

# Infantile spasms: A prognostic evaluation

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## Abstract

**Background:** Few papers address the comprehensive prognosis in infantile spasms and look into the seizure profile and psychomotor outcome. **Objective:** We aimed to follow up children with infantile spasms to study: a) the etiology, demographics, semiology, electroencephalogram (EEG), and radiological pattern; b) seizure control, psychomotor development, and EEG resolution with treatment; c) the effects of various factors on the control of spasms, resolution of EEG changes, and psychomotor development at 3-year follow-up. **Materials and Methods:** Fifty newly diagnosed cases with a 1-12 month age of onset and who had hypsarrhythmia in their EEG were recruited and 43 were followed up for 3 years. **Results:** Of the children followed up, 51% were seizure-free and 37% had a normal EEG at the 3-year follow-up. Autistic features were seen in 74% of the children. Only 22.7% among the seizure-free (11.6% of the total) children had normal vision and hearing, speech with narration, writing skills, gross and fine motor development, and no autism or hyperactivity. On multivariate analysis, two factors could predict bad seizure outcome — the occurrence of other seizures in addition to infantile spasms and no response to 28 days of adrenocorticotrophic hormone (ACTH). No predictor could be identified for abnormal psychomotor development. **Discussion and Conclusion:** In our study, we could demonstrate two factors that predict seizure freedom. The cognitive outcome and seizure control in this group of children are comparable to the existing literature. However, the cognitive outcome revealed by our study and the survey of the literature are discouraging.

## Key Words

Development, infantile spasms, cognitive outcome, prognosis, psychomotor development, seizure freedom, outcome, West syndrome

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*Ann Indian Acad Neurol* 2016;19:228-235

## Introduction

It is known that seizures and electrical epileptogenic activity result in cognitive decline.<sup>[1]</sup> Infantile spasms (West syndrome) is an epileptic encephalopathy characterized by spasms and hypsarrhythmia on the electroencephalogram (EEG).<sup>[2]</sup>

Despite treatment, the prognosis of West syndrome is poor with the majority (88-96%) having psychomotor retardation at follow-up.<sup>[3-5]</sup> The pathophysiology is still unknown; two-third patients have a demonstrable underlying cause and there is no consensus on the treatment. Applying logic, the etiology is different in the developing countries with a greater burden of birth-related problems. As the

most accepted treatment modality [adrenocorticotrophic hormone (ACTH)] involves immunosuppression, the treatment in the same region has to be tailored to the needs of the population (exposed to increased risk of infectious diseases). Earlier studies observed that in the subgroup of cryptogenic patients, a delay in the initiation of treatment may be associated with a worse outcome.<sup>[3,6]</sup> However, different groups have described different prognostic factors for outcome in infantile spasms.

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**How to cite this article:** Iype M, Saradakutty G, Kunju PA, Mohan D, Nair MK, George B, *et al.* Infantile spasms: A prognostic evaluation. *Ann Indian Acad Neurol* 2016;19:228-35.

**Received:** 23-07-15, **Revised:** 08-09-15, **Accepted:** 09-10-15

## Access this article online

Quick Response Code:



Website:

www.annalsofian.org

DOI:

10.4103/0972-2327.173314

## Objectives

- To describe the semiology and the demographical, etiological, EEG and radiological patterns in children with infantile spasms.
- To describe seizure control, psychomotor development (using standardized psychometric assessments), and EEG resolution with treatment in children with infantile spasms.
- To evaluate the effects of various factors on the control of spasms, resolution of EEG changes, and psychomotor development at 3 years after initiation of treatment.

## Materials and Methods

We prospectively recruited 50 consecutive patients in this longitudinal follow-up study conducted in a tertiary care pediatric neurology center in South India from August 2009 to February 2012.

### Inclusion criteria

- Newly diagnosed children fulfilling the International League Against Epilepsy (ILAE) criteria for infantile spasms;<sup>[7]</sup>
- An age of onset between 1 month and 12 months;
- Presence of hypsarrhythmia or modified hypsarrhythmia on EEG

### Exclusion criteria

The present study excluded nonconsenting patients and those previously treated with ACTH, steroids, or vigabatrin.

### Ethical considerations

The study protocol was approved by the Ethical Review Committee of our institution. Informed consent was obtained from caretakers of every patient enrolled.

### Definitions<sup>[8]</sup>

A child was considered seizure-free at 28 days of age when he was free of seizures for a minimum period of 7 days. At a 3-year follow-up, a child was considered seizure-free if he had no seizures for at least the past 3 months.

The term symptomatic infantile spasms was used for children who had a clearly defined underlying cause and/or significant developmental delay prior to the onset of spasms.<sup>[9]</sup> Each child was classified as symptomatic or cryptogenic at the end of the study, sometimes after a long-lasting diagnostic workup. The cryptogenic cases included those in whom no underlying cause could be detected.

Parents recorded the type and number of seizures using daily record cards. Each patient had at least a monthly visit. At each visit, the investigator confirmed the seizure assessment and screened for presence of psychomotor retardation using the Trivandrum Developmental Screening Chart (TDSC).<sup>[10]</sup> Socioeconomic status was assessed using modified Kuppuswamy Scale 2003.<sup>[11]</sup>

### Tools and techniques

A semi-structured pretested questionnaire was used to collect demographic details and the clinical and treatment history.

Chromosomal analysis and metabolic workup were done in cases where it was clinically deemed necessary. Magnetic resonance imaging (MRI) scan of the head using a 1.5 Tesla machine and if necessary an additional computed tomography (CT) scan of the brain in cases of suspected calcification were performed.

At 1-year age, the Developmental Assessment Scale for Indian Infants (DASII) was administered by trained developmental therapists at the Child Developmental Centre, Thiruvananthapuram, Kerala, India and each child's mental and motor developmental quotients were obtained.<sup>[12]</sup> At 3 years follow-up, each child had the Childhood Autism Rating Scale (CARS) administered at the Child Developmental Centre, Thiruvananthapuram, Kerala, India and the children were classified as nonautistic, having mild to moderate autism, and having severe autism.<sup>[13]</sup> The presence of hyperactivity was judged based on the DSM-IV-TR criteria for attention-deficit/hyperactivity disorder (ADHD). Visual acuity testing was performed in the cognitively normal child by picture card matching and letter recognition if the child was old enough. In the cognitively abnormal child, fixation of eyes on colored objects and light and following of light or object was used to assess vision. Behavioral observation audiometry was performed in the majority of cases to assess hearing at the 3-year follow-up. Patients who could not cooperate were assessed using auditory brain stem-evoked response. Gross and fine motor skills were assessed using TDSC. Writing skills of the child was assessed depending on the age of the child at the 3-year follow-up. The minimum standard was set at being able to copy a circle. An informal picture story narration test was used to assess narrative skills.

After clinical evaluation and laboratory tests, every patient had initially 28 days of ACTH. Synthetic ACTH was used at a dose of 20 IU subcutaneously (s/c) per day for all infants more than 5 kg weight and 10 IU s/c per day for infants who weighed less than 5 kg. As a low dose was used, a daily regimen was given instead of the alternate day regimen. Other antiepileptics were tapered and stopped initially. No standardized treatment protocol was implemented after the initial 28 days for this follow-up study. Patients who were controlled with ACTH were continued on the oral medications; if they showed a partial response or no response, another 28 days of ACTH was given. Later other oral antiepileptics including vigabatrin, lamotrigine, topiramate, and benzodiazepines were given as the situation warranted, depending on the response and emergence of adverse effects. Vigabatrin was withdrawn after 6 weeks if there was no response. In patients who responded, vigabatrin was continued for 6-8 months and tapered. Patients who remained seizure-free were continued on sodium valproate monotherapy wherever possible or drug combinations for 2 total years of seizure freedom and EEG normalization (a normal EEG). Potential worsening by phenobarbitone, phenytoin, and carbamazepine was kept in mind and these drugs were avoided.

At each monthly or more frequent follow-up visits, treatment emergent adverse effects were recorded. Patients on vigabatrin were seen by an ophthalmologist every 3 months and retinal changes were assessed as in this age group, visual fields could not be examined and a large number of patients already had cortical blindness due to the initial cerebral insult.

### Statistical analysis

The data were coded, entered, and analyzed using Windows Statistical Package for the Social Sciences (SPSS) version 11. Descriptive statistics was used to describe the social and demographic profiles, the seizure semiology, and the EEG. Bivariable analysis was performed using *t*-test and chi-square as appropriate for the variable. A *p* value <0.05 was considered to be significant. For multivariate analysis, binary logistic regression was used. Statistical analysis was performed by the second author (an epidemiologist).

### Observations and Results

Fifty consecutive cases of infantile spasms with hypsarrhythmia in their EEG were recruited over a 2.5-year period. The eligible study candidates were 55. The caretakers of two children refused to give consent to join the study. Three cases were excluded as the initial EEG was normal.

### Baseline characteristics

Table 1 shows the baseline characteristics of the 50 children. Among the children with family history of epilepsy, only one had family history of infantile spasms. The vast majority of our patients belonged to the middle income group – 36/50. Table 2 shows the patient details and characteristics of the seizures of the group.

### Etiology

Six out of the total 50 were cryptogenic. The symptomatic group included 20 patients with perinatal problems including hypoxic ischemic encephalopathy (HIE), neonatal jaundice (NNJ), and hypoglycemic brain injury (HBI), 10 patients with cerebral malformation, 5 patients with intrauterine infections, 4 patients with inborn errors of metabolism, 1 patient with neonatal meningitis, 1 patient with postneonatal ventilation induced anoxic brain damage, and 3 patients with tuberous sclerosis. For analysis, the symptomatic group was reclassified into two groups:

1. Perinatal; including HIE, NNJ, HBI, neonatal meningitis, and postneonatal ventilation anoxic damage, and
2. A structural metabolic group, which included brain malformations, the inborn errors of metabolism, intrauterine infections, and tuberous sclerosis.

### Outcome

#### Early outcome

#### Seizure status

After 14 days of ACTH, 20% only were seizure-free. After 28 days of ACTH, 40% had full control of seizures, 28 (56%) had partial control, one had aggravation, and one died. Of the 20 children who were seizure-free at 28 days, 15 relapsed at some point to be controlled later; only 5 continued to be seizure-free without any relapse.

#### EEG at 28 days after adrenocorticotrophic hormone

After 28 days of ACTH, EEG showed normalization in only 2 (4%) patients; 66% of the patients showed no change in their hypsarrhythmic pattern; 28% had some change for the better with more normal sleep patterns emerging and less of spiking, and one child died before the EEG on the 28<sup>th</sup> day.

**Table 1: Baseline characteristics of the study population**

Characteristic	Total 50
Gender – male	21
Place of residence – rural	48 (96%)
Family:	
Nuclear	20
Joint	30
Socioeconomic status	
Middle income	36
Low income	12
High income	2
Born by Caesarean section	22 (42%)
Birth order:	
First	32
Second	15
Third	3
Family history of epilepsy	3 (6%)
Developmental delay prior to onset of spasms	46 (92%)
Microcephaly	38 (78%)
Spastic	31 (62%)
Abnormal MRI† brain	62%

†MRI = Magnetic resonance imaging

**Table 2: Seizure, patient, and EEG characteristics**

Age at presentation	2-12 months [mean 6.79 (2.6)]; mode 6 months
Age <3 months	3/50
Age of onset	1-12 months [mean 4.84 (2.6)]; mode 6 months
The latent period for presentation	1-7 months (mode – 3 months)
Mean latent period	2.01 (1.8) months
Etiology – symptomatic	44
Hypsarrhythmia:	
Typical	27
Abnormal focus of discharge	20
Other atypical hypsarrhythmia	3
Voltage attenuation on EEG§	16
Seizure	
Spasms only	31
Focal seizure also	8
Absences also	4
Multiple coexistent seizures also	7
Clustering of spasms	92%
Cluster*	
Uniform spasms	32
Crescendo	2
Decrescendo	9
Crescendo-decrescendo	3
Related to sleep	36 (83% of them on awakening)
Asymmetric spasms	26%
Movement of all 4 limbs	34
Upper limbs predominantly	15
Lower limb predominantly	1

\*4 had single seizures, §EEG = Electroencephalogram

**Psychomotor development at one year age**

At 1 year of age, 88% of the children were available for follow up, four were lost to follow-up, one child died at 2 weeks after enrolment, and one child died at 1 year. DASII was administered to 86% of the children at 1 year as one child who subsequently died at 14 months was too sick. Only 4/43 (9.3%) of the group showed normal motor and mental developments.

**Associations with seizure freedom at 28 days of adrenocorticotrophic hormone**

On bivariable analysis, no factor had an association with seizure-free status at 28 days after initiation of ACTH.

**Associations with psychomotor development at 1-year age**

On bivariate analysis, no factor had an association with the psychomotor development of the children at 1 year of age.

**Late outcome**

Only 43 children were available for follow-up at 3 years as three died and four were lost to follow-up.

**Mortality**

One child who had severe pneumonia at the time of death, died at 2 weeks after enrolling into the study while on ACTH (had hyperammonemia but the metabolic defect could not be further characterized). The other two who died were not on ACTH at the time of death. Both had gross cerebral malformation — one had holoprosencephaly and cleft lip and palate and the other had lissencephaly.

**Seizure status**

At 3-year follow-up, 22 were seizure-free, 13 continued to have infantile spasms alone, 7 had other seizure types also, and 1 had Lennox Gastaut syndrome. However, among those who were seizure-free, 2 were off drugs and 10 each were on one drug and multiple drugs. Only 16/22 seizure-free children had a normal EEG, 5 had an interictal EEG, and 1 had persisting hypsarrhythmia. Though 22 (51.2%) of the 43 who could be followed up to 3 years were seizure-free for 3 months, only 16/43 (37.2%) had a normal EEG. Sixteen (37.2%) had an interictal EEG, 8 (18.6%) had persisting hypsarrhythmia, and 3 (6.9%) had a Lennox-Gastaut syndrome (LGS) type EEG (one of them had the semiology of LGS and the others continued to have multifocal myoclonic jerks only).

Though the number of children who attained seizure freedom at 28 days after treatment initiation and at 3-year follow-up were nearly the same — 20/49 (40.8%) — (one died at 2 weeks after recruitment) and 22/43 (51.2%), EEG normalization was markedly more at 3 years — 4% (2/49) at 28 days versus 37.2% (16/43) at 3-year follow-up.

**Comprehensive outcome at 3-year follow-up**

At 3-year follow-up ( $n = 43$ ), visual impairment was seen in 30% children, hearing impairment in 16% children, normal fine and gross motor skills in 14% and 16% children, respectively, normal speech skills in 16% children and no autism in 25.5% children. Only 11.6% were seizure-free with no motor or cognitive sequelae (no autism or ADHD and

normal learning, writing, and speech) and normal vision and hearing. However, only 7% children had the above attributes with a normal EEG as well. Of the children, 4.6% were seizure-free with a normal EEG and normal motor and cognitive development and were off drugs for at least 3 months. Only 5/22 (22.7%) who were totally seizure-free had normal gross motor and fine motor developments, no autism or hyperactivity, normal speech with narration, normal writing skills, and normal vision and hearing.

There was no statistically significant relation between age and latent period for presentation with seizure freedom at 3-year follow-up. To attempt to find the prognostic factors for seizure freedom at 3 years, bivariable analysis was performed using various factors.

**Result of bivariable analysis of factors related to seizure freedom at 3-year follow-up [Table 3]**

Seizure control at 28 days after the initiation of ACTH, occurrence of infantile spasms only versus occurrence of other seizure types along with the infantile spasms, no autism at 3-year follow-up, being part of a joint family, and being the first born had a significant positive association with seizure freedom at 3-year follow-up.

**Result of multivariate analysis of factors to predict persistence of seizures at three years**

On multivariate analysis, two factors were significant — the occurrence of other seizure types in addition to the infantile spasms  $p = 0.007$ ; adjusted odds ratio (OR) [95% confidence interval (CI)] 11.105 (1.939-63.612) and no response to 28 days of ACTH  $p = 0.007$  and adjusted OR (95% CI) 10.350 (1.896-56.491).

**Association of etiology with electroencephalogram at 3-year follow-up and autism**

The etiology when classified as cryptogenic, perinatal insult and structural metabolic, showed no association with the EEG at 3 years ( $p = 0.67$ ) and to the development of autism as assessed with the CARS score at 3 years ( $p = 0.30$ ).

**Predictors of abnormal psychomotor development and abnormal electroencephalogram at 3 years**

On bivariable analysis, no factor could be statistically significantly associated with abnormal psychomotor development or abnormal EEG at 3-year follow-up.

**Treatment emergent adverse events**

Out of the 50 children administered ACTH, 12 each had significant weight gain and severe infection, 15 had hypertension, and 1 had hypocalcemia with features of rickets. Of the 12 patients who developed severe infection while on ACTH, one died (pneumonia) and the rest survived. Among the survivors of severe infection, one each had chicken pox, severe conjunctivitis, orbital cellulitis, staphylococcal scalded skin syndrome, and measles. The rest had severe respiratory infection. Three children who were on ACTH developed oral candidiasis, two complained of high-pitched cry, five developed hyperpigmentation, and one had increased irritability and grunting. One patient on topiramate ( $n = 24$ ) had loss of appetite at a 6 mg/kg dose. None of the patients on Vigabatrin ( $n = 17$ )

**Table 3: Result of bivariate analysis of factors associated with seizure control at 3-year follow-up**

Factor studied	Seizure controlled (n = 22) n (%)	Seizure uncontrolled (n = 21) n (%)	Chi-square	df	P value	Odds ratio
Gender (male)	8 (36.4%)	8 (38.1)	0.14	1	0.907	
Kuppuswamy scale (lower)	17 (77.3)	14 (66.7)	0.601	1	0.438	
Joint family	18 (81.8)	10 (47.6)	5.532	1	0.019	0.202
Delayed development	19 (86.4)	20 (95.2)	0.227	1	0.634*	
Age of presentation						
>.6 months	13 (59.1)	9 (42.9)	1.133	1	0.287	
Age of onset >.6 months	5 (22.7)	5 (23.8)	0.007	1	0.7	
Latent period <1 month	10 (45.5)	15 (71.4)	2.987	1	0.084	
No microcephaly	6 (27.2)	3 (14.3)	1.095	1	0.295	
MRI <sup>§</sup> normal	10 (45.5)	8 (38.1)	0.239	1	0.625	
Hypsarrhythmia – typical	12 (54.5)	9 (42.9)	0.587	1	0.443	
Absence of voltage attenuation following bursts on EEG <sup>‡</sup>	16 (72.7)	15 (71.4)	0.009	1	0.924	
EEG at 28 days (some change or normal)	11 (50)	5 (23.8)	3.154	1	0.076	
Seizure free at 28 days	15 (68.2)	5 (23.8)	8.503	1	0.004	0.146
Patients with infantile spasms only	18 (81.8)	8 (38.1)	8.592	1	0.003	0.137
Normal delivery vs LSCS <sup>¶</sup>	10 (45.5)	11 (52.4)	0.205	1	0.650	
Duration of spasm <5 s	14 (63.6)	11 (52.4)	0.559	1	0.455	
Flexor spasms	11 (50)	10 (47.6)	0.24	1	0.876	
<100 spasms/day	14 (63.6)	10 (47.6)	1.118	1	0.290	
Related to sleep	15 (68.2)	16 (76.2)	0.343	1	0.558	
Symmetric	15 (68.2)	16 (76.2)	0.343	1	0.558	
No spasticity	10 (45.5)	7 (33.3)	0.660	1	0.416	
Normal vision <sup>†</sup>	18 (81.8)	13 (61.9)	2.118	1	0.146	
Normal hearing <sup>†</sup>	19 (86.4)	18 (85.7)	0.004	1	0.951	
Normal gross motor development <sup>†</sup>	7 (31.8)	1 (4.8)	3.561	1	0.059	
Normal fine motor development <sup>†</sup>	7 (31.8)	0	5.817 <sup>a</sup>	1	0.016	
No autism <sup>†</sup>	10 (45.5)	2 (9.5)	6.894	1	0.009	0.126
CARS <sup>#</sup> in normal range <sup>†</sup>	10 (45.5)	1 (4.8)	13.748	2	0.001	
Normal psychomotor development at one year	4 (18.2)	0	2.331	1	0.127	
First born	17 (77.3)	10 (47.6)	4.044	1	0.044	0.267
Perinatal injury as etiology	10 (45.5)	11 (52.4)	0.206	1	0.650	
Structural/metabolic etiology	14 (63.6)	13 (61.9)	0.14	1	0.907	

\*Continuity correction applied, <sup>†</sup>On follow-up at 3 years, <sup>§</sup>MRI = Magnetic resonance imaging, <sup>‡</sup>EEG = Electroencephalogram, <sup>¶</sup>LSCS = lower segment caesarean section, <sup>#</sup>CARS = Childhood autism rating scale

had new visual deficits or macular changes (monitored by an ophthalmologist at three monthly intervals). Two children developed allergic skin reaction and consequently had to discontinue vigabatrin. One child each on valproate ( $n = 50$ ) and lamotrigine ( $n = 7$ ) had allergic skin reaction and had to discontinue the same. Three children who were on valproate showed a dose-dependent increase in liver enzymes. We did not look for brain atrophy as a side effect of ACTH or vigabatrin as described in the literature due to the cost involved.

#### *The group with metabolic diseases*

The metabolic diseases identified in this group included a child with Gaucher (enzyme proved) a case of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (tandem mass spectroscopy), a case of hyperammonemia not further characterized and a case of biotinidase deficiency. Two of them continued to have seizures at 3 years and were autistic, the child with MCAD deficiency was seizure-free but was severely autistic and the child with hyperammonemia was lost to follow-up.

#### *The children with intrauterine infection*

There were two cases of rubella and three with *Cytomegalovirus* (CMV) infection. The two with CMV were lost to follow-up. The third was seizure-free but autistic at 3-year follow-up. Both the children with rubella had seizures and were autistic at 3-year follow-up.

#### *Magnetic resonance imaging abnormality*

The MRI was abnormal in 31/50; (25/43 who came for follow-up). Nine children had cerebral malformation (three hemimegalencephaly, two schizencephaly, one lissencephaly, one holoprosencephaly, one corpus callosal agenesis — as part of Aicardi syndrome and one with altered gyral morphology). One child had hydrocephalus, nine had cerebral atrophy, three had old infarcts, two had bilateral cystic encephalomalacia, two had extensive calcification (one frontal and the other basal ganglia), one each had bilateral thalamic hyperintensities and nonspecific white matter hyperintensities, and the three with tuberous sclerosis had multiple cortical tubers. Out of the 25 children with MRI abnormality, only 12 children were seizure-free at 3-year follow-up and only six children were nonautistic.

## DISCUSSION

There are difficulties in comparing the results of a clinical series of infantile spasms from the literature because of their nonhomogeneity and different definitions of response rates. Table 4 shows the comparison of age, gender, etiology, and EEG with other studies. The other studies shown were all conducted a few years earlier and had fewer symptomatic cases. It is a known fact that patients diagnosed more recently are often subject to "more sensitive investigative techniques" that will lead to identified diagnoses. Surprisingly, our study showed more females than males in the group as observed in a few studies only.<sup>[17,19]</sup> None of the factors in our study correlated significantly with the etiology as observed by Mohammed *et al.*<sup>[19]</sup> The dose of ACTH used in our study was the same as that recommended by the American Academy of Neurology in its evidence-based guideline update 2013.<sup>[20]</sup>

### Developmental outcome

Though 51.2% of the children who came for follow-up in our study were seizure-free, it is noteworthy that only 11.3% were seizure-free and developmentally normal. However, the available literature also supports this observation. A review of 67 published studies with an average follow-up period of 31 months found that only 16% of the patients with infantile spasms had normal development.<sup>[21]</sup> Of the symptomatic patients, 80% and in the idiopathic group, 50% remained developmentally delayed and 60% only of the total remained seizure-free at a median follow-up of 2.38 years in a retrospective long-term follow-up study by Lagae *et al.*<sup>[22]</sup> In one population-based survey by Trevathan, 80% of 10-year-old children with a diagnosis of infantile spasms had some form of mental retardation.<sup>[15]</sup> In the series by Basheer, 87.5% had abnormal neurodevelopmental outcome.<sup>[19]</sup> Most studies have shown the best outcomes in the cryptogenic group, with normal development seen in 30-70% of these infants, especially when treated early.<sup>[3,14]</sup> In the series by Ibrahim, only 4/56 children (7.2%) showed normal developmental milestones after follow-up for 6 months.<sup>[17]</sup>

Only few studies have addressed autism as sequelae in children with infantile spasms. In a study by Saemundsen, only 6/17 (35.3%) showed autism spectrum disorder while we had 74.4% with autism, possibly reflecting the small number studied by Saemundsen.<sup>[23]</sup>

### Predictors of abnormal developmental outcome and autism

On bivariable analysis, we could not find any predictor for an abnormal developmental outcome or autism. Poor prognostic

factors for mental development in the 1981 study by Matsumoto were delayed development before the onset of spasms, neurological abnormalities, prenatal and perinatal etiologies, relapse after initial ACTH therapy, laughing attacks, and evolution into other types of fits.<sup>[6]</sup> Only in the cryptogenic cases in the available literature, was there a significant correlation between the delay in treatment and the long-term prognosis for mental development.

### Long term seizure control

Among randomized controlled trials, the response rate (cessation of clinical spasms and normalization of the hypsarrhythmic EEG) to natural or synthetic ACTH ranged from 42-87% of the patients and up to 100% in the cryptogenic group.<sup>[2,24,25]</sup>

Baram recorded 87% spasm freedom with EEG normalization when he used the highest dose of 150 units/m<sup>2</sup> twice daily of natural ACTH for 14 days followed by taper.<sup>[25]</sup> Lux used 40 units synthetic ACTH on alternate days and got 76% seizure freedom without EEG normalization.<sup>[2]</sup> Hrachovy *et al.* compared high-dose and low-dose natural ACTH in a class I randomized control trial. Primary outcome measurement was cessation of clinical spasms and the abolition of hypsarrhythmia on EEG. There were no differences in efficacy for each dosing group, with 50% responders in the high-dose group and 58% response in the low-dose group.<sup>[26]</sup> The adverse effect profile was similar except for a higher rate of hypertension in the high-dose group. The seizure control with high dose ACTH is contradictory in many well-quoted studies with Kivity and Yanagaki showing 91.89% and 100% suppression of hypsarrhythmia and total cessation of seizure with high dose ACTH, respectively.<sup>[14,24,25]</sup> In the study by Mohammed BP, 77.5% continued to have seizures.<sup>[19]</sup>

### Predictors of seizure control on long term follow up

The factors that we could discern on bivariable analysis included being part of a joint family (possibly with the grandparents involved in bringing up the child and hence, a better drug compliance) and being first born (and possibly consequently having a younger mother and with less time allotted to other siblings). One other factor seen to be significantly associated with better seizure control was no autism at 3-year follow-up, which could be a consequence of the seizure control. On multivariate analysis, two of the five factors remained significant (seizure control at 28 days after the initiation of treatment and occurrence of infantile spasms alone with no other seizure type). These two factors could be an indicator of less severe initial pathology. Table 5 compares the factors predicting seizure

**Table 4: Comparison of age, gender, etiology, and EEG with other studies**

Reference	Age of onset in months mean (SD)	Age in months* (SD <sup>†</sup> )	Latent period months (SD)	M (%)	Symptomatic %	Typical EEG <sup>‡</sup> %	Total no. studied
Current study	4.84 (2.6)	6.79 (2.6)	2.01 (1.8)	42	88	54	50
Zhu <i>et al.</i> <sup>[16]</sup>	5.36 (2.5)	6.6 (3.6)	1.3 (1.2)	60	72.5	57.5	47
Ibrahim <i>et al.</i> <sup>[17]</sup>	5 (1.4)	6.5 (2.3)	1.4 (1.3)	62.5	64.3	92.8	58
Prathibha Singhi <i>et al.</i> <sup>[18]</sup>	6.1 (3.4)	14.7 (11.4)	6-7	67.9	71	44	165
Mohammed <i>et al.</i> <sup>[19]</sup>	5.97 (95% CI <sup>§</sup> 3.6-15.94)	6.81(95% CI 4.32-17.31)	31.3 days (95% CI 27.69-47.95 days).	43	68	60	75

\*Age at presentation, <sup>†</sup>Typical hypsarrhythmia, M = Male, <sup>‡</sup>SD = Standard deviation, <sup>§</sup>CI = Confidence interval

**Table 5: Predictors for seizure control in various studies irrespective of drug combinations and doses used**

Reference	Predictor	Year	Number	Type of study
Present study	Presence of infantile spasms alone vs with other seizure types also Seizure control at 28 days after commencement of treatment	2014	43	Prospective
Singhi, Ray <sup>[18]</sup>	Developmental improvement	2005	165	Prospective study
Ibrahim <sup>[17]</sup>	Response to first-line treatment Etiology other than symptomatic Younger age at diagnosis	2010	56	Retrospective
Basheer <sup>[19]</sup>	Cryptogenic spasms who responded to first-line therapy	2011	75	Retrospective
Kivity <i>et al.</i> <sup>[14]</sup>	Early initiation of treatment before 1 month of onset	2004	37	Prospective
Matsumoto <sup>[6]</sup>	Nonevolution into other seizure types, nonrelapse of seizures after ACTH <sup>†</sup> therapy, no other seizures concomitant with spasms, and no convulsions before the onset of spasms	1981	162	A retrospective-prospective study

<sup>†</sup>ACTH = Adrenocorticotrophic hormone

control in other studies with the factors we have identified. No delay in the initiation of treatment has been endorsed in the studies by Lombroso and in an Indian study to be related to good outcome.<sup>[5,27]</sup> Singhi and independently Basheer, like us, did not find that correlation.<sup>[18,19]</sup> In the North Indian paper by Singhi and Ray, no factor other than developmental improvement could predict seizure control.<sup>[18]</sup> Matsumoto *et al.* as in the present study, have identified the presence of other seizures in addition to infantile spasms, a predictor of continuing seizures.<sup>[6]</sup> As observed in our study, Ibrahim *et al.* and Basheer *et al.* have identified early seizure control as a factor predicting seizure freedom later.<sup>[17,19]</sup> As in our study, Basheer also observed that etiology could not predict seizure control.<sup>[19]</sup>

### Mortality

The mortality rate associated with infantile spasms has been estimated to be between 5% and 30%.<sup>[15,25]</sup> Our study had a mortality of 6.97% (3/43) and all died of infection as reported in other series.<sup>[28]</sup> Riikonen and Glaze and Hrachovy independently reported a mortality of 5%.<sup>[3,4]</sup> Death due to septicemia while on ACTH was reported in two out of 56 patients by Ibrahim.<sup>[17]</sup>

### Side effect profile

Our study showed that ACTH has not negligible side effects in a large number of children. With regard to the side-effect profile, Ibrahim found that vigabatrin was better than ACTH with only 2/38 patients experiencing the adverse effects, as opposed to ACTH, where 6/18 patients reported ACTH induced hypertension.<sup>[17]</sup> In our study, 30% developed hypertension on ACTH. In other studies, hypertension has been reported in 0-37%.<sup>[24,26]</sup> Riikonen reported death in 5%, hypocalcemia in two patients, and hypertension in 11/162 children.<sup>[29]</sup> Irritability has been reported in 37-100%.<sup>[24,26]</sup> Only one each of our patients had hypocalcemia and severe irritability and grunting.

### Conclusions

The two factors identified in our study to predict a good seizure outcome — the presence of infantile spasms alone versus with other seizure types and seizure control at 28 days after commencement of treatment could help us to predict seizure control in children with infantile spasms early in the disease course. The fact that we could demonstrate a seizure-free state lasting for at least 3 months at 3-year follow-up with low dose of ACTH in 51% should encourage us to persist in treating

children with infantile spasms. However, it is alarming to note that only 11.6% were seizure free with no neurodevelopmental sequelae in spite of 51% being seizure free and that no factor in our study could predict the occurrence of these sequelae.

Though the number of patients with seizure freedom at 28 days after the commencement of treatment and 3-year follow-up were comparable, EEG normalization was of no comparison, pointing to the necessity for the continuation of antiepileptics until EEG normalization even if spasms are controlled.

### Study Limitations and Strengths

The study was prospective and a formal cognitive assessment could be done at 1 year of age and at 3-year follow-up. Studies with larger numbers of patients should be undertaken to assess the developmental and cognitive outcomes of treated children with infantile spasms with and without EEG normalization.

### Acknowledgement

The study was funded by the Sree Avittom Thirunal (SAT) Endowment fund of the State Government of Kerala. We would also like to acknowledge the work done by Prasanna GL, Rajee Krishnan R, Resmi VR, and Sunitha RM, developmental therapists and Lekshmi MA and Letha S, preschool teachers of the Child Development Centre, Thiruvananthapuram, Kerala, India.

### Financial support and sponsorship

The study was funded by the Sree Avittom Thirunal (SAT) Endowment fund of the State Government of Kerala. The sponsoring agent had no role in the design and conduct of the study.

### Conflicts of interest

There are no conflicts of interest.

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