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Response to first-line treatment, epilepsy and developmental outcome in Infantile Spasms syndrome—A Retrospective cohort study

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Abstract

The use of first-line treatments for Infantile Spasms Syndrome (ISS) has challenges and varied impacts on outcomes, especially in developing countries with resource-limited settings. We sought to identify the impact of Adrenocorticotropic Hormone (ACTH), high-dose oral corticosteroids, and vigabatrin as the first-line treatment on cessation of spasms, short and long-term (3 months to 3 years) epilepsy and developmental outcomes along with the influence of etiology and lead time to treatment. Electronic case records of infants between 3 months and one year of age diagnosed with infantile spasm in a tertiary care hospital in south India, who received first-line treatment, including combination therapy between 2014 and 2018, were retrospectively reviewed for clinical details, electroencephalogram (EEG), etiology, treatment modality and their adverse effects, Infantile spasm cessation, developmental and long-term epilepsy outcomes.

The study included forty-four cases (32 male, 12 female), with a mean age of onset of infantile spasms at 7.6 months ± 3.5 months, median delay in diagnosis at two weeks (range of 1 day – 24 weeks), median lead time to treatment at 3.5 weeks (range one day – 28 weeks). First-line management was associated with cessation of spasms determined via parental report obtained through follow-up history every two weeks in the majority (67%) of patients. A relapse at three months follow-up was observed only in 1 out of 44 patients (2% relapse rate). There was no statistically significant difference in outcome based on the choice of first-line agents. However, the need for more than one first-line agents was associated with a relatively more unfavorable long-term outcome. Structural etiology of Infantile Spasm was associated ($p = 0.001$) with long-term epilepsy. Early treatment of Infantile Spasms Syndrome (<2 weeks) was associated with better ($p = 0.014$) developmental outcomes.

In conclusion, there is a high chance of cessation of Infantile Spasms Syndrome based on existing protocols of use of first-line agents in its treatment, irrespective of etiology. Early treatment of Infantile Spasms Syndrome can significantly improve developmental outcomes in patients with Infantile Spasms Syndrome.

Keywords: Infantile spasms syndrome, West syndrome, Steroid, Corticosteroid, Prednisolone, Hypsarrhythmia, Epilepsy.

Introduction

Infantile Spasms Syndrome (ISS) is an age-dependent epilepsy syndrome with an incidence of 0.25 to 0.43 per 1000 live births with a peak age between 4 and 7 months [1]. It is slightly more common in males accounting for approximately 60% of cases [2, 3]. A common term used to refer to Infantile Spasms Syndrome is "West Syndrome," which is a triad of epileptic spasms, hypsarrhythmia on electroencephalogram (EEG), and subsequent or concurrent developmental delay [1, 4]. According to a US consensus report, Infantile Spasms Syndrome can be classified as symptomatic and cryptogenic. The former refers to patients with clear etiology, like congenital malformations, perinatal asphyxia, and tuberous sclerosis, and the latter refers to patients where the cause remains unknown [5, 6]. Spasms typically involve brief symmetrical contractions of the neck, trunk, and extremities of musculature, lasting up to 5 seconds and frequently occur in clusters [5]. This spasm can be flexor, extensor, or mixed [6]. Infantile Spasms Syndrome is most often mistaken for gastroesophageal reflux, benign sleep myoclonus, and a variety of normal infant behaviors. The diagnosis and treatment are often delayed with potentially catastrophic consequences [7].

EEG is the single most important test for diagnosis [6]. Interictal EEGs of IS are characterized by hypsarrhythmia with chaotic non-rhythmic, asynchronous, disorganized, high voltage spike, and slow wave activity [5]. MRI is recommended to identify patients with structural etiology and potentially surgically remediable causes [5]. MRI should be obtained before therapy as the treatment may cause transient abnormalities [5]. In resource-limited settings, repeated use of EEG may be challenging to evaluate the electrographic resolution of hypsarrhythmia.

The optimal treatment of West syndrome continues to be studied, with the most effective treatments being hormonal therapies like high-dose oral corticosteroids, synthetic adrenocorticotropic hormone (ACTH), and non-hormonal agent vigabatrin (VGB),

primarily used in patients with tuberous sclerosis complex [8]. Synthetic ACTH is often proposed as the first line; however, it requires daily intramuscular injections and is expensive [8].

A comparison of hormonal treatment with vigabatrin has shown that the absence of spasms on days 13 and 14 was more common with hormonal treatment than with vigabatrin [9]. Also, the comparison between hormonal treatment versus combination therapy (with vigabatrin) for infantile spasms indicates that the combination therapy was associated with more infants achieving the primary outcome of spasm cessation between days 14 and 42 of treatment [11]. However, developmental outcome measurement, as indicated through the VABS score, between hormonal treatment and combination therapy did not indicate any significant differences between the two treatment groups [12].

Prognosis depends on the cause, the interval between the onset of clinical spasm and hypsarrhythmia, and the rapidity of treatment and control of the abnormal EEG pattern [6]. Gulati et al., in a study in 2015 on clinical characteristics and treatment of Infantile Spasms Syndrome in a developing country, noted that, in a resource-limited setting, unawareness along with treatment costs cause longer median lag time for appropriate treatment initiation [17]. A greater lead time of spasm onset to treatment was found to be associated with poor neurological outcomes [17], a lower rate of spasm cessation [11], poorer longer-term epilepsy prognosis [11, 12], and worse developmental outcomes [9, 12].

Analysis of the impact of etiology on neurodevelopmental outcomes indicates that the Infantile Spasms Syndrome of unknown onset has a better prognosis in motor, cognitive, and receptive language functions than symptomatic etiology [13, 14]. The impact of etiology has been ignored in various studies conducted in developing countries [17–19]. In developing countries, the cost of treatment significantly impacts delaying the start of an effective treatment. Coupled with a lack of focus on identifying etiology leads to inefficient outcomes. Developing countries need simplified guidelines for managing Infantile Spasms Syndrome, as identified by Vaddi et al. in a study in 2018 [19].

This study aimed to study:

1. The response rate of Infantile Spasms Syndrome to first-line treatment (ACTH, high dose oral corticosteroids, vigabatrin).
2. The impact of first-line treatment (ACTH, high-dose oral corticosteroids, vigabatrin) on long-term epilepsy.
3. The impact of first-line treatment (ACTH, high dose oral corticosteroids, vigabatrin) on developmental outcomes.

Methods

Subjects

A retrospective observational study was conducted in a single tertiary care center in Bangalore over five years between 2014 and 2018, both years included. A total of 60 children with ISS were identified; 16 were excluded from analysis as early-onset below three months of age, treatment details, or 1-month follow-up was unavailable. Hence, 44 infants aged between 3 months and one year were included. The subjects had presented to the Outpatient department or emergency and were diagnosed with Infantile Spasms Syndrome per ILAE criteria. Electronic case records were reviewed for clinical details, EEG, etiology, treatment modality, adverse effects, infantile spasms cessation, and developmental and long-term epilepsy outcomes.

Treatment

The patients were either treated with a low dose ACTH (20–30IU) or high dose prednisolone (40 mg/day for two weeks with a taper over two weeks). As data emerged about the equal effectiveness of low-dose ACTH and high-dose prednisolone, the treatment regime was predominantly switched to high-dose oral prednisolone.

Patients were administered vigabatrin (50–150 mg/kg/day) if they had Tuberous Sclerosis complex, if they refused to take steroids or for whom it was not possible to monitor for steroid side effects on follow-up closely. Patients on prednisolone were also administered vigabatrin (with steroid tapered over two weeks) if they presented at two weeks follow-ups with no response. Vigabatrin was used from 50 mg/kg/day to 150 mg/kg/day at 2-week follow-ups until spasm cessation.

Patients who did not respond to the hormonal treatment were treated using combination therapy. They were treated sequentially using prednisolone (40 mg/day for two weeks) followed by vigabatrin (50–150 mg/kg/day). Out of the 44 children included in the study, five children (11%) received low-dose ACTH (20–30 IU), 16 children (36%) received high-dose oral prednisolone (40 mg/day for two weeks with a taper over two weeks), four children (9%) received vigabatrin (50–150 mg/kg/day). A total of 19 children (43%) received combination therapy.

Measurement and evaluation

All the patients were evaluated by the pediatric neurologist at the tertiary center based on history, clinical examination, developmental assessment, neuroimaging studies (MRI), and EEG. EEG was performed on all the patients, and the presence of hypsarrhythmia or its variants was used to diagnose the patients with Infantile Spasms Syndrome. MRI was performed using a 1.5T MRI machine at the tertiary center, and the pediatric neurologist and neuroradiologist evaluated the results. Patients were evaluated for genetic and metabolic disorders. The results were used to classify them into two groups by etiology: one with known underlying causes (symptomatic group) and those children with no underlying causes. A neurodevelopmental evaluation was conducted through history, neurological examination, and developmental assessment at the initial encounter to determine the baseline for the developmental outcome.

Once the treatment was initiated, the children had follow-ups every two weeks at the same tertiary care center. The children were evaluated at each follow-up session, using history and examination to identify the occurrence of Infantile Spasms Syndrome in the preceding weeks or adverse effects. The cessation of spasms within one month was noted to group the patients into cessation, reduction in spasms, and no cessation. The remission of the spasms was also measured at the 3-month follow-up to

Table 1. Patient characteristics for the different categories of 1st line of treatment

Category	Number of patients	Avg Age at spasm onset (months)	% of patients with Developmental delay at onset	Average delay to diagnosis (weeks)	Average delay to treatment (weeks)	Percentage of Patients with Known Etiology	Average follow-up Time in months
Low Dose ACTH	5	6.4	100%	2.4	2.4	100%	52.8
High dose Prednisolone	16	5.5	88%	6.8	7.2	44%	11.6
Vigabatrin	4	5.8	75%	11.8	11.8	75%	23.0
Combination	19	5.1	100%	5.4	6.1	68%	13.3
Overall	44	5.4	91%	6.2	6.7	64%	18

group the patients into sustained remission, relapse, or persistent Infantile Spasms Syndrome. EEG was performed at the 1-month follow-up to evaluate the presence of hypsarrhythmia.

Long-term epilepsy outcome was evaluated at the last follow-up visit to group the patients again into seizure-free (no Infantile Spasms Syndrome or epilepsy), controlled epilepsy (no IS, epilepsy controlled on medications), and persistent IS/epileptic encephalopathy. The developmental outcome was also evaluated at three months/the last follow-up. The children were grouped into normal, mild, or severe delay based on the treatment providers' perception of overall development. Additional information was also gathered on the lead time from spasm onset to treatment for the children.

Statistical analysis

The data collected was analyzed using Microsoft Excel. Results on continuous measurements are presented as Mean $\pm$ SD (Min-Max), and results on categorical measurements are presented in Numbers (%).

The Chi-square test was performed at a 95% confidence level to find the significance of study parameters on a categorical scale (remission of infantile spasm at 1 and 3 months with different first-line agents, developmental outcome at last follow-up and developmental outcome by Lead time to treatment) between two or more groups. A P-value of <0.05 was considered significant.

Results

Patient characteristics on initial evaluation

Forty-four children were studied, including 32 males and 12 females. The mean age of onset of IS was 7.6 Months $\pm$ 3.5 months. Ninety-one percent (40 out of 44) of children had a developmental delay at the onset. Neuroimaging (MRI Brain) was done in 33 out of 44 patients; 27(61.3%) had a structural abnormality. Neuroimaging abnormalities included periventricular leukomalacia (PVL) in 10, neonatal hypoglycaemic brain injury (NHBI) in 7, hypoxic-ischaemic encephalopathy (HIE) changes in 4, malformations of cortical development (MCD) in 4 and others (atrophy, cyst) in 2; 6 had normal MRI Brain. Sixty-four percent of the children (28 out of 44) had etiologic classification as symptomatic (27 with a structural brain abnormality, 1 with Down syndrome and delayed development), while 36% were classified as cryptogenic. The median delay in diagnosis was two weeks (range one day to 24 weeks). The median lead time to treatment was 3.5 weeks (range one day and 28 weeks). The overall patient characteristics across the different treatment groups have been summarized in Table 1.

Initial outcome

The cessation of spasms was measured at the end of one month for each group of children who received first-line treatment. The intervention using first-line treatment resulted in IS remission in 56%–75% based on etiology (Table 2) and 53–100% based on the choice of first-line agent (Table 3). The remission of ISS was achieved in 75% of the cases when the lead time to treatment was less than two weeks, as opposed to 64% when the lead time was more than two weeks.

A Chi-square test was performed to evaluate the impact of etiology, choice of first-line agent, and lead time to treatment on cessation of spasms, spasms at three-month period, long-term epilepsy, and development delay (moderate to severe).

Statistical analysis indicated that Etiology, treatment choice, or the lead time to treatment did not significantly impact the IS remission at the end of one month.

Long-term outcome on intervention

The remission of infantile spasms was evaluated at three months post-intervention. Long-term epilepsy outcome results are also analyzed by etiology, choice of first-line agent, and lead time to treatment (Table 1, Table 2, and Table 3).

This remission was sustained at three months in 56%–64% based on etiology and 58%–75% based on the choice of first-line agent. There was, however, no significant association for etiology or choice of first-line agent on the sustained remission at three months. Sustained remission was observed in 82% of the patients when the lead time to treatment was less than two weeks, compared to 58% when the lead time was more than two weeks. The lead time indicated a trend towards statistical significance, with lead time to treatment indicating potential association at higher sample rates.

The statistical analysis between long-term epilepsy outcome and etiology indicated a significant association between the

Table 2. Impact of Etiology on short and long-term Infantile Epilepsy outcomes

	Results of Cessation at one month	Remission of spasms at the end of 3 months		Long-term epilepsy outcome			Developmental Outcome	
	Cessation of spasm	Sustained	Persistent	Seizure free	Controlled epilepsy	Persistent IS/ Epileptic encephalopathy	Normal/Mild Delay	Severe Delay
Etiology – Structural	21 (75%)	18 (64%)	10 (34%)	4 (4.3%)	14 (50%)	10 (35.7%)	14 (50%)	14 (50%)
Etiology – Infantile Spasms Syndrome of unknown onset	9 (56%)	9 (56%)	2 (12%)	9 (56.25%)	2 (12.5%)	2 (12.5%)	12 (81%)	3 (19%)
P Value	0.20	0.29		0.002			0.055	

Table 3. Impact of First Line of Treatment on short and long-term Infantile Epilepsy outcomes

	Results of Cessation at one month	Remission of spasms at the end of 3 months		Long-term epilepsy outcome			Developmental Outcome	
	Cessation of spasm	Sustained	Persistent	Seizure free	Controlled epilepsy	Persistent IS/ Epileptic encephalopathy	Normal/Mild Delay	Severe Delay
ACTH administered	3 (60%)	3 (60%)	2 (40%)	2 (40%)	3 (60%)	0	4 (80%)	1 (20%)
Prednisolone administered	13 (81%)	10 (62%)	2 (12%)	5 (31.25%)	5 (31.25%)	3 (18.75%)	10 (66%)	5 (33%)
Vigabatrin administered	4 (100%)	3 (75%)	1 (25%)	1 (25%)	2 (50%)	1 (25%)	3 (75%)	1 (25%)
Combination therapy	10 (53%)	11 (58%)	8 (42%)	5 (26.3%)	6 (31.6%)	8 (42%)	9 (47%)	10 (53%)
P Value	0.15	0.71		0.65			0.43	

Table 4. Impact of Lead time to treatment on short and long-term Infantile Epilepsy outcomes

	Results of Cessation at one month	Remission of spasms at the end of 3 months		Long-term epilepsy outcome			Developmental Outcome	
	Cessation of spasm	Sustained	Persistent	Seizure free	Controlled epilepsy	Persistent IS/ Epileptic encephalopathy	Normal/Mild Delay	Severe Delay
Lead time $<$ 2 week	15 (75%)	14 (82%)	3 (18%)	7 (39%)	8 (44%)	3 (16%)	12 (60%)	8 (40%)
Lead time $>$ 2 weeks	14 (64%)	11 (58%)	8 (42%)	6 (29%)	6 (29%)	9 (43%)	13 (62%)	8 (38%)
P value	0.32	0.11		0.206			0.013	

seizure-free rates and the etiology. The Infantile Spasms Syndrome of the unknown onset group showed much higher seizure-free rates.

Children in the Infantile Spasms Syndrome of unknown onset group showed lower (19%) rates of moderate-severe delay compared to the symptomatic etiology group, which showed 50% of children with moderate-severe delay. There was a borderline strong association between the etiology and moderate-severe developmental delay.

Analysis of lead time to treatment showed a significant association between lead time to treatment with first-line agents exceeding two weeks and delayed developmental outcomes

Table 5. Side effects in patients by choice of first-line treatment

	ACTH	High Dose prednisolone	VGB	Hormonal and VGB
Obesity (4)	1			3
Irritability (8)	2	5		1
Infection (7)		3		4
Hypertension (1)				2
Sleep Disturbance (5)		1		4
Vigabatrin Toxicity (1)				1

among infants with ISS. Table 4 summarizes the association and indicates a greater chance of normal development if the children are initiated on first-line treatment within two weeks.

Side effects with first-line treatment were noted in 22(50%) children. Minor side-effects in 41% in the form of irritability/sleep issues (8), minor infections (6), and obesity (4) were seen. Severe side-effects in 9% included infection requiring hospitalization (2), hypertension (1), and neuroradiological features of VGB toxicity (1). A greater proportion of side effects were observed in combination therapy (69%), followed by high-dose prednisolone (41%), with ACTH having side effects in 14% of patients. Table 5 shows the breakup of this distribution. Follow-up EEGs were done on 25/44, and resolution of hypsarrhythmia was seen in 24/25, but other epileptiform abnormalities were noted in 16/25. The Median follow-up duration was ten months (IQR 3.4-31.5 months).

Discussion

Our findings indicate that introduction of first-line treatment leads to the cessation of spasms in the majority of patients within the first month of treatment. However, we found no significant difference in the proportion of children who are spasm free when analyzed between groups who were administered ACTH, high-dose oral prednisolone, vigabatrin, and sequential combination (hormonal and VGB) therapy. Developmental outcome evaluation also indicated no difference between the groups administered different first-line treatments. The ICISS study also underlines the finding that long-term epilepsy and the developmental outcome did not differ by different treatment groups [12].

Our study found that the longer lead time to treatment was associated with mild to severe delays in the developmental outcome, which is similar to findings from the ICISS study [11, 12]. The UKISS study also emphasized that reduced lead time is critical to achieving better developmental outcomes [9].

Our findings also indicate that children who required more than one first-line agent or combination therapy had higher though statistically insignificant long-term epilepsy and worse developmental outcome. This is similar to the ICISS study, which reports that the combination therapy resulted in successful remission of IS; however, it also found that they have worse developmental outcomes [12].

Our study also found that the long-term epilepsy outcome was significantly associated with etiology, with the symptomatic etiology being more prone to long-term epilepsy. This is consistent with other studies on the long-term impact of infantile spasms [13, 14]. The symptomatic etiology group also had a larger percentage of children with moderate to severe delay, which was similar to findings in other studies [13, 14].

Side effects of treatment were mostly minor, with the uncommon vigabatrin-associated neuroradiologic changes seen in one child with combination treatment (hormonal and VGB).

Conclusions

Our study shows that first-line treatment can lead to cessation of spasms in a majority of cases of Infantile Spasms Syndrome within the first month of treatment, irrespective of etiology. Our study also underlines the need to reduce the lead time to treatment in children with infantile spasms to reduce changes of delays in developmental outcomes. The long-term epilepsy outcome also has a significant association with etiology, with the symptomatic etiology being more prone to long-term epilepsy and also associated with moderate to severe delay, which is consistent with other studies [13, 14].

Limitations

Limitations of the study include retrospective design and single-center only, which may lead to bias and unavailability of development assessment on standardized scales. The lack of statistically significant difference between different first-line agents on outcomes could have been due to smaller sample sizes. A larger sample size with an evaluation done over a longer term can help evaluate if there are any significant differences between first-line agents. The lack of EEGs at follow-ups in patients with logistical and financial issues also impacted the study, as cessation of spasms was determined via parental report alone.

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Declaration of conflicting interests

Authors have no potential conflicts of interest concerning this article's research, authorship, and publication.

Author Contributions

Deepthi Gopinathan Nair: Analysis and Interpretation of data, manuscript drafting, and revisions. Bidisha Banerjee:

Study design, Data analysis, statistical analysis, manuscript revision. L. Gowthami: Data acquisition, data interpretation, manuscript revision. Chitra Sankar: Data analysis and Interpretation, manuscript revision.

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