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Prognostic Utility of Clinical Epilepsy Severity Score Versus Pretreatment Hypsarrhythmia Scoring in Children With West Syndrome

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Abstract

This cross-sectional study assessed the impact of clinical epilepsy severity and pretreatment hypsarrhythmia severity on epilepsy and cognitive outcomes in treated children with West syndrome. Thirty-three children, aged 1 to 5 years, with infantile spasms were enrolled if pretreatment EEG records were available, after completion of ≥1 year of onset of spasms. Neurodevelopment was assessed by Development Profile 3 and Gross Motor Function Classification System. Epilepsy severity in the past 1 year was determined by the Early Childhood Epilepsy Severity Score (E-Chess). Kramer Global Score of hypsarrhythmia severity was computed. Kramer Global Score (≤8) and E-Chess (≤9) in the past 1 year were associated with favorable epilepsy outcome but not neurodevelopmental or motor outcome.

Keywords

West syndrome, outcomes, neurodevelopment, epilepsy, motor, Kramer Global Score, E-Chess

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Introduction

West syndrome is an early infantile epileptic encephalopathy characterized by epileptic spasms that occur in clusters and have a characteristic chaotic electroencephalographic (EEG) pattern of hypsarrhythmia with or without cognitive deterioration or developmental arrest.[1]

Epilepsy severity is an important determinant of epilepsy burden for a young child where cognition is still under development and amenable to effects of near-continuous epileptic activity. Literature search did not reveal any former study that may have analyzed the impact of epilepsy severity on current epilepsy status and cognitive outcome in children with infantile spasms. The severity scales validated for older children cannot be used in this population. Hence, the epilepsy severity scale used in this study was the Early Childhood Epilepsy Severity Score (E-Chess).[2] This has been validated on infants with tuberous sclerosis who usually have epileptic spasms as one of the seizure type, usually have epilepsy onset in infancy and have multiple seizure types.

Moreover, although the concept of "epileptic encephalopathies" like West syndrome is based on the assumption that aggressive ongoing ictal and electrographic epileptogenic activity during the period of brain maturation is the main cause of progressive cognitive deterioration possibly mediated by changes in brain connectivity, and decreased neurogenesis; limited attempt has been made so far to quantify the pretreatment clinical and electrographic measurements in order to find out a pretreatment clinical or electrographic cutoff that may predict a favorable epilepsy and neurodevelopmental outcome. Especially in developing countries where the appropriate diagnosis and treatment is often delayed, the pretreatment epilepsy burden may be huge.[3,4]

Materials and Methods

In the present cross-sectional study, 33 children, aged 1 to 5 years enrolled in the Pediatric Neurology Clinic with the diagnosis of West syndrome based on clinical semiology and electroencephalographic (EEG) pattern of classical or modified hypsarrhythmia were enrolled in the study after obtaining written informed consent. Institutional ethical committee clearance was taken.

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The following were the inclusion criteria: Age between 1 and 5 years, past history of or ongoing infantile spasms diagnosed on history or witnessed by physician, EEG pattern of classical or modified hypsarrhythmia documented any time during treatment, availability of pretreatment digital EEG in EEG laboratory and under follow-up for at least 1 year and 3 months.

The following were the exclusion criteria: Patients with one or more of the following were excluded from the study: significant systemic illness interfering with developmental assessment or non-availability of primary caregiver at the time of enrollment or nonavailability of exact date of birth due to home delivery and illiteracy prevalent in India.

Definitions Used in the Study

Clinical spasms, West syndrome and Lennox Gastaut syndrome were defined as per the standard definitions.[1] Etiologic categories were 2—unknown cause and known cause groups were defined. Unknown cause group was one in which there was no identifiable organic neurological insult and children had a normal baseline head size and developmental milestones before onset of spasms. In the Known cause group there was an identifiable underlying specific etiology like tuberous sclerosis, brain malformations, perinatal insults, abnormal neuroimaging, metabolic or genetic conditions, prior central nervous system infection, and traumatic or vascular insults. Infants whose baseline development and neurological status were abnormal prior to onset of spasms were grouped with Known cause group, even if no specific etiology could be determined.

Treatment lag was defined as onset of spasms to start of appropriate treatment (adenocorticotrophic hormone [ACTH]/prednisolone/vigabatrin). Clinical response was defined as clinical cessation of spasms for ≥ 28 days after initiating appropriate treatment. Failure to respond in terms of spasm cessation was considered after 4 weeks of trial with a drug. Electroclinical response was defined as clinical response with resolution of hypsarrhythmia. It was measured in all patients by clinical assessment and repeating EEG. Clinical outcome—relapse: A clinical relapse of infantile spasms at any stage after a primary clinical response has been obtained in form of any episode of spasms occurring in clusters or 2 or more episodes of spasms that occur singly but not in clusters or subtle spasms if accompanied by an EEG showing appropriate changes. A single witnessed spasm would not be reliable and was not classified as a relapse of clinical spasms. Persistent spasms were considered if clinical response not achieved for ≥28 days.

Assessment Protocol. Demographic details, clinical features, treatment received, and responses to treatments were noted for each child in a prestructured datasheet. The demographic variables studied included gender and age at onset of spasms. The clinical features included associated other seizure type, relationship with sleep-wake cycle, perinatal asphyxia, neonatal sepsis, hypoglycemia, focal signs, spasticity, and extrapyramidal features. Therapeutic variables included treatment lag ≤3 months, response to first-line antiepileptic drugs and use of hormonal therapy or vigabatrin. The diagnostic workup included radiological imaging: noncontrast computed tomography in 3 patients and magnetic resonance imaging (1.5 T) in 30 patients. Metabolic screening in form of blood ammonia, arterial lactate, tandem mass spectrometry (TMS) for acylcarnitines and aminoacids and urinary gas chromatography mass spectroscopy (GCMS) was done in 5 patients whose neuroimaging was normal. Neurodevelopmental, motor, and epilepsy outcome was measured for each child using clinical assessment tools described subsequently and EEG scoring was also done. The details of EEG recording and scoring are described in the following sections.

Treatment Protocol. Hormonal therapy (injection adrenocorticotrophic hormone [synthetic Inj acton prolongatum; ACTH] or prednisolone) was used as the first line in treatment except tuberous sclerosis where vigabatrin was used. Vigabatrin was also used as first line in case of contraindications to ACTH, namely active infection like tuberculosis. ACTH or vigabatrin were used as second line whichever was not used earlier in case of nonresponse. ACTH was used in the dosing regimen of 40 IU imtramuscular once daily for 4 weeks followed by tapering over next 4 weeks. Prednisolone was used at the dose of 2 mg/kg/d for 4 weeks followed by tapering over subsequent 4 weeks. In case of nonresponse to both, other antiepileptic drugs were used in standard doses and titrated as per patient response.

Clinical Assessment Tools

Neurodevelopment of each child was assessed using standardized tools, namely Developmental Profile 3 (DP-3)[5] and Gross Motor Function Classification System (GMFCS).[6] DP-3 was applied under 5 domains: physical, adaptive, social-emotional, cognitive, and communication. The interpretation of the scale for each domain was done and a composite General Development Standard score (GDS) was computed by the clinical psychologist.

GMFCS is defined in a 5-level classification system based on functional limitations, the need for assistive technology and to lesser extent, quality of movement.

History regarding epilepsy frequency and control in the past 3 months was also taken to score epilepsy outcome. Seizure outcome in past 3 months was assessed in terms of 3 categories. It was adapted from Partikian and Mitchell.[7] Category I was seizure free with or without anticonvulsant, category II was controlled seizures (<1 seizure per month on any anticonvulsant drug), and category III was poorly controlled or intractable seizure despite treatment. Favorable epilepsy outcome included categories I and II. Quantification of epilepsy severity in past 1 year preceding the 3-month assessment period was done using E-Chess.[2] The important features of E-Chess include frequency of seizures, time period over which seizure occurred in past 1 year, number of seizure types, number of anticonvulsants used, and response to treatment. E-Chess was quantified using an interview with the caregiver and going

through the Pediatric Neurology Clinic and the Outpatient Department medical records of the team of Pediatric Neurology and seizure log maintained by the family. When there was a disagreement between these sources, additional information from doctors and the family was obtained to identify the most valid score. When a child had more than one type of seizure during the year of life being scored and there was a difference in the frequency of the different seizure types, the "frequency of seizure" score was defined by seizure type occurring most frequently.

Outcome Criteria

Favorable neurodevelopmental outcome was defined as General Development Score (GDS) by DP-3 ≥70 and GMFCS level I or II. Favorable motor outcome was defined as Physical Domain score by DP-3 ≥70 and GMFCS level I or II. Favorable epilepsy outcome was defined as seizure free or controlled seizures in past 3 months.

EEG Recording and Scoring

Pretreatment EEGs of 33 patients showing classical or modified hypsarrhythmia were available for review. All 33 were routine EEGs of at least 30-minute duration recorded by international 10-20 system of electrode placement, including natural/drug-induced sleep, arousal, and awake states. Hypsarrhythmia was defined as EEG pattern characterized by chaotic appearance of random high-voltage (>200 μV) slow waves with variable amplitude, spikes and waves from many foci (≥3), and varying with time and lack of synchrony. Amplitude of slow waves was measured from peak to trough in standard longitudinal bipolar recording in the channel in which the pattern was most readily appreciated. EEG severity was quantified by the criteria and global score proposed by Kramer et al.[8] Scoring was performed by 2 independent observers having an experience in neurology and electroencephalography of 15 years and 3 years, respectively, for presence of parameters of hypsarrhythmia severity proposed by Kramer et al.[8] The disagreements were resolved by mutual discussion in the 3-member team with the third member also having more than 15 years of experience in neurology and electroencephalography. All 3 were blinded to neurodevelopment outcome.

Items scored included disorganization of background, percentage of delta activity, amplitude of slow waves, and frequency of spikes and sharp waves each scored on a scale from 0 to 3, according to their severity in a representative 10-second epoch, with the highest degree of hypsarrhythmic pattern in the record, whether during the awake or asleep state, was chosen for scoring as adjudged by consensus of 3 epileptologists. The items, namely electrodecremental discharges, burst suppression in sleep, absence of normal sleep pattern, relative normalization, were scored as present (score of 1) or absent (score of 0) as seen throughout the record. Other additional features, including hemihypsarrhythmia, occipital hypsarrhythmia, increased interhemispheric synchronization, and burst suppression (BS) throughout the EEG, were noted as present or absent in the entire record but were not used for scoring.

Table 1. Characteristics of the Study Subjects (N = 33).

Characteristic	Value
Age at onset, mo, mean ± SD (95% CI)	5.63 ± 0.73 (4.1-7.1)
Age at enrolment, mo, mean ± SD (95% CI)	30.7 ± 13.7 (21.6-34.3)
Male:female	29:4
Preexistent normal development, n (%)	5 (15.2)
Known underlying cause group, n (%)	31 (93.9)
Microcephaly, n (%)	19 (57.6)
Focal signs, n (%)	1 (3.0)
Spasticity, n (%)	17 (51.5)
Extrapyramidal signs, n (%)	9 (27.3)

Statistical Analysis

The data were analyzed using STATA version 11 software.[9] The techniques applied were chi-square test or Fischer's exact test wherever necessary to compare qualitative data. The continuous data were compared by applying Student's *t* test or Mann-Whitney test if required. *P* value ≤.05 was considered significant. Multivariate regression analysis was done to find significant predictor variables. Diagnostic accuracy of E-Chess and Kramer's global score to predict epilepsy outcome was assessed using receiver operating characteristic (ROC) curves and determining the area under ROC curves (AUC). Decision plots of sensitivity and specificity were generated from the ROC curves. The cut point for dichotomizing the scores was defined using the Youden index.

Results

Baseline Characteristics

In the cohort of 33 children studied, mean age at assessment was 30.7 ± 13.7 months with 29 males and 4 females. The semiology of spasms was flexor (75.8%), extensor (9.1%), and mixed (15.2%). The baseline characteristics of the study group are presented in Table 1.

Etiology

Prenatal causes were identified in 6/33 (18.2%) patients (central nervous system [CNS] malformations 5 and tuberous sclerosis 1]. Perinatal asphyxia was causative in 18 of 33 (54.5%) children. Postnatal causes included CNS infections in 6 and stroke in 1 of the children. Only 2 patients had West syndrome of unknown etiology.

Neuroimaging findings included white matter paucity in 15, CNS malformations in 5, focal gliosis and diffuse cortical atrophy in 2 each; and tuberous sclerosis, multicystic encephalomalacia, stroke, and delayed myelination, respectively, in 1 each of the children. It was normal in 5 children. CNS malformations

Table 2. Distribution of Scores in Different Domains of Developmental Profile 3 (DP 3) in 33 Children With Infantile Spasms.

Domain	Mean Score ± SD (Range)	95% CI
Physical	59.9 ± 2.7 (50-107)	54.4-65.3
Adaptive	60.2 ± 2.7 (50-105)	54.7-65.6
Social-Emotional	63.4 ± 3.1 (50-109)	57.1-69.7
Cognitive	55.5 ± 1.2 (50-94)	51.5-59.6
Communication	60.5 ± 1.2 (50-107)	55.4-65.6
General Development Score	47.9 ± 2.3 (40-94)	43.1-52.8

included lissencephaly (1), holoprosencephaly (1), isolated corpus callosum agenesis (3). Metabolic workup was negative in the 5 patients tested whose neuroimaging was normal.

Treatment

Hormonal treatment (ACTH 17 and prednisolone 5) was received by 22 patients, 17 as first line and 5 as second line. Total 19 patients received vigabatrin; 11 as first line; of these 1 had tuberous sclerosis, 5 had positive tuberculin test and a relative contraindication to steroids, 2 had active infection at time of presentation and 3 were unwilling for steroid therapy. Other drugs used were pyridoxine, valproate, levetiracetam, topiramate, zonisamide in cases of treatment failure and titrated as per response.

Outcomes

Neurodevelopmental Outcome. Favorable neurodevelopmental outcome was seen in 3/33 (9.1%) patients. Distribution of scores in different domains of Developmental Profile 3 is as in Table 2. The cohort of West syndrome had delayed development as evidenced by mean general development score (GDS) less than 70. Cognitive domain lagged behind the other domains. The motor impairment was less pronounced in the study cohort as 16 of 33 (48.4%) patients had GMFCS levels I/II.

Epilepsy Outcome. Favorable epilepsy outcome was seen in 15 of 33 (45.6%) patients. For each patient, EEG was studied for hypsarrhythmia patterns. Global score by Kramer et al[8] was computed.

Motor outcome: Favorable motor outcome was seen in 16 of 33 patients (48.4%).

Electroencephalography Results

Hypsarrhythmia Scores. In the present study, the hypsarrhythmia score ranged from 6 to 14 with a mean ± standard deviation of 9.1 ± 0.3 (95% CI = 8.4-9.7). There were 20 patients with global score ≤8 and 13 with >8. Mean score for patients with unknown etiology West syndrome was 8.9 ± 0.3 (95% CI = 8.3-9.6) that was not significantly different from known etiology cases whose mean score was 9.7 ± 0.9 (95% CI = 7.8-11.5) ($P = .69$, Man-Whitney U test).

Hypsarrhythmia Patterns. The association of various hypsarrhythmia patterns with favorable epilepsy outcomes were studied in the 33 EEGs reviewed. The patterns are presented in Table 3. Only 1 patient had hemihypsarrhythmia and had unfavorable epilepsy outcome.

In none of the patients, ictal event could be captured during recording. The frequency of spikes was also measured during interictal recording of hypsarythmia. Multiple regression analysis was used to test if hypsarrhythmia components or patterns significantly predicted epilepsy outcome. A significant regression equation was found, $F = 8.15$, $P = .001$ with an R^2 of .761. It was found that spikes less than 1/second ($\beta = 0.27$, $P = .001$) predicted favorable epilepsy outcome as did delta less than 75% of the record ($\beta = 0.26$, $P = .003$).

Diagnostic Accuracy of E-Chess and Global Score

The diagnostic accuracy of E-Chess and Global Score (Kramer et al) to predict epilepsy outcome was assessed using ROC curve analysis. Area under the E-Chess ROC curve was, n (95% CI) = 0.952 (0.82-0.99) and area under the Global Score by Kramer et al ROC curve was, n (95% CI) = 0.99 (0.88-1.00). Thus, both E-Chess and Global Score had AUC ≥0.95 for discrimination of patients with favorable and unfavorable epilepsy outcomes and are depicted in Figure 1. Based on the ROC curves, favorable E-Chess score was defined as ≤9 and favorable Global Score by Kramer et al was defined as ≤8. Both E-Chess and Kramer Score have high sensitivity and specificity and their respective cutpoints on ROC curves are shown in Table 4.

Favorable E-Chess, Global Score, and Outcomes

Both favorable E-Chess score signifying lesser epilepsy burden over past 1 year and favorable Global Score were significantly associated with favorable epilepsy outcome and not motor or neurodevelopmental outcome (Table 5).

Favorable E-Chess, Global Score, and Associated Demographic, Clinical, Etiological, and Therapeutic Variables

Subgroup analysis of favorable and unfavorable clinical and EEG scores was also done in relation to the demographic, etiological, clinical, and therapeutic variables to find any possible association.

The univariate analysis of these variables is presented in Table 6. Of all predictor variables, on multiple regression analysis, favorable E-Chess was significantly associated with treatment lag less than 3 months ($\beta = 0.39$, $P = .05$; Table 7) while global score was associated with none of the variables.

Discussion

The present study is an attempt to quantify epilepsy burden and to find a cutoff score of already available and clinically ready to use clinical and electroencephalographic scoring systems to predict epilepsy and neurodevelopmental outcomes before

Table 3. Hypsarrhythmia Patterns and Epilepsy Outcome.

Hypsarrhythmia Pattern	Favorable Epilepsy Outcome (N = 15), n (%)	Unfavorable Epilepsy Outcome (N = 18), n (%)	*P*
Grade I preserved organization of background	10 (66.7)	10 (55.6)	.59
<75% Delta	14 (93.3)	10 (55.6)	.01*
Voltage <500 μV	14 (93.3)	14 (77.8)	.19
Spikes at frequency <1/second	13 (86.7)	4 (22.2)	.01*
Absence of electrodecremental discharge	4 (26.7)	7 (38.9)	.45
No interhemispheric asymmetry	13 (86.6)	17 (94.4)	.44
No burst suppression	14 (93.3)	17 (94.4)	.89
Relative normalization	3 (20)	7 (30.9)	.24
Presence of normal sleep pattern	7 (46.7)	7 (38.9)	.65
Increased interhemispheric synchronization	3 (20)	9 (50)	.20
Occipital hypsarrhythmia	1 (6.7)	1 (5.6)	.20

*$P \leq .05$.

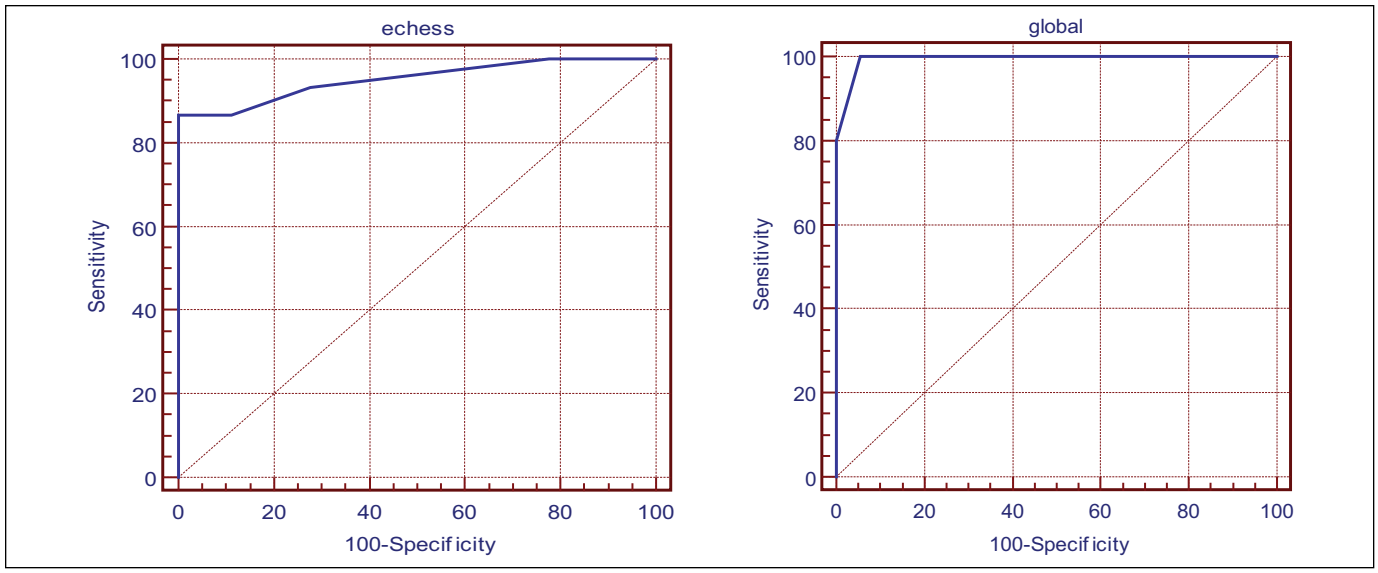

Figure 1. Receiver operating characteristic (ROC) plots for diagnostic accuracy of E-Chess and Kramer's Global Score for epilepsy outcome.

Table 4. Diagnostic Accuracy of Early Childhood Epilepsy Severity Score (E-Chess) and Global Score.

Criterion	Sensitivity (95% CI)	Specificity (95% CI)
E-Chess, score ≤9	86.7 (59.5-98.0)	100 (81.3-100)
Global score ≤8	100.0 (78.0-100.0)	94.4 (72.6-99.1)

treatment in children with the catastrophic epileptic encephalopathy, that is, infantile spasms. The study paves the way for future development of a composite score that includes both clinical and electrographic epilepsy burden and possibly treatment lag for prognostication.

The male:female ratio of subjects in the present study is 29:4.This skewed gender ratio is common in India due to gender discrimination in health care seeking by the parents and also possibly because of small sample size.[10]

Clinical Epilepsy Severity Scoring—E-Chess: Utility, Outcomes, Limitations

West syndrome is an age-dependent catastrophic epileptic encephalopathy, heterogeneous in etiology, wherein the epileptic activity per se is believed to result in severe cognitive impairment that is disproportionately more than the underlying pathology alone.[11]

Moreover, the resolution of hypsarrhythmia in West syndrome is also associated with an improvement in cognitive outcome and therefore electroclinical resolution is the therapeutic endpoint. It is highly debatable what actually contributes to the neurological impairment. Whether it is the number of seizures, the duration of individual seizures, the duration over which seizures occur in the concerned individual, associated multiple seizure types, or the epilepsy that is refractory to conventional antiepileptic drugs or a combination of all these, is highly

Table 5. Distribution of Outcomes in Subgroups With Favorable and Unfavorable Global Score and Early Childhood Epilepsy Severity Score (E-Chess).

Outcomes	Favorable Kramer's Global Score (≤8) N = 20	Unfavorable Kramer's Global Score (>8) N = 13	*P*	Favorable E-Chess (≤9), N = 13	Unfavorable E-Chess (>9), N = 20	*P*
Favorable epilepsy (n = 15)	13	2	.005*	13	2	.001*
Favorable development (n = 3)	2	1	.82	2	1	.31
Favorable motor (n = 16)	11	5	.35	9	7	.055

*Significant values ($P \leq .05$).

Table 6. Distribution of Outcomes in Subgroups With Different Etiologies.

Outcome	Prenatal Etiology (N = 6)	Perinatal Etiology (N = 18)	Postnatal Etiology (N = 7)	Unknown Etiology (N = 2)	*P*
Favorable epilepsy outcome	3	7	3	2	.52
Favorable developmental outcome	1	1	1	0	.48
Favorable motor outcome	4	7	3	2	.36

Table 7. Distribution of Demographic, Etiological, Clinical, and Therapeutic Variables Among Subgroups With Favorable Global Score and E-Chess Score on Univariate Analysis.

Variable	Favorable Kramer's Global Score (≤8), N = 20	*P*	Favorable E-Chess (≤9), N = 13	*P*
Male gender (n = 29)	9	.45	11	.64
Age at onset ≥3 months (n = 25)	8	.77	11	.34
Relation with sleep-wake cycle present (n = 23)	8	.78	9	.96
Associated seizure type other than spasms (n = 6)	2	1.0	0	.03*
Etiology				
Prenatal	2	.32	2	.32
Perinatal	12		6	
Postnatal	4		3	
Unknown	2		2	
Absence of microcephaly (n = 14)	3	.21	4	.27
Absence of focal signs (n = 32)	11	.47	13	.41
Absence of spasticity (n = 16)	6	.62	7	.61
Absence of extrapyramidal signs (n = 24)	13	.21	11	.21
Treatment lag ≤3 months (n = 7)	4	.13	5	.05*
Response to first line antiepileptic drug (n = 11)	7	.009*	7	.04*
Hormonal treatment used (n = 22)	7	.79	10	.31
Vigabatrin used (n = 19)	6	.80	7	.72

*$P \leq .05$.

controversial. So to bridge this knowledge gap, the present study attempted to quantify the epilepsy burden using a score that encompasses all these attributes, that is, E-Chess.

The scales validated for older children, such as the VA rating scale, cannot be used in this population,[12,13] as the young children are not able to describe auras, or avoidable precipitant. Also, it does not consider associated absence seizures. Liverpool seizure severity scale overlooks information regarding minor seizures. Chalfont-National Hospital Seizure Severity Scale includes measures difficult to rate for children like *descriptions of headache severity*.[12,13] Also, in the context of ongoing brain maturation, it may be important to consider the effects of all seizure activity. Thus, E-Chess is an appropriate choice for quantification of seizure burden. It was presumed that favorable epilepsy outcome could be predicted with high sensitivity and specificity below a quantitative cutoff that was calculated to be ≤9. Literature search did not reveal any study that attempted to find a similar clinical cutoff.

However, favorable E-Chess score signifying lesser epilepsy burden over past 1 year was not significantly associated with either motor outcome or neurodevelopmental outcome. However, only 3 children in the cohort had favorable neurodevelopment. This number is too small to find any meaningful association. Larger studies may help identify that group of children that has better neurodevelopment.

In the previous study, E-Chess score was significantly predictive of scores at 24 and 36 months as well.[2] Although this

score has not been used widely so far, it has been used to quantify epilepsy severity in a study where impact of pediatric epilepsy severity was studied on sleep patterns and behaviors in children and parents.[14]

The use of retrospective seizure acquisition data for computing E-Chess in the present study, is a limitation of the study. However, it is standard practice in this clinic for all patients to maintain a detailed seizure diary and all 33 families included in the study maintained it. This was further corroborated by records maintained in the clinic.

Electrographic Measurements: Hypsarrhythmia Scoring and Patterns

EEG scoring was done by multiple reviewers who were blinded to the outcome. This is one of the strengths of this study. In fact, in the present study, the lowest hypsarrhythmia scoring, by method proposed by Kramer et al[8] was 6. Also, in the present study, the epilepsy outcome was favorable with global score ≤8 as compared with ≤10 in the study by Kramer et al. This scoring was initially devised in 1997 in pre-ACTH EEG records of 53 consecutive patients with infantile spasms.[5] All patients who had hypsarrhythmia and could be scored had scores of 8 or more. The results of present study are similar to a subsequent study by Muzykewicz et al,[15] where the mean hypsarrhythmia score was 7.1 ± 3.8 by Kramer's method in 20 EEGs of patient with tuberous sclerosis.

The lower scores in the present study were possibly because of higher frequency of modified hypsarrhythmia with partially formed anteroposterior gradient with some synchrony and also possibly because of greater age at enrollment where the severity of hypsarrhythmia may be partially mitigated.

In fact, the earliest hypsarrhythmia severity scoring was done by Jeavons and Bower[16] using a 30-point scoring system. However, the score was not correlated with prognosis.

Recent researchers are looking at further abbreviated scales to ascertain hypsarrhythmia and assess interrater agreement of hypsarrhythmia using 2 criteria only like the "BASED" (Burden of Amplitudes and Epileptiform Discharges) score where the reviewers had favorable interrater agreement in interpreting hypsarrhythmia ($\kappa = .87$) compared with when using the traditional Kramer's method of EEG analysis ($\kappa = .09$). [17]

Others have devised a 3-parameter EEG scoring system based on the presence of disorganization, multifocality, and high amplitude.[15] A hypsarrhythmia severity (range 0-3) score was calculated on the basis of the presence or absence of these 3 parameters. It was found to be comparable to severity score devised by Kramer et al. Also, lower IQ was significantly associated with higher hypsarrhythmia severity scores on EEG report. A relationship between poor cognitive outcome and poor epilepsy outcome was also found.

The validity of these observations needs to be further confirmed in larger prospective studies.

Hypsarrhythmia Patterns and Outcomes

Asymmetry, burst suppression, and absence of sleep pattern were found less frequently in the present study compared with the study by Kramer et al[8] (9.1% vs 38%, 6.1% vs 41%, and 57.6% vs 69%, respectively). However, electrodecremental discharges, increased interhemispheric synchronization were more frequent (66.6% vs 29% and 36.4% vs 13%, respectively). EEG findings described in the Korean National Survey also showed atypical hypsarrhythmia in 39.4% of cases but the author acknowledged that difference of interpretation between the EEG readers could have skewed these data.[18]

In the present study, spikes at frequency of less than 1 per second and delta less than 75% were associated with favorable epilepsy outcome. However, in the study by Kramer et al,[8] the presence of electrodecremental discharge was associated with poorer epilepsy and developmental outcome ($P = .03$). In another study, the correlation of seizure control and a high disorganization in background on actual EEG approached significance ($P = .05$) in 20 patients with tuberous sclerosis.[15] In the same study, lower IQ was significantly associated with the presence of background disorganization on EEG report and the absence of normal sleep patterns on EEG.[15]

Another study reported that low-voltage discharges did not have any prognostic significance in infantile spasms.[19]

Hypsarrhythmia Global Score and Outcomes

In the present study, Global Score (≤8) proposed by Kramer et al could predict favorable epilepsy outcome with high sensitivity of 100 (CI = 78-100) and specificity of 94.4 (CI = 72.6-99). However, it was associated neither with neurodevelopment nor with motor outcomes (Table 4).

Although, the presence of hypsarrhythmia in the EEG of an infant is regarded as predictor of poor prognosis since late 1960s; there is paucity of literature on prognostic accuracy using cut off levels. In a previous study, 105 children who had shown the EEG features of hypsarrhythmia in the first year of life (1956-1962) were assessed in 1969 in respect of death and mental development. The mortality in the group was as high as 25% and the incidence of mental abnormality in the survivors was 77%.[20]

Ictal Correlates of Infantile Spasms

In the present study, ictal record was not obtained for any patient. Ictal EEG in patients with infantile spasms may have high voltage slow waves, fast waves superimposed on slow waves, spikes, and slow wave complex, and decremental activity following slow wave. In previous studies on possible correlation of ictal EEG with short-term seizure outcome or psychomotor prognosis, no statistically significant association was found.[21-23]

The main significance of infantile spasms lies in the potential that it severely impairs neurodevelopment. From the present study, it seems that children with favorable epilepsy control

may have favorable motor control but cognition is affected. The main strengths of the study include use of validated easily available soring systems, blinding of EEG reviewers, and scrupulously collected data. Prediction of outcome pre- and peritreatment will help the caregivers in understanding the multifaceted affliction by the disease in their child and help the physician in planning the therapy.

However, this study is limited by retrospective design and small sample size. A larger prospective study shall help in resolution of the enigmatic question of prognosis. Video EEGs to record actual seizure burden may also help. Furthermore, a composite score utilizing both epilepsy burden and EEG abnormality may be developed in future to aid in this dilemma of prognosis.

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Author Contributions

RS contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. SG contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. SS contributed to conception and design; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MT contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. RMP contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MK contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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