Original Article

Neuro-Developmental and Epilepsy Outcomes of Children with West Syndrome: A Cross-Sectional Study from North India

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Abstract

Objectives: To assess the neurodevelopmental outcome of West syndrome (WS) in Indian children, who differ in their clinical profile from the western population. **Materials and Methods:** This cross-sectional study enrolled children aged 2--5 years with prior diagnosis of WS between November 2013 and March 2015. They were assessed for epilepsy outcome and developmental outcome using developmental profile 3 (DP3) and vineland adaptive behavioral scale II (VABS II). **Results:** Sixty-one children were enrolled. Perinatal asphyxia (40.9%), neonatal hypoglycemia (14.8%), and neonatal meningitis (9.8%) were predominant causes among the children with known etiology. Favorable epilepsy outcome (seizure freedom for >6 months) was observed in 29/61 patients (47.5%). Moderate to severe developmental delay was observed in 55/61 children (91.8%). Favorable developmental outcome (GDS by DP3 >70) was observed in just 5/61 (8%) patients. **Conclusions:** This study highlights the high prevalence of developmental delay in this population of children with WS, with adverse perinatal events being the most common etiology.

Keywords: Autism, developmental delay, epileptic spasms, infantile spasms, neuro-developmental outcome, West Syndrome

Introduction

West syndrome (WS) is an epileptic encephalopathy which is characterized by triad of epileptic spasms, hypsarrhythmia, or its variants on EEG with or without psychomotor retardation.[1,2] It is difficult to treat epilepsy[3,4] due to multiple factors like delayed identification of spasms by both parents and physicians[5] and poor response to antiepileptic drugs. The developmental outcome of WS is variable but usually poor ranging from profound developmental delay to normal outcome.

There is a scarcity of studies on developmental outcome of these children and most of them have not used formal age appropriate psychometric tools. Autism has been found to be associated with WS[6] but the data on autistic features in children with WS especially in developing countries is limited. Outcomes are expected to be different in Indian population in view of higher proportion of symptomatic cases[5-7] and difficulty in procuring expensive drugs like adrenocorticotrophic hormone (ACTH) and vigabatrin.[3]

Therefore, the present study was planned to enhance the understanding of neurodevelopmental outcomes and factors affecting them in children with WS using formal psychometric tools and to find out the prevalence of autism and other comorbidities.

Materials and Methods

The present study was a hospital based, cross-sectional study carried out over a period of 2 years in a tertiary care, teaching hospital in New Delhi, India. The study was approved by Institutional ethics committee. Children in the age group of 2–5 years who had a prior diagnosis of WS (on basis of history of infantile spasms with hypsarrhythmia or its variants on EEG) and follow-up of at least 6 months were enrolled after written informed consent from parents/guardians. Children whose follow-up records were not available and who had chronic systemic illnesses or severe anemia were excluded.

For each patient, detailed history of perinatal events, seizure onset and outcome, development, treatment received, was taken based on parental interview, clinic records, and perinatal records. A detailed physical and neurological examination was done and details of all investigations were noted. The etiology was ascertained by corroborating history, birth records (if available), clinical findings, neuroimaging findings, and other investigations as indicated. EEG was done at the time of presentation with infantile spasms, then after clinical resolution (to document hypsarrhythmis resolution) and

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thereafter depending on the clinical indications. Genetic testing was not performed due to nonavailability.

The development of each child was assessed by two psychometric tools: developmental profile- 3 (DP-3), vineland adaptive behavioral scale II (VABS-II). The tools were administered by JG and SBM in the form of parental interview conducted during their regular visits to the epilepsy clinic. Each interview took 45 min to 1 h to complete.

Psychometric tests used

Developmental profile-3 (DP-3)

The tool consists of 180 items that cover five domains: physical, adaptive, social–emotional, cognitive, and communication. The total raw scores were converted manually into standard scores and domain quotient (DQ) was calculated for each domain and general development scores (GDS) was obtained based on normative conversion tables given in the manual. In each domain, the least score was <50 and the least general developmental scale was <40. [Alpern GD. Developmental Profile 3, 2007].

Vineland adaptive behavioral scale II (VABS II)

This tool consists of 297 items that covers four domains and corresponding subdomains which are socialization (interpersonal/play and leisure time, coping), communication (receptive, expressive, written), daily living skills (personal, domestic, community), and motor (fine and gross). The scores of VABS obtained were then entered into software VABS ASSIST to get the computer-generated final adaptive composite score. Maladaptive behavior index scoring was performed in children aged >3 years. [Sparrow SS *et al*. Vineland Adaptive Behavior Scales, 1984].

Outcome variables

The outcome variable assessed were proportion of children with unfavorable developmental outcome, defined as moderate to severe developmental delay (GDS by DP3 <70 [-2SD]), proportion of children with favorable epilepsy outcome (seizure freedom for more than 6 months), autistic behavioral phenotype (by VABS II profile), other forms of epilepsies, and comorbidities. VABS II profile suggestive of autistic behavioral phenotype was defined as a score of less than 2SD in the communication and socialization domains. A favorable developmental outcome was defined as GDS by DP3 >70.

Statistical analysis

Data was analyzed using STATA version 9. Descriptive statistics were used to describe various variables. Chi-square test, Fisher's exact test, and '*t*' test were used to assess the association of different variables with favorable epilepsy outcome. *P* values <0.05 were considered to indicate statistical significance.

Results

Clinical and demographic profile

A total of 76 children were screened, 61 (56 males) were found to be eligible for enrolment. Fifteen children were excluded: nonavailability of the primary caregiver (10), refusal to give consent (5). The mean age at enrolment was 35.6 months [standard deviation (SD) 10.9]. Fifty-seven children (93.5%) were delivered at term. Twenty (33%) children were small for gestational age.

Seizure profile at onset

The mean age at onset of spasms was 7.5 months (SD 0.7). Most common semiology was flexor spasms (96.7%). In 50 (82%) children, spasms occurred in clusters and in 32 (52%), they were associated with sleep–wake cycle. Fifty-one (83.6%) out of 61 children had hypsarrhythmia on EEG while 10 (16%) had hypsarrhythmia variants.

Etiology

Etiology could be ascertained in 51/61 children (83.6%) and unknown in 16.4% (10/61). The perinatal cause accounted for majority of the cases with perinatal asphyxia (40.9%) being the commonest, followed by neonatal hypoglycemia (14.8%) and neonatal meningitis (9.8%). Prenatal causes were found in 7.8% cases and postnatal meningitis accounted for 6% of the cases. We did not find any particular congenital infection as an etiology. Neuroimaging findings have been detailed in Table 1.

Comorbidities

Ophthalmic assessment was found to be normal in 60.6% cases. Refractory errors were found in 15% children. Bilateral optic atrophy was found in 13.1% of children. Seventy-seven percent children had normal brainstem auditory evoked responses (BERA), whereas 23% had delayed latencies on BERA. Global developmental delay prior to onset of spasms was found in 90.1% of children. Cerebral palsy (CP) was found in 41 (67.2%) cases. Thirty-eight children with CP had spastic quadriparetic CP, whereas 3 had dyskinetic CP. Feeding difficulties were seen in 32.7% children.

Treatment profile

All children received oral steroids; 52 children had received 4 mg/kg/day prednisolone and the rest had received 2 mg/kg/day prednisolone. Mean treatment lag was 7.5 months

Table 1: Distribution of various MRI findings of study population

MRI Finding (*n*=53)	*n* (%)
Diffuse cerebral atrophy	7 (13.2)
Cystic encephalomalacia	9 (17)
Periventricular leucomalacia	11 (20.7)
Diffuse thinning of corpus callosum	5 (9.4)
Focal gliosis	4 (7.5)
Bilateral frontal atrophy	5 (9.4)
Arachnoid cyst	1 (1.8)
Hydrocephalus	1 (1.8)
Tuberous sclerosis	1 (1.8)
Lissencephaly	1 (1.8)
Dandy Walker syndrome	1 (1.8)
Normal	7 (13.2)

(SD 3.3 months; 95% CI 6.6--8.3 months). Overall spasm cessation rate of prednisolone was 40% and partial response rate (>50 --99% reduction in spasms) was 42%. Relapses were found in 21 children (34.4%). Sodium valproate and vigabatrin were two most common drugs used for relapse of spasms (28.5% each). Repeat oral prednisolone was used for 14.2% children. At enrolment into the present study, the majority of children were on sodium valproate (44.2%); 42.6% children were on more than one antiepileptics; 9.8% children were not on any antiepileptic drugs. Modified Atkins diet was used for 14.2% children.

Developmental outcome

Overall developmental profile was assessed by GDS obtained by DP3; average GDS (+1SD to −1SD, 85--115) was found in one child (1.67%), below average (−2SD to −1SD, 70--84) in four children (6.67%), and delayed (−2SD to −3SD, 55--69) in one child (1.67%); 55 (90.1%) of children had GDS below −3SD (40--54). The mean GDS was 42.9 (SD 1.9; 95% CI 39.13--46.66). It was observed that the percentage of children with moderate to severe developmental delay (defined as GDS <70) was 91.8%. The mean, maximum, and minimum scores in various DP3 domains are tabulated in Table 2. The distribution of clinically significant factors in patients with favorable and unfavorable neurodevelopmental outcomes have been tabulated in Table 3.

Adaptive function (VABS II)

The mean adaptive behavior composite score was found to be 48.59. None of the children had an adequate score. Mean scores were comparable across all domains [Range 43.90 (SD 11.40) to 54.90 (SD 8.67) and were below −2 SD (low] [Table 4]. Since the maladaptive domain of VABS II is applicable only in children 3 or more than 3 years of age, it was assessed in 28 children. Out of those, Maladaptive Behavior Index was found to be significant for 3/28 children (10.7%).

VABS II adaptive behavioral profile for ASD (Autistic Spectrum Disorders)

None of the children had isolated delay in socialization and daily living domains. Majority (55/61) of children had low scores in all domains (91.8%) [Table 4]. The typical VABS II profile for ASD was not found in any child in our study group. The mean standard scores were uniformly distributed across domains. Mean standard scores of socialization were not found to be lower than mean standard scores of daily living domain ($P < 0.62$, *t*-test with equal variance).

Epilepsy outcome

Favorable epilepsy outcome (seizure freedom >6 months) was found in 29 (47.5%, 95% CI 34.6--60.7%) children. Thirty-two children (52.4%) had persisting seizures, of which epileptic spasms were the most common (46%). One child had both spasms as well as generalized tonic-clonic seizures (GTCS). Other seizure types were GTCS (5%), myoclonic (3.2%), and focal (1.6%).

Resolution of hypsarrhythmia was found in 13 (21.3%) while 48 (78.6%) continued to have EEG abnormalities. The last EEG finding at the time of enrolment in the study in majority of subjects was hypsarrhythmia or hypsarrhythmia variant (54.09%). EEG features consistent with a diagnosis of Lennox Gastaut syndrome were found in two children. Multifocal epileptiform discharges were noted in 11.4% and focal epileptiform discharges in 5% children. Thirteen children (21.3%) had normal

Table 2: Developmental Profile (DP) 3 Domain scores in the study population

Domain	Mean Score, Standard deviation	Minimum	Maximum	95% Confidence intervals
Physical	53.62, 1.68	<50	95	50.21--56.98
Adaptive	52.90, 1.48	<50	97	49.91--55.88
Social Emotional	52.95, 1.55	<50	97	49.76--56.03
Cognitive	52.9, 1.54	<50	101	49.79--56.00
Communication	53.62, 1.65	<50	93	50.26--56.93

Table 3: Factors affecting the neuro-developmental outcomes in children with West syndrome (*n*=61)

Factors	Favourable Neuro-developmental Outcome (*n*=5)	Unfavorable Neuro-developmental Outcome (*n*=56)
Mean age at onset (months)	8.2	7.45
Mean lag to treatment (months)	6.8	7.54
Male gender, *n* (%)	4 (80)	41 (73)
Birth Asphyxia, *n* (%)	0	25 (44.6)
Known etiology, *n* (%)	2 (40)	49 (87.5)
Pre-existing developmental delay, *n* (%)	2 (40)	53 (94.6)
Developmental regression after onset of spasms, *n* (%)	5 (100)	54 (96.4)
Comorbid cerebral palsy, *n* (%)	0	41 (73.2)
Microcephaly, *n* (%)	2 (40)	39 (69.6)

Table 4: VABS II Domain Scores in children with WS (*n*=61)

Domain	Mean standard Score	Maximum Score	Minimum Score	Standard Deviation
Communication	50	89	31	13.05
Daily Living	54.9	78	38	8.67
Socialization	54.21	72	38	9.29
Motor	43.9	64	25	11.4

Table 5: Factors affecting epilepsy outcomes in children with WS (*N*=61)

Factors	Favorable Epilepsy[$] Outcome (*n*=29)	Unfavorable Epilepsy Outcome (*n*=32)	'*P*'
Mean age at onset **(months)	7.05	7.93	0.50
Mean lag to Treatment ** (months)	7.03	7.89	0.31
Male gender*, *n* (%)	23 (79.3%)	23 (71.8%)	0.50
Birth Asphyxia*, *n* (%)	11 (38%)	14 (43.7%)	0.64
Children with known etiology[#], *n* (%)	25 (86.2%)	26 (81.2%)	0.73
Co-morbid Cerebral Palsy*, *n* (%)	16 (55.17%)	25 (78%)	0.057
Microcephaly*, *n* (%)	17 (58.6%)	24 (75%)	0.66
Term gestation*, *n* (%)	25 (86%)	32 (100%)	0.30

*Chi-square; [#]Fisher's exact; ** *t*-test with equal variance; [$]Favorable Epilepsy outcome - seizure freedom >6 months

EEG. None of the analyzed factors were found to be significantly associated with favorable epilepsy outcome [Table 5].

Discussion

Our study reports the clinical spectrum, and epilepsy and neurodevelopmental outcome in children with WS in a developing country.

Demographic profile

The percentage of males in the study population was 73.7% and male:female ratio of subjects in present study was 2.8:1. Other studies from India have also reported male preponderance in their study populations.[5] This can be attributed to gender bias in our country where male children are brought more often to medical attention. Western studies have also reported a male:female ratio of 60:40 in their studies.[8] There could be a possible biological predisposition of male gender for this epilepsy.

Seizure profile at onset

Mean age at onset of spasms was 7.5 months. This is comparable to other studies from our country.[3,9] Mean age of onset has been reported to be between 3 and 7 months in western literature.[10] Mean lag to treatment is reported between 25 and 45 days in Western literature.[11] It is 7.5 months in our study which is much higher as compared with Western data. This can be attributed to lack of awareness about this epilepsy among public as well as medical fraternity, healthcare-seeking behavior of Indian parents, use of inappropriate antiepileptics, for example, phenobarbitone, phenytoin, lack of proper referral services.[3]

Etiology

Etiology could be ascertained in majority of the cases (83.6%), with most common etiology being perinatal asphyxia (40.9%). Etiology could not be determined in 10 cases (16.4%). This is consistent with other studies from India, where symptomatic cases were reported in the range of 78--83%.[4,7] In United Kingdom Infantile Spasms study (UKISS),[12] etiology could be ascertained only in 61% of cases where prenatal etiologies formed the majority (30%) as compared with perinatal (18%) causes. However, most common individual etiology was perinatal asphyxia.[12] Other studies from the West also report prenatal factors like cortical malformations, neurocutaneous syndromes, genetic–metabolic syndromes as more common etiologies. This is in contrast to Indian data, where birth asphyxia and other adverse perinatal events are the most common causes. This highlights the need of appropriate antenatal services, institutional delivery, referral system, and improving perinatal care.

Comorbidities profile

Forty-one children were found to have cerebral palsy (67.2%) (out of which 38 were spastic quadriplegic type and 3 were dyskinetic type). Similar proportions of cerebral palsy has been reported in studies from our country.[7] Children with significant vision problems are 39.3% of which 15% had refractory errors, 13% have optic atrophy, 3% had bilateral optic atrophy and 8% were found to have bilateral disc pallor on fundus examination. Children with abnormalities on BERA were 14 (23%). Microcephaly was found in 67.2% children. This data is comparable to that reported earlier from India[7] with cerebral palsy reported to be 40%, vision impairment 29%, hearing impairment 11%, and microcephaly in 72.7%. We found that 90.1% children in our study had developmental delay prior to the onset of spasms. This is consistent with prior studies.

Epilepsy outcome

A total of 29/61 (47.5%) children were found to be seizure free for more than 6 months, which is comparable to previous studies. Seizure type at the time of enrolment in the study was epileptic spasms in majority (81.2%), followed by generalized tonic clonic in 9.5%, myoclonic in 6%, and focal in 3%. Seizure freedom rates (47.5%) are comparable to other studies from India[3,5] and Western world (30--61%).[4,12] None of the factors were found to be significantly associated with favorable epilepsy outcome. This can be attributed to the small sample size of the study. Sehgal *et al*.[5] reported significantly

less time lag to treatment was found in favorable response group (complete spasm cessation at last follow up). In the UKISS,[12] no significant difference in the proportion free of spasms with an identified etiology versus those without an identified etiology in the two treatment groups (ACTH versus Vigabatrin) was found. This is similar to our study where we have not found any association of etiology with favorable epilepsy outcome.

Neuro-developmental outcome

Children with favorable neurodevelopmental outcome (i. e., GDS by DP 3 >70) were 5/61 (8.2%). Unfavorable developmental outcome (GDS <70) was found in 56/61 study subjects (91.8%). None of the children in our study group had isolated delay in socialization and communication domains of VABS II scale which is typically found in children with autism. A total of 8 factors were statistically analyzed for their association with unfavorable neurodevelopmental outcome. Three factors were found to have significant association with unfavorable outcome, symptomatic etiology (*P* value = 0.02), cerebral palsy (*P* value = 0.003), and pre-existing developmental delay (*P* value = 0.005). We did not find any correlation between lag to treatment and favorable outcome. However, in a recent meta-analysis,[13] it was found that lag to treatment <4 weeks was associated with better neurodevelopmental outcome (risk ratio 1.519). In the study by Sehgal *et al*.[5] where the favorable outcome was similarly defined as GDS >70 by DP 3, 8.4% were found to have favorable developmental outcome. None of the factors were found to correlate significantly with favorable outcome. The favorable developmental outcome has been reported to be much higher in Western data ranging from 5 to 19% in symptomatic group to 30 to 70% in cryptogenic group.[8] This can be attributed to lesser proportion of symptomatic cases, better access to costly drugs like ACTH, vigabatrin, shorter lag to treatment, better awareness about the disease leading to early diagnosis.

There were certain limitations to our study. These included a cross-sectional study design and small sample size. It would have been desirable to perform a neurodevelopmental assessment at the time of diagnosis of WS before starting therapy and then repeat at periodic intervals during treatment and rehabilitation. Small sample size limited us to study factors predictive of unfavorable neurodevelopmental outcomes. We also could not perform formal screening for autism using standard screening tools, although none of the children had typical VABS II profile for autism. Furthermore, many patients could have had malnutrition which could be contributory to a suboptimal neurodevelopment (although not causing moderate to severe delays). It would have been desirable to collect growth parameters.

Conclusion

This study highlights the dismal neurodevelopmental outcome of children with WS in a developing country. This again emphasizes the need to improve the perinatal care to prevent birth asphyxia, early treatment of infantile spasms, and focus on neurorehabilitation while managing children with infantile spasms.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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