■ Original article

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Predictors of outcome among 31 children with infantile spasms syndrome

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ABSTRACT

Objective. Infantile spasms syndrome is a severe epileptic encephalopathy. Management of infantile spasms remains challenging because of pharmacoresistant forms and relapsing seizures. A high number of patients with this syndrome have neurodevelopmental delay. The main objective of our study was to determine predictors to measure the neurodevelopmental outcome of patients with infantile spasms.

Methods. We prospectively evaluated 31 patients with infantile spasms from 2014 to 2017 at three hospitals in Tbilisi, Georgia. Various demographic data were evaluated at the first visit; video-EEG, brain MRI and neurodevelopmental evaluation were performed upon admission. A diary to record spasms was provided and completed by all parents/caregivers. Seizures were recorded on video and the phenomenology of infantile spasms was studied. Children were followed for one and two years after the first assessment.

Results. Neurodevelopmental deterioration was revealed in 61.1% on the second and 53% on the third evaluation in patients with onset of spasms before seven months of age. The mean score on the ASQ communication domain was low among structural cases. Eleven patients with pre-existing delay had developmental regression based on the second evaluation (Fisher's exact test: 7.2; df 1; p=0.01).

Significance. Our study reveals that age at onset of infantile spasms at less than seven months, pre-existing developmental delay, low ASQ scores and structural abnormalities on MRI are predictors of poor developmental outcome. Our data suggest that clinicians should inform parents at the first clinical evaluation about prognosis, and intervention should be started as early as possible in order to improve development.

Key words: West syndrome, infantile spasms, neurodevelopment, autism spectrum disorder, prospective study

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According to the definition of the ILAE 2017 operational classification of seizure types, an epileptic spasm presents as a sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles. They commonly occur in clusters and most often during infancy. Infantile spasms syndrome is a term proposed to encompass both West syndrome as well as infants presenting with epileptic spasms who do not fulfil all the criteria for West syndrome [1]. We use the term "infantile spasms" as it may include epileptic spasms occurring at infantile age according to the new classification [2].

Infantile spasms syndrome is an age-dependent epilepsy syndrome, with peak onset at three to seven months

and only rare reports of onset at up to four years of age [3]. It is accompanied by a specific EEG pattern known as hypsarrhythmia and delay or arrest of psychomotor development [4, 5]. However, some patients with infantile spasms do not have hypsarrhythmia. A modified hypsarrhythmia, or consistent focal features may be present, including focal spasm complexes [1]. In up to 80-90%, patients with infantile spasms often have profound developmental delay [6]. Studies have suggested disparate variables affecting long-term outcome [7, 8]. Only few prospective cohorts aimed to study developmental outcome. Recent studies about this condition are more focused on genetic aspects and specific treatments.

For many years, it was often stated that the only factor influencing later cognitive outcome of patients with infantile spasms was the underlying aetiology, with a worse outcome for those with structural aetiologies [9].

Unidentified aetiology, normal pre-spasm development, absence of other seizure types pre- and post-infantile seizure diagnosis, short duration of hypsarrhythmia, EEG normalization, and prompt treatment of relapses of spasms and multifocal epileptic discharges are all associated with a better cognitive outcome [10, 11].

Another important aspect is the association between autism and epilepsy that has long been recognized and is now well established [12]. Autism should be considered as a major comorbidity among a number of epilepsy syndromes beginning in infancy [13], and infantile spasms are associated with autism spectrum disorders in up to 35% cases [14]. Early intervention for children with autism spectrum disorder (ASD), as well as developmental delay, reduces the risk of disability and there is a greater chance for improved social, communicative, adaptive, and cognitive outcomes [15].

The main objective of our study was to assess neurodevelopment prospectively among patients with infantile spasms and to determine predictors that could affect outcome.

Materials and methods

Study design

This was a prospective clinical cohort study of patients with infantile spasms diagnosed from 2014 to 2017 at three hospitals in Tbilisi, Georgia.

- ***Patients***

Overall, 31 newly diagnosed 2-18-month-old patients with infantile spasms and abnormal EEG were included. Previously treated patients and patients with tuberous sclerosis complex were excluded from the study (*figure 1*).

Various demographic and clinical data were assessed at first evaluation. Full neurological examination was performed in all patients and prolonged sleep and awake video-EEGs were recorded. Magnetic resonance imaging (MRI) of the brain was performed for all patients. ASQ® questionnaires data, two months before the onset of infantile spasms, was recorded retrospectively from parents/caregivers. Seizures were recorded on video and the phenomenology of infantile spasms was studied - treatment strategies were marked.

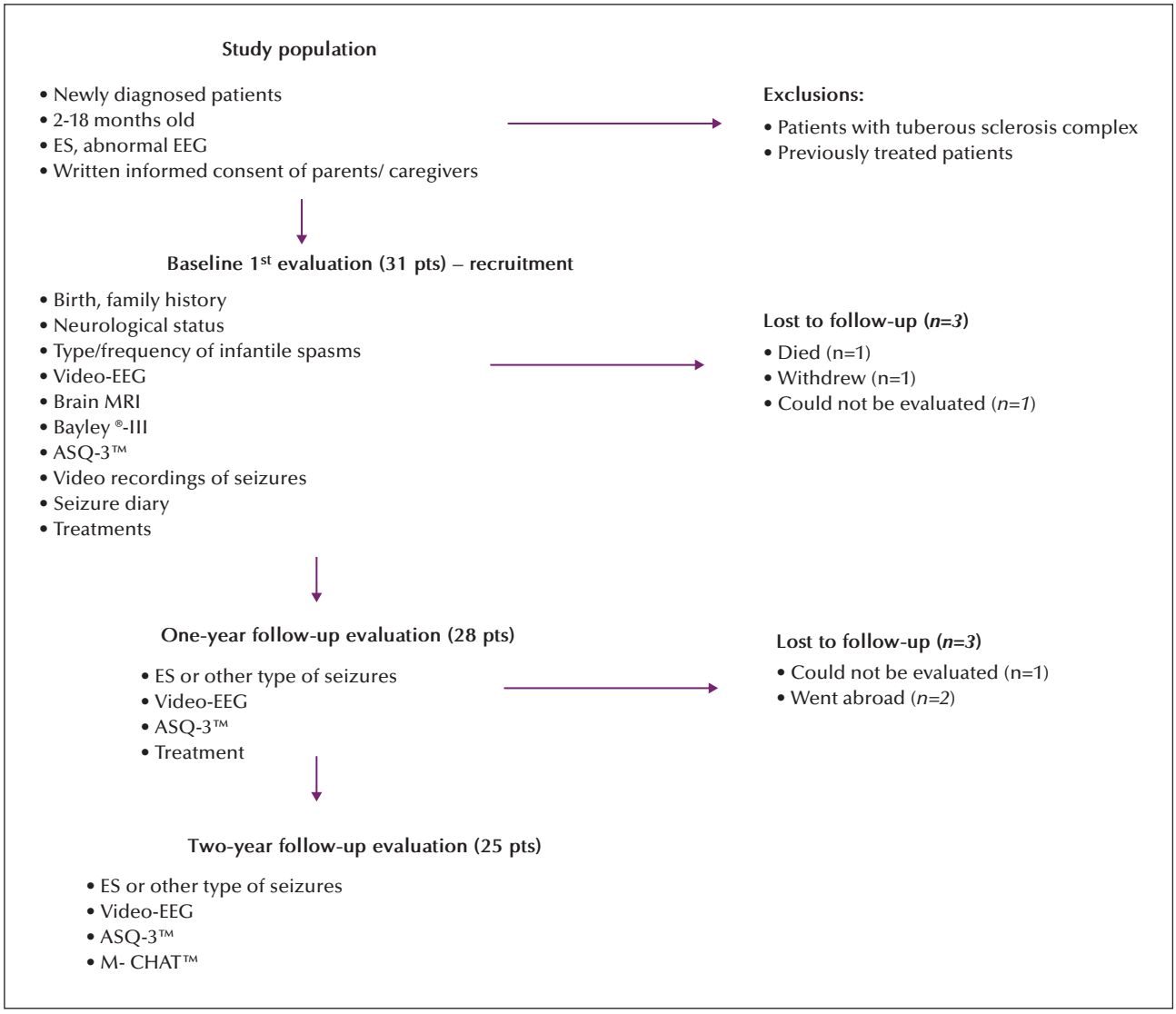
The cut-off point for early seizure onset was set at younger than seven months. We divided patients into two groups: before and after seven months, as the initial age at onset in 90% of cases was before 12 months of life, with peak onset at six months [16]. Every patient was assessed with screening tools for developmental delay and autism.

- ***Developmental instruments and screening tools***

The Bayley Scales of Infant and Toddler Development III (Bayley-III) was administered in all 31 patients on the first assessment. This is recognized internationally as one of the most comprehensive tools to assess children between one month and 42 months of age. Children were assessed on five key developmental domains of cognition, language and social-emotional, motor, and adaptive behaviour. Three scales were administered for child interaction, cognition, motor function and language, and two scales were conducted using parent questionnaires for social-emotional and adaptive behaviour. Composite scores (for cognitive, language and motor function) of less than 90 were considered abnormal and composite scores of less than 69 indicated severe developmental delay.

Ages & Stages Questionnaires®, Third Edition (ASQ-3™) is a developmental screening tool designed for use in children between the ages of one month and 5½ years. It is the most widely used developmental screen across the globe [17]. ASQ was performed at the time of admission in all 31 cases and then at every yearly assessment. Development was divided into three subgroups according to ASQ-3 scores: normal development (scores from 40 to 60), developmental delay (scores from 25 to 40) and severe delay (scores less than 25). It should be mentioned that ASQ is based on the caregiver's subjective answers about his/her child's development.

Children at risk of autism were detected using the M-CHAT (M-CHAT™; Robins, Fein, & Barton, 1999)- a modified checklist for autism in toddlers. This is a validated developmental screening tool for toddlers between 16 and 30 months of age; ideal for use at their



■ **Figure 1.** Flow chart of patients with infantile spasms over two years of follow-up. IS: infantile spasms; pts: patients; EEG: electroencephalography; MRI: magnetic resonance imaging; Bayley ®-III: Beyley scales for infant and toddler development - third edition; ASQ-3™: Ages & Stages Questionnaires® - Third Edition.

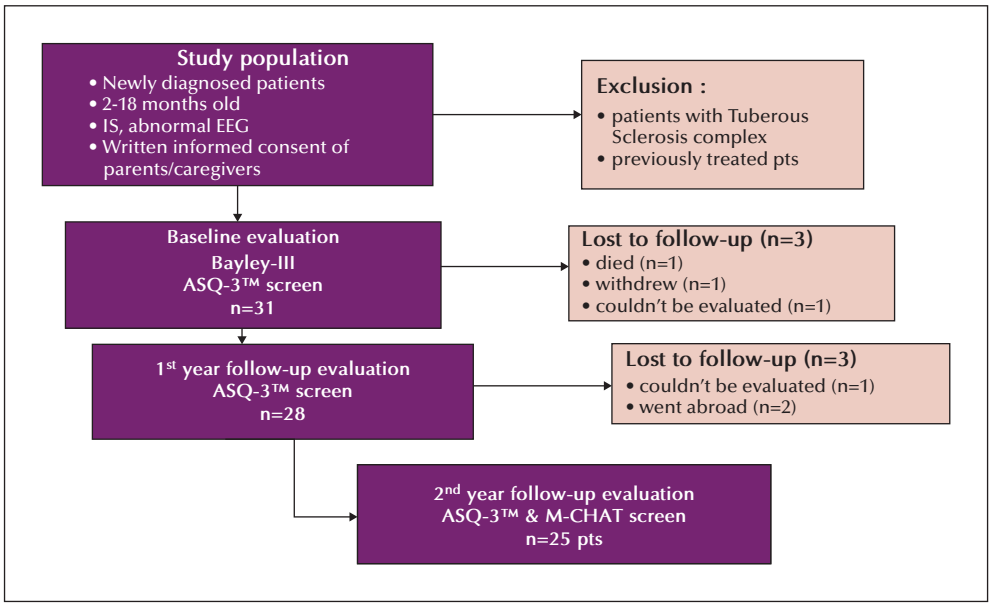
18- and 24-month visit. It is designed to be administered by parents/caregivers and interpreted by paediatric providers [15].

The M-CHAT was performed during the last year of evaluation, and the ASQ was completed at the same time. M CHAT screening revealed a subgroup of patients at high risk of developing autism based on a number of critical questions. These patients were assigned to the M-CHAT risk subgroup based on more than three positive answers to critical questions, in contrast to those with no risk of ASD (M-CHAT-N subgroup).

Every parent/caregiver provided written informed consent for their child's participation in this study (*figure 2*).

Investigations

All children underwent brain MRI using a Philips-MRINTERA-ACHIEV A 1.5T, CT-BRILLIANCE-64 and 1.5T Siemens Magnetom Avanto scanner. Overall, 31 patients were investigated with prolonged sleep and awake video-EEG using the Micromed system plus program. For interictal EEG, a 21-channel system was



■ **Figure 2.** Number of patients screened by ASQ and M-CHAT over three years of follow-up. ASQ-3™: Ages & Stages Questionnaires® - Third Edition; M-CHAT™: Modified Checklist for autism in toddlers.

used (standard 10-20 system of electrode placement [18] generally with longitudinal bipolar montage and other montages - common average, referential montages - as needed). Recording time averaged 90 minutes at first evaluation and from 20 to 90 minutes at the subsequent follow-up visits. Video-EEG recordings were performed more than three times during the study, however, only three recordings performed one year after the first assessment were included. Background activity was recorded five minutes before and after enhancing manoeuvres (photostimulation at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 50, 40, 35, 30, and 20 Hz). The international 10-20 electrode system was used and an electromyogram (EMG) was simultaneously recorded from the bilateral deltoid muscles [19]. EEG monitoring was performed several times after the first recording, and this decision was made on an individual basis relative to patients' characteristics. We recruited only three sets of EEG data; at one and two years after the first EEG recording.

The EEG pattern was divided into three main subgroups: hypsarrhythmia, modified hypsarrhythmia and other changes.

Patients were assigned to the subgroup of hypsarrhythmia when EEG showed continuous arrhythmic, high-amplitude, chaotic, asynchronous, and disorganized delta activities with independent, multifocal spike/sharp-wave discharges.

Modified hypsarrhythmia was defined based on EEG showing periodic regular synchronous or asynchronous bursts of high-amplitude spike/sharp waves, mostly bilaterally, hypsarrhythmia with a consistent focus of abnormal discharge, with episodes of attenuation comprising primarily high-voltage slow activity with low sharp-wave or spike activity, as well as asymmetrical hypsarrhythmia. According to background activity, EEG data were divided into four groups: epileptiform, normal, slow and fast activities. At admission, most patients had epileptiform activity. In the subsequent year, background activity remained epileptiform and/or changed into fast or normal activity.

Treatment regimens

Each patient was treated either with adrenocorticotropic hormone (ACTH), antiepileptic drugs, or combination therapy. At the start, first-line treatment was conducted with ACTH intramuscular injections. Antiepileptic drugs were added in case of ACTH contraindications or adverse effects or in non-responders to ACTH therapy (*table 1*). We used ACTH at a single dose of 0.2 mg via intramuscular injections for two months for all patients. Treatment regimens started with daily injections over the first 7-10 days, then on alternate days for two weeks, twice a week for two weeks, and once a week for two weeks at the end [20].

Overall, 28 patients were treated with ACTH, with or without antiepileptic drugs, at the beginning. Sixteen patients were treated with ACTH only, three patients with antiepileptic drugs (clonazepam, vigabatrin, and valproic acid) because of ACTH contraindications, and

▼ **Table 1.** Hormone (ACTH) and antiepileptic drug therapy over three years.

Patient number	1st year		2nd year	3rd year
	Treatment 1	Treatment 2	Treatment	Treatment
1	ACTH	VPA	No treatment	LEV
2	ACTH		No treatment	No treatment
3	ACTH*	VGB; LEV	VGB; LEV	AED
4	ACTH*		Died	Died
5	ACTH		No treatment	No treatment
6	ACTH	TPM; VPA	VGB	ACTH; LEV
7	ACTH		LEV	LEV
8	ACTH	CZP; VGB	No treatment	No treatment
9	ACTH*	VPA	VPA; LEV	VPA
10	ACTH*	VPA; CZP	VPA; CZP	CZP
11	ACTH	VPA; CZP	VPA; LEV	?
12	ACTH		No treatment	No treatment
13	ACTH		VPA	VPA
14	ACTH		VPA	VPA; CZP; LEV
15	ACTH		No treatment	No treatment
16	ACTH*	VPA	VPA	VPA, VGB
17	ACTH		VPA; CZP	VPA; PHB
18	ACTH*		LEV	LEV; VGB
19	ACTH	PHB; VPA	?	VPA; CZP
20	ACTH		no treatment	LEV; CBZ
21	ACTH		VPA	VPA
22	ACTH	VGB; VPA	TPM	AED
23	VGB		VPA; PHB	VPA; LEV; PHB
24	ACTH*	VPA	VPA	VPA
25	ACTH*		No treatment	No treatment
26	ACTH		CZP; VPA	CZP; VPA
27	ACTH		ACTH	no treatment
28	VPA		No treatment	No treatment
29	VPA		VPA	VPA
30	ACTH*	LEV	LEV	?
31	ACTH		No treatment	LEV

*adverse effects of ACTH therapy
? no data on treatment
ACTH: adrenocorticotropic hormone; VPA: valproic acid; CZP: clonazepam; LEV: levetiracetam; VGB: vigabatrin; TPM: topiramate; PHB: phenobarbital.

12 patients were treated with ACTH in combination with antiepileptic drugs. Nine of the 28 patients had adverse effects while using ACTH therapy. Fever was revealed in four patients, weight gain, vomiting and swelling each in one patient, and diarrhoea and abdominal signs in two patients.
At the first evaluation (second year), 18 patients were on antiepileptic drugs, 10 patients were without treatment, and one patient died; no treatment data were available for two patients. At the second evaluation (third year), 20 children were treated with antiepileptic drugs, eight children were without treatment, and one patient died; no treatment data were available for two patients.

Statistical analysis

Descriptive statistics were used for demographic variables. The Pearson Chi-Square test (or Fisher's exact test when appropriate) was used to detect associations between categorical variables. Normality of distribution of the continuous variables was assessed through Kolmogorov– Smirnov and Shapiro–Wilk tests. Pearson's or Spearman's correlation coefficients were used to detect a linear correlation between contiguous numeric variables. A Mann-Whitney U test was used to detect differences between independent means. Holm-Bonferroni correction was used for multiple comparisons. A probability of less than 0.05 was considered statistically significant.
Multiple logistic regression with forward selection was used to establish independent predictors for developmental delay at the second evaluation (variables of MRI structural abnormalities, aetiology and pre-existing delay were included). A Nagelkerke R Square and non-standardized beta coefficient (B) were calculated. An odds ratio was calculated through exponentiation of the B coefficient (Exp [B]). Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

Baseline measurements

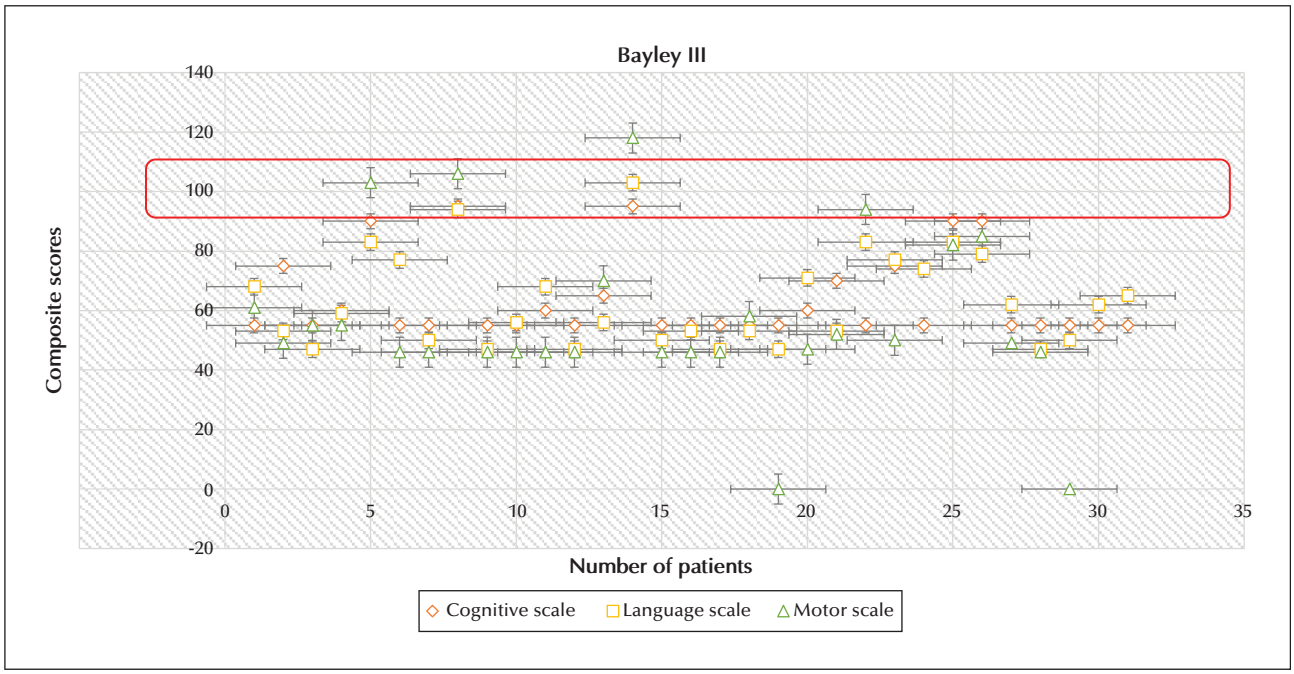
We previously reported preliminary results of this study [21]. Thirty-one patients with infantile spasms were enrolled in the study; 14 (45%) female and 17 (55%) male. Spasms started before seven months of age in the majority of cases (61%). Only one child had a family history of epilepsy. In 29 (94%) individuals, spasms appeared in clusters. In the majority of patients, symmetric spasms were observed (25; 81%), and in the remaining cases (6; 19%), asymmetric spasms were revealed. More details can be found in *table 2*. Twenty patients had a hypsarrhythmic pattern on EEG; modified hypsarrhythmia and other changes were seen in nearly equal numbers of patients (six and five, respectively).
According to background activity, most patients had epileptiform activity at admission. In the subsequent year, the background activity remained epileptiform and/or changed into fast or normal activity.
All 31 patients were assessed using Bayley III as well as the ASQ screening test at the first evaluation. Most of the participants showed a delay (12; 39%) or severe delay (12; 39%) at the first assessment (*figure 3*).
The vast majority of patients (23; 74%) had structural abnormalities on MRI, whereas normal MRI was seen in the remaining eight patients (*table 3*). Only MRI structural abnormalities (B: 2.9; p=0.004) was retained in the final regression model as an independent predictor for neurodevelopmental delay at the second evaluation.

Follow-up

Twenty-eight patients out of 31 were included in the first follow-up and 25 patients in the second follow-up; five were lost to follow-up and one patient died. We found a significant association between MRI abnormalities and poorer neurodevelopmental outcome at the second year of follow-up. In particular, neurodevelopmental delay was detected in 15/20 (75%) patients with MRI abnormalities, whereas no developmental delay was observed among those with normal MRI (Fisher's Exact Test: 11.8; df: 1; p=0.001).
The same was observed after the first year of follow-up. Neurodevelopmental delay was observed in 19/22 (86%) patients with MRI abnormalities, whereas poor neurodevelopmental outcome was reported in only 2/8 (25%) children with normal MRI.
The dynamics of neurodevelopment (worsening vs no worsening) during follow-up was significantly associated with spasm onset. In particular, development did not deteriorate or showed a slight improvement at the second follow-up evaluations in 12 patients, in whom spasms started after seven months of age, compared to neurodevelopmental worsening in 8/16 (50%) patients with seizure onset before the age of seven months (Fisher's exact test: 7.8; df: 1; p=0.008). The same trend was observed during the first follow-up period, in which neurodevelopmental deterioration was observed in 11 (61%) of 18 patients with early-onset infantile spasms, whereas there was no worsening among those with seizure onset at seven months of age or later (Fisher's exact test: 11.6; df: 1; p=0.001). More details can be found in *table 4*.
A strong correlation was seen between aetiology and developmental outcome. Of patients with structural aetiology, 20/22 (86.4%) had developmental delay after

▼ **Table 2.** Demographic/clinical characteristics in patients with infantile spasms (*n*=31).

Gender, *n* (%)	
Female	14 (45)
Male	17 (55)
Age (months), mean, ±SD (Min, Max)	7.6 ± 2.9 (3; 17)
Age at seizure onset (months); mean, ±SD (Min, Max)	6.3 ± 2.6 (2; 14)
Age at seizure onset (< 7 month), *n* (%)	19 (61)
Time lag to treatment (days), median, [IQR], (Min, Max)	14.0 [7, 30] (1; 120)
Time lag to treatment	
Less than 2 weeks, *n* (%)	18 (58)
More than 1 month, *n* (%)	13 (42)
Full-term or premature	
Full-term, *n* (%)	20 (65)
Premature, *n* (%)	11 (35)
Family history (yes)	1
Spasm type	
Asymmetric, *n* (%)	7 (23)
Symmetric, *n* (%)	24 (77)
Single spasm or cluster	
Single spasm, *n* (%)	2 (6)
Cluster, *n* (%)	29 (94)
EEG changes	
Hypsarrhythmia, *n* (%)	20 (65)
Modified hypsarrhythmia, *n* (%)	6 (20)
Other changes, *n* (%)	5 (17)
MRI findings	
Normal MRI	8 (26)
Structural abnormalities	23 (74)
Neurological status	
Normal	19 (62)
Spastic quadriplegia	7 (23)
Spastic hemiparesis	3 (10)
Hypotonia	2 (7)
Development at baseline	
Normal	7 (23)
Delay	12 (39)
Severe delay	12 (39)



■ **Figure 3.** The range of composite scores is 40-160. Scores of 85-115 (red frame) are within the normal range and indicate no difficulty in this area, scores between 70 and 85 are equivalent to a mild learning difficulty, scores between 55 and 70 indicate moderate learning difficulty, and scores less than 55 suggest severe learning difficulty for a given test. The majority of our patients had developmental delay and composite scores of less than 70.

▼ **Table 3.** MRI findings of 31 patients with infantile spasms.

MRI findings	*n* (%)
Normal MRI	8 (26)
Cortical atrophy	6 (20)
Hydrocephalus	7 (23)
Leukoencephalopathy	3 (10)
Callosal dysgenesis	7 (23)
Encephalomalacia	1 (4)
MCD*	1 (4)
Gliosis	1 (4)
Lobar hypoplasia	5 (17)
Porencephalia	1 (4)
Ventriculomegaly	1 (4)
Multicystic lesion	1 (4)
Neurofibromatosis	1 (4)

*MCD: malformation of cortical development.

a year from first recruitment, while no developmental delay was seen among eight idiopathic cases (Fisher's exact test: 10.5; df: 1; p=0.003) (*figure 4*).

A statistically significant correlation was seen between ASQ – Communication domain and structural aetiology (mean: 47.0; SD: 18.9). The mean score was importantly low in structural cases (mean: 21.0; SD: 24.2) (Mann-Whitney U: 17.5; p=0.024). A similar association was not found with the problem-solving domain.

Developmental delay before the onset of spasms was documented in 11 patients.

At the second evaluation, 8/17 patients without developmental delay before spasm onset had normal development, whereas all 11 patients with pre-existing delay had developmental delay (Fisher's exact test: 7.2; df: 1; p=0.01).

We did not reveal any association between the dynamics of hypsarrhythmia (resolution of hypsarrhythmia or other EEG abnormalities after treatment initiation) and neurodevelopmental outcome; likewise, the time lag of treatment initiation (less than two weeks, from two to four weeks, more than one month) was not associated with neurodevelopmental outcome.

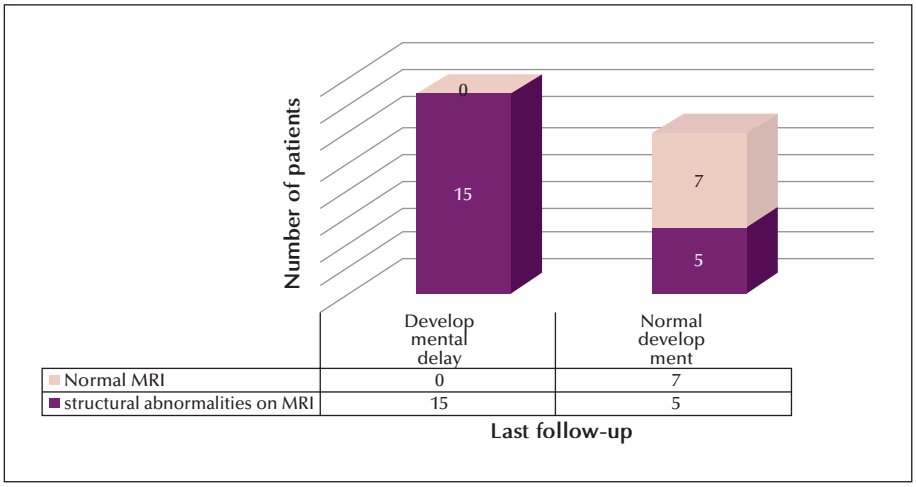
▼ **Table 4.** Individual patient developmental scores and characteristics at the first and last assessment (*n*=25).

				ASQ3 domain scores								
				At first evaluation				At last evaluation				
Patient number	Sex	Age at ES onset (months)	Pre-existing developmental delay	Communication	Problem Solving	Personal-emotional	Development	Communication	Problem Solving	Personal-emotional	Development	M CHAT
1	M	4	No	50	20	20	Delay	60	60	60	N	N
2	M	4	No	35	45	30	Delay	55	60	50	N	N
3	M	6	No	60	60	60	N	60	60	60	N	N
4	M	7	Yes	40	10	20	Severe delay	10	0	0	Severe delay	R
5	M	6	No data	40	10	10	Delay	10	5	0	Severe delay	R
6	M	4	No	50	55	55	N	55	30	30	N	N
7	M	6	Yes	20	0	5	Severe delay	10	5	5	Severe delay	R
8	F	3	No	35	25	0	Delay	5	0	5	Severe delay	R
9	M	12	No	30	0	0	Delay	40	50	50	Borderline	N
10	F	5	No	60	60	60	N	45	45	50	Borderline	N
11	F	14	Yes	0	0	0	Severe delay	55	55	45	Borderline	N
12	F	8	No	25	10	5	Severe delay	0	0	0	Severe delay	N
13	F	7	Yes	45	0	5	Severe delay	5	0	0	Severe delay	R
14	M	4	No	25	30	10	Delay	5	0	0	Severe delay	R
15	F	7	Yes	30	0	0	Severe delay	0	0	0	Severe delay	R
16	M	6	Yes	20	30	45	Delay	40	45	40	Borderline	N
17	F	5	No	55	30	50	N	0	0	0	Severe delay	R

▼ **Table 4.** Individual patient developmental scores and characteristics at the first and last assessment (*n*=25) (*continued*).

				ASQ3 domain scores								
				At first evaluation				At last evaluation				
Patient number	Sex	Age at ES onset (months)	Pre-existing developmental delay	Communication	Problem Solving	Personal-emotional	Development	Communication	Problem Solving	Personal-emotional	Development	M CHAT
18	F	2	Yes	25	0	5	Delay	0	0	0	Severe delay	Severe global delay*
19	M	6	no	20	10	10	Delay	10	10	10	Severe delay	R
20	M	10	No	20	10	30	N	55	60	60	N	N
21	M	6	No	45	50	45	N	15	25	25	Borderline	N
22	M	3	No	55	50	50	N	60	60	60	N	N
23	F	8	No data	30	5	25	Delay	60	55	50	N	N
24	F	8	No	5	0	10	Severe delay	0	0	0	Severe delay	R
25	F	7	yes	20	15	10	Severe delay	0	0	0	Severe delay	R

*M CHAT could not be performed in one patient due to severe global delay.
F: Female; M: male; N: normal development; M CHAT (modified checklist for autism in toddlers) - two subgroups: R: risk of autism spectrum disorder (ASD); N: no risk of ASD.



■ **Figure 4.** Developmental delay and structural abnormalities on MRI.

Multivariate analysis

Variables that demonstrated significant association with neurodevelopmental outcome were included in the multivariate regression model. Only MRI structural abnormalities (B: 2.9; p=0.004) was retained in the final regression model as an independent predictor for neurodevelopmental delay at the second evaluation. Calculations showed (Exp [B] - 19.0) that patients with abnormalities on MRI have a 19-fold increased chance of having developmental delay at the second evaluation compared to children with normal MRI. Nagelkerke R Square 0.394 indicated that 40% of the variation of unfavourable neurodevelopmental outcome can be explained by MRI brain abnormalities.

Risk of ASD

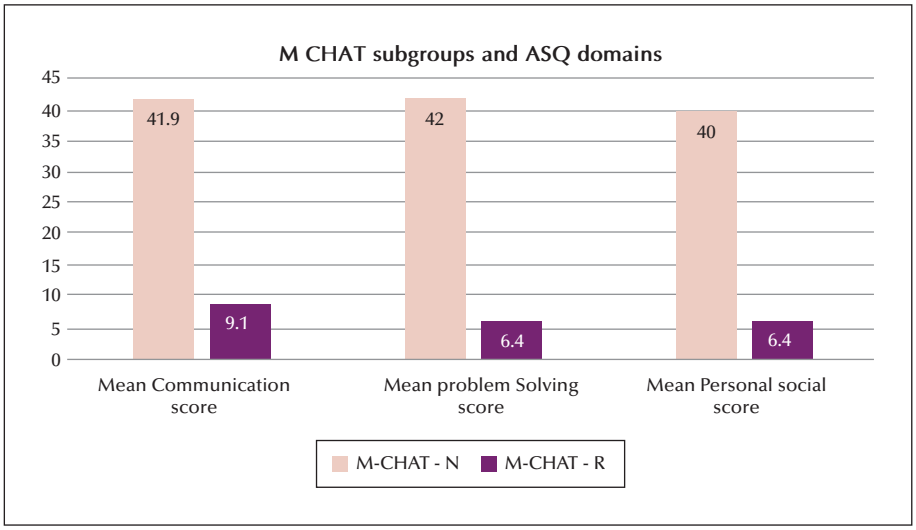
Twelve of 25 patients were shown to be at risk of ASD based on M-CHAT screening at the last follow-up visit. The mean ASQ communication score for the M-CHAT-N subgroup (41.9) was significantly higher compared to the risk subgroup (9.1). This association was statistically significant (Mann-Whitney U: 23.5; p=0.004). The same association was revealed regarding the problem-solving domain (M-CHAT-N group mean score: 42.0, risk subgroup mean score: 6.4; Mann-Whitney U: 23.0; p=0.004) and personal-social domains (M-CHAT-N group mean score 40.0; risk subgroup mean score: 6.4; Mann-Whitney U: 23.5; p=0.004) (*figure 5*).

Discussion

Existing literature on the outcome of patients with infantile spasms is retrospective. To-date, there are several prospective studies on infantile spasms that have focused on outcome factors [8, 10, 11, 22]. Infantile spasms remain a severe neurological disorder because of their frequent association with delayed development, with a severe impact on the developing brain. The vast majority of studies on the outcome and prognosis of West syndrome have been undertaken by Riikonen and colleagues. In one of these articles, the authors list favourable prognostic factors that include short treatment lag and late (≥four months) onset of seizures.

Deterioration was greater in the subgroup of patients in whom spasms started before seven months compared to the subgroup with seizures that started after seven months. Some studies have reported similar findings regarding the association between age at seizure onset and outcome [22-24], with aetiology being the strongest predictor of outcome [11].

Our analysis showed that patients with abnormalities on MRI had a 19-fold increased chance of having developmental delay at the second evaluation compared to children with normal MRI. Many studies show that structural cases have poorer developmental outcomes [8, 10, 11, 22, 25, 26]. Koo and colleagues assessed the outcome of patients in the so-called "cryptogenic and symptomatic" groups separately. They reviewed 56 patients retrospectively within the past five years. Cognitive outcome in the cryptogenic group was much more favourable than in the symptomatic group [27]. In their prospective study of outcome, Glaze and colleagues found that long-term outcome in 64 patients with infantile spasms was poor, and 41 patients (67%) had developmental delay. The better outcome was seen in the cryptogenic group [28].



■ **Figure 5.** Association between mean scores of three ASQ domains and M-CHAT subgroups. M-CHAT-N: no risk of autism; M-CHAT-R: risk of autism.

In the long-term follow-up study of Hamano *et al*., the authors described 60 patients with infantile spasms and different structural aetiologies, and reported that cryptogenic West syndrome had a better prognosis whereas structural groups had worse outcomes [29]. Another retrospective study aimed to determine a possible correlation between aetiology and outcome among 50 with symptomatic and 30 with cryptogenic spasms. Of all identified (structural) patients, only one child with a diagnosis of cerebral atrophy showed normal development at the last follow-up visit [25]. According to one study, genetic and structural/metabolic terms should be modified because most epilepsies associated with structural brain malformations or inborn errors of metabolism are also genetic [30]. Moreover, no aetiology is identified in up to nearly 40% of infantile spasm cases. Genetic studies, conducted in children with unexplained infantile spasms, suggest genetic heterogeneity [31]. Pathogenic variants were identified in 30 genes as causes of infantile spasms [32]. In our study, mild structural abnormalities were seen on MRI, *e.g.* cortical atrophy in six patients and gliosis in one patient. These cases should be considered as having a genetic cause.

Current studies suggest that epilepsy, autism, and intellectual disability commonly coexist [13]. In our study, a significantly high correlation was found between three ASQ domains (communication, problem-solving and personal-emotional) and M-CHAT (p=0.004). A similar association was found in one study where the ASQ-3 communication domain alone identified 95% of the diagnosed children with autism spectrum disorders [15]. Though the screening test does not have sufficient sensitivity for detecting autism, it should be noted that a high correlation between M-CHAT and ADOS was identified in the study by Bitton and colleagues. The authors performed CHAT in 42 and ADOS in 44 of 69 patients with epileptic spasms, and 10 of 11 M-CHAT responders were diagnosed with autism spectrum disorders using ADOS. It was suggested that M-CHAT could help identify patients at risk of ASD in order to intervene early [14].

One study aimed to determine the sensitivity of the ASQ-3 domains in children detected by M-CHAT-R screening and follow-up, who then received a diagnosis of ASD. The study also examined each of the five domains of the ASQ-3 to see which domain(s) was most useful in detecting autism cases. Based on the core symptoms of autism and the nature of early parent concerns, the authors hypothesized that the Personal/Social and Communication domains were most sensitive [15].

In our study, there was a statistically significant association between developmental delay before spasm onset and neurodevelopmental outcome based on the second evaluation. To our knowledge, there is a scarcity of data describing a precise association between these two variables, however, normal development before the onset of spasms may be considered as an indicator for good prognosis.

Treatment remains problematic and challenging, as there is no consensus on appropriate treatment dosage and duration for infantile spasms [23]. A Cochrane review reported that hormonal treatment

is the best single treatment for the cessation of spasms [33]. Based on a multicentre study (ICISS), hormonal therapy with vigabatrin was significantly more effective at stopping spasms after between 14 and 42 days, compared to hormonal therapy alone [34].

There is a limited number of studies on second-line treatment for infantile spasms. Antiepileptic drugs used as second-line treatments are: topiramate, zonisamide, valproic acid, felbamate, clonazepam and nitrazepam [23, 35]. Three retrospective and two prospective studies reported the ketogenic diet to be effective and safe in infantile spasms [36]. Epilepsy surgery is considered in the minority of cases, where infantile spasms are caused by focal cortical dysplasia and other structural abnormalities.

It is not clear whether treatment lag is a risk factor for the outcome of West syndrome or not [15], however, several studies have found that delayed treatment can lead to poor outcome [37]. Some studies have demonstrated an association between short treatment lag and good developmental outcome [8, 23, 34]. In other studies, treatment lag was not related to neurodevelopmental outcome [7, 27]. Moreover, lag time to initiation of treatment was also not predictive of any outcome in a retrospective study of 109 patients with infantile spasms [22]. In our study, no correlation between treatment lag and neurodevelopmental outcome was identified.

Conclusion

The current study highlights predictors of poor outcome in children with infantile spasms syndrome. In conclusion, age at seizure onset – less than seven months, pre-existing developmental delay and structural abnormalities on MRI appear to predict poor outcome. Our study demonstrates that the clinician may be able to suspect a poor prognosis using low-cost and easy-to-perform screening tests at early stages, and start interventions as early as possible. Low Bayley (III) and ASQ® scores at first admission indicate poor neurodevelopmental outcome. Early detection of developmental delay and ASD and referral for early intervention greatly improves long-term outcome. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors have no conflicts of interest to declare.

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TEST YOURSELF

(1) According to the study results, did spasm onset age predict outcome?

(2) Which screening tools may be helpful to predict neurodevelopmental outcome among children with infantile spasms?

(3) Does resistance to seizure treatment influence neurodevelopmental outcome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com