In a retrospective study where a ketogenic diet was used as first-line therapy, the authors reported that eight (62%) of 13 newly diagnosed patients became spasm-free and had a normalized EEG within 2 months [27]. The ketogenic diet has been widely used in drug-resistant epilepsy, especially in infants. The efficacy of the diet has been proven in many studies, including one randomized controlled study [16,28]. The frequent adverse effects are constipation, poor feeding, gastro-esophageal reflux, acidosis, and renal stones. Clinicians should be aware of these potential side-effects.

There are many opinions about the order of treatment for infantile spasms. According to the two recent reports, ACTH is the most evidenced first line drug; the short-term spasms cessation with ACTH was 72–76%, however, with vigabatrin 40–54% [15,17]. For the long-term results, the United Kingdom Infantile Spasms Study (UKISS) showed the proportion of infants with spasms cessation without subsequent relapse was similar in the 2 treatment arms (hormonal therapy – 40%, vigabatrin – 37%) [22]. These results are very similar to our study. If ACTH is not available, vigabatrin is usually recommended. There is no consensus concerning oral steroids as a first-line therapy [15,17]. This study provides some evidence about the use of vigabatrin as a first-line drug and topiramate as second-line drug. Although a ketogenic diet was tried after the failure of two or more antiepileptic drugs, it can be used as a second line treatment or co-first line method. Future studies of the ketogenic diet as a first-line therapy with/without antiepileptic drugs are needed to confirm its role as a primary treatment option for infantile spasms.

Epilepsy surgery can be effective for patients with intractable epilepsy [9]. However, there is limited data regarding the outcomes in epilepsy surgery in intractable infantile spasms. In one study of 23 infants with intractable infantile spasms, 65% of the patients became seizure-free [29]. Another study described epilepsy surgery in 24 patients including 11 who had epileptic spasms [30]. Seventeen of the patients became seizure-free, and five of the patients achieved >90% seizure reduction. The patients with infantile spasms were younger, and they had a lower developmental quotient at presentation than the patients with other types of seizure. However, they showed a greater increase in the developmental quotient following surgery [30]. Although the patient in this study became seizure-free after the operation, more evidences need to be collected for validation of its efficacy in infantile spasms.

There have been some efforts to use the initial EEG for predicting outcomes in infantile spasms [31–33]. Variant patterns or atypical features of hypsarrhythmia were quite common. A low severity score usually represented relative preservation of normal background activity, little high amplitude delta activity or a spike/sharp wave, and a generalized attenuation pattern [31]. We analyzed the individual components of the initial EEGs, in addition to background activity, presence of atypical features of hypsarrhythmia, frequency of generalized attenuation patterns, and evidence of focal epileptic loci. According to previous studies, a higher severity score was associated with a poor outcome [31,33]. Another study revealed that lowering the severity score with initial treatment was associated with better outcome [32]. However, there were no significant prognostic factors associated with the characteristics of the initial EEGs in this study.

The limitations of this study are the uneven use of the ketogenic diet and the absence of development score in some patients. In our institution, the ketogenic diet began to be widely prescribed from the middle of 2000. Therefore, about one-third of the patients were not exposed to the diet.

In conclusion, the results of this study suggest that cryptogenic etiology and later onset of spasms are significant prognostic factors for infantile spasms and that medical treatment with antiepileptic drugs led to a 60.9% spasm-free rate. In addition, the ketogenic diet was effective in treating intractable infantile spasms. Therefore, early diagnosis and prompt application of treatment options, such as antiepileptic drugs, ketogenic diet, or epilepsy surgery will ensure favorable outcomes in cases of infantile spasms.

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