West syndrome: clinic etiological profile, and response to treatment in Western India

Shah Nawaz¹, Mona P. Gajre¹, Arpita Adhikari¹*, Shagufta²

1Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India
2Department of Obstetrics and Gynaecology, Holy Family Hospital, Mumbai, Maharashtra, India

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*Correspondence: Dr. Arpita Adhikari, E-mail: arpitathakker@gmail.com

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ABSTRACT

Background: Information on the profile of infants with West syndrome in developing countries is limited. This study was done to determine clinico-etiological profile and clinical response of infantile spasms to various medications in children with west syndrome in a developing country.

Methods: It was a retrospective cohort study from January 2017-January 2020 done in a tertiary care hospital in western India. Records of 39 children with west syndrome who visited this pediatric neurology division during study period were analysed. 6 were excluded in view of incomplete data. Detailed history, examination, investigations and medications given were noted. Follow up records were assessed to look for long term control of spasms, relapse rates after cessation, or progression to other seizure types.

Results: Mean age at onset of infantile spasms was found to be 8.12 months (1 - 36 months). Mean lag time to treatment was 5.35 months. Etiology was found in 69.7% children with perinatal causes being most common. With oral prednisolone, 54.5% had complete cessation of spasms, and with ACTH also 54.5% had complete spasm cessation. Favourable clinical response at 6 months follow up was found in 8 (47.05%) of the 17 children. Surprisingly, lag time (p=0.381) and symptomatic etiology (p=1.00) did not have any significant impact on outcome.

Conclusions: This study highlights the developing country perspective of west syndrome. Increased lag time, different etiological profile and poor outcome are the challenges. High dose prednisolone is a good first line alternative treatment option in resource poor settings.

Keywords: Infantile spasms, Prednisolone, West syndrome

INTRODUCTION

West syndrome is an epileptic encephalopathy characterized by the triad of

- Infantile spasms, usually clustered;
- Evidence of hypsarrhythmia in the electroencephalogram (EEG), with tracings showing a chaotic, multifocal and bilateral pattern of high-amplitude waves; and
- Regression of psychomotor development, although the latter may be absent.¹

Incidence ranges from 2 to 4 in 10 000 individuals, and therefore it is the most frequent form of epilepsy in infancy except neonatal and febrile seizures.² It is often categorized into different diagnostic groups due to numerous aetiologies and varied outcome. The most common classification is the one proposed by the International League Against Epilepsy (ILAE), which
categorizes infantile spasms as symptomatic or cryptogenic.\(^3\)

The underlying cause is identified in 70% of the patients after an adequate history-taking, physical examination and magnetic resonance imaging of the head.\(^4\) Several studies have evaluated the yield of other diagnostic tests, such as genetic and metabolic investigations.\(^5,6\)

It is estimated that this approach achieves aetiological diagnosis in an additional 10%-15% of cases.

The prognosis of West syndrome is poor despite treatment.\(^3,9\) Overall, 5-12% of patients have normal mental and motor development. Approximately fifty percent are left with motor impairment and 70-78% are mentally retarded.

Information on the profile of infants with West syndrome in developing countries is limited.\(^10,11\) Management of children in developing countries has distinct challenges in the form of delay in presentation, delay in diagnosis and high cost of investigations (MRI, Genetic panel, metabolic workup) and drugs such as adrenocorticotropic hormone (ACTH) and vigabatrin. This study is a retrospective observational study, done to obtain a baseline clinical and etiological profile, response of infantile spasms to various medications, and clinical outcome of children with west syndrome in a tertiary care hospital.

**METHODS**

This study was conducted at Lokmanya tilak municipal medical college, a tertiary care hospital in Mumbai. All cases of west syndrome who had visited this hospital from January 2017- January 2020 were enrolled for study. Data was obtained from prefilled proformas preserved in this department. Following data was collected from the patient's records: sex, age of onset of infantile spasms, age at diagnosis, type of spasms, and average number of spasms per day. History of antenatal, natal and postnatal events, developmental milestones and relevant family events were recorded. Physical Examination findings suggestive of microcephaly, neurocutaneous markers, dysmorphism, and organomegaly were documented.

The diagnosis of West syndrome was based on the presence of epileptic spasms, along with electroencephalographic (EEG) findings of hyspsarrhythmia or its variants. Hyspsarrhythmia was defined as EEG Showing high voltage chaotic slow waves intermixed with spike and sharp wave discharges. Modified hyspsarrhythmia was defined in presence of any of the following: increased interhemispheric synchronization consistent voltage asymmetries; consistent focus of abnormal discharge; episodes of generalized/regional or lateralized voltage attenuation; or primarily high-voltage bilaterally asynchronous slow wave activity.\(^12\)

The 'lag time' was defined as the time from initial observation of spasms to diagnosis.

CT Brain and MRI brain findings were noted as available. Metabolic workup (serum ammonia, arterial lactate, arterial blood gas, tandem mass spectroscopy) and genetic workup details were documented if available. Based on the history, examination findings and investigation results, patients were divided into symptomatic (known cause), and cryptogenic (unknown cause).

Various medications given for treatment of this severe syndrome were documented along with response to medications and relapse after tapering of medications. Clinical response was defined as complete cessation of spasms after starting of treatment.

Follow up records were assessed to look for long term control of spasms, relapse rates after cessation, or progression to other seizure types. Favourable response was defined as complete cessation of spasms without relapse for at least 6 months follow up and no progression to other seizure types as done by Kaushik et al.\(^11\)

Data was analysed using MS Excel and SPSS V 23.0 software in consultation with statistician. Data was given as Mean (SD) for continuous data and number and percentage for categorical data. Comparison of continuous variables was carried out using the Student t-test. Comparison of categorical variables was carried out with Chi- square test. Multivariate logistic analysis was done using SPSS V23.0. Level of Significance was taken as p<0.05.

**RESULTS**

Total of 39 children with west syndrome were analysed. 6 were excluded in view of incomplete data. 33 were included in final study. 23 (69.69%) children were males. Mean age at onset was found to be 8.12 months (1.36 months) and mean age at diagnosis was 13.46 months (3.58 months). Mean lag time to treatment was 5.35 months. 32% children were born of third-degree consanguineous marriage. Average spasms per cluster were found to be 6.33 (1-20) and average clusters per day were 5.87 (1-20). Majority (87.5%) of children had flexor spasms. 2 children had extensor spasms and 2 had mixed type of spasms. Records of head circumference of 29 children were documented. 20 out of 29 had microcephaly (68.96%). 1 child had dysmorphism. Only 2 children (6%) had normal development prior to onset of spasms. 13 children had hyspsarrhythmia on EEG (Table 1). Etiology was found in 23 (69.7%) children. Birth asphyxia was most common among symptomatic group. Among natal and postnatal causes, birth asphyxia was found in 12 (52.2%), hypoglycaemia in 4 (17.39%), and
meningitis in 5 (21.73%) children. Among antenatal causes; CNS malformation (1), Neurofibromatosis (1) and tuberous sclerosis (1) were found. In 10 children, no etiology was found on history, examination and/or neuroimaging (Table 2).

Various drugs used for treatment include prednisolone, ACTH, vigabatrin, valproate, nitrazepam, topiramate, clobazam, levetiracetam and keto diet. With oral prednisolone, 6 (54.5%) out of 11 had complete cessation of spasms. Complete spasm cessation was found in 6 (54.5%) out of 11 children with use of ACTH. With vigabatrin, 3 (33.33%) out of 9 had complete spasm cessation. With nitrazepam, 3 (50%) out of 6 had spasm cessation. 01 (12.5%) out of 8 responded with valproate, 2 (40%) out of 5 with topiramate, 1 (50%) out of 2 with clobazam and none of 5 with levetiracetam (Table 3).

Among 17 children had follow-up records of at least 6 months. 10 belonged to symptomatic group and rest were cryptogenic. 13 of the 17 having follow-up records had initially responded to treatment. 10 (76.92%) of the 13 were spasm free at 6 months.

All children who relapsed belonged to symptomatic group. Overall, 6 out of 10 (60%) were spasm free among symptomatic group, whereas 4 out of 7 (57.14%) in cryptogenic group. 4 out of 17 (23.52%) progressed to other seizure types. 3 (33.3%) were among symptomatic group and 1 (16.6%) among cryptogenic group.

Favourable clinical response at 6 months follow up was found in 8 (47.06%) of the 17 children.

Surprisingly, lag time and symptomatic etiology did not have any significant impact on favourable outcome. Multivariate logistic analysis revealed that mean age at onset (p=0.468), lag time (p=0.381), male gender (p=0.714), symptomatic etiology (p=1.00), developmental delay prior to spasms (p=0.379), microcephaly (p=1.00), average spasms per day (p=0.336) and birth asphyxia (p=0.507) did not have any significant effect on favourable outcome (Table 4).

### Table 1: Baseline characteristics of study population.

| Baseline characteristics (n=33) | Values |
|-------------------------------|--------|
| Mean age of spasm onset in months (SD) | 8.12 (8.13) |
| Mean age at diagnosis in months (SD) | 13.46 (11.38) |
| Mean lag time in months (SD) | 5.35 (6.70) |
| Male gender (%) | 23 (69.69%) |
| Mean number of spasms per cluster (SD) | 6.33 (4.35) |
| Mean number of clusters per day (SD) | 5.87 (4.29) |
| Mean number of spasms per day (SD) | 45.8 (73.33) |
| Type of spasms | Flexor spasms 28/32 (87.5%) | Extensor spasms 2/32 (6.25%) | Mixed spasms 2/32 (6.25%) |
| Developmental delay prior to onset of spasms | 31/33 (93.9%) |
| Microcephaly | 20/29 (68.96%) |
| Dysmorphism | 1/33 (3.03%) |

### Table 2: Etiological profile of study population.

| Etiology | Number (percentage) |
|----------|---------------------|
| Symptomatic | 23 (69.7%) |
| Cryptogenic | 10 (30.3%) |
| **Antenatal causes** | |
| CNS malformation | 1 (6.67%) |
| Neurofibromatosis | 1 (6.67%) |
| Tuberous sclerosis | 1 (6.67%) |
| **Natal causes** | |
| Birth asphyxia | 12 (52.2%) |
| Postnatal causes | |
| Hypoglycaemia | 4 (17.39%) |
| Meningitis | 5 (21.73%) |

### Table 3: Clinical response in the form of complete spasm cessation to various medications used in study population.

| Drug | Number of patients | Complete response |
|------|-------------------|------------------|
| Prednisolone | 11 | 6 (54.5%) |
| ACTH | 11 | 6 (54.5%) |
| Vigabatrin | 9 | 3 (33.33%) |
| Na valproate | 8 | 1 (12.5%) |
| Nitrazepam | 6 | 3 (50%) |
| Topiramate | 5 | 2 (40%) |
| Clobazam | 2 | 1 (50%) |
| Levetiracetam | 5 | 0 (0) |
| keto diet | 1 | 1 (100%) |

### Table 4: Effect of various factors on outcome of West syndrome using Multivariate logistic analysis.

| Factors (n=17) | Adjusted OR | p value | OR |
|----------------|-------------|---------|----|
| Male sex | -2.240 | 0.714 | 0.106 |
| Age at onset | -1.695 | 0.468 | 5.446 |
| Lag time | 0.389 | 0.381 | 1.476 |
| Birth Asphyxia | -13.107 | 0.507 | 0.000 |
| Microcephaly | -1.188 | 1.000 | 0.305 |
| Developmental delay prior to spasms | -7.316 | 0.379 | 0.001 |
| Symptomatic etiology | 11.319 | 1.000 | 82408.155 |
| Spasms per day | 0.065 | 0.336 | 1.068 |
DISCUSSION

This retrospective observational study describes clinical and etiological spectrum, response to treatment and outcome in children with infantile spasms in a tertiary care hospital of Mumbai. Mean age at onset in this study was found to be 8.12 months which was higher than found in other studies. Mean age at onset of spasms was 6.1±3.4 months, and 5.3 months in previous two similar Indian studies.\(^\text{11,13}\)

Mean age at diagnosis in this study was found to be 13.46 months, with lag time to diagnosis of 5.35 months. It was comparable to other studies from developing countries with lag time of 7.9 in Kaushik et al, and 9.29 in Chandra et al, but much higher then found in developed countries (25-45 days).\(^\text{11,14-16}\) Higher lag time found in this study could be due to poor health awareness of general public as well as limitation of knowledge regarding west syndrome of general physicians. Spasms are mistaken for startles by most parents. Many of these cases were diagnosed only when they visited healthcare facilities for other complaints like developmental delay or other acute illnesses and on direct questioning revealed regarding spasms. There is evidence to suggest that earlier treatment (within one month of onset) is more effective in controlling spasms and may improve outcomes.\(^\text{10,17}\)

Average spasms per cluster were found to be 6.33(1-20) and average clusters per day were 5.87. Majority (87.5%) had flexor spasms which was similar to findings from previous Indian studies. 85% cases in Chandra et al, had flexor spasms whereas percentage of flexor spasms was 76.3% in Kaushik et al.\(^\text{11,14}\) 93.9% of these children had developmental delay prior to onset of spasms which was comparable to other studies. Developmental delay prior to onset of spasms was found to be 92.5% in Kaushik et al, 88% in Chandra et al, and 92% in Lyte et al.\(^\text{11,14,18}\) Majority of the studies report predominance of male children.\(^\text{11,14}\) Percentage of male children was 69.69% in this study.

After history, physical examination, EEG and MRI brain are performed, about 70% of patients with west syndrome have an etiological diagnosis.\(^\text{19}\) Kaushik et al, found aetiologies in 81% cases while Lyte et al, in 88% cases. In United Kingdom infantile spasms study, etiology was found in 61% cases.\(^\text{3}\) In this study, etiology was found in 23(69.7%) children. Perinatal causes are more commonly reported in developing studies.\(^\text{12,14}\)

Similar pattern of aetiologies was found in this study with perinatal causes being most common. Among natal and postnatal causes, birth asphyxia was found in 12, hypoglycaemia in 4 and meningitis in 5 children. In developed countries, etiological profile is different from developing countries with antenatal cause being more common.\(^\text{12,20,21}\) Among antenatal causes, one case each of CNS malformation, Neurofibromatosis and tuberous sclerosis were found.

ACTH is one of the most studied first line therapy in treatment of infantile spasms.\(^\text{22-25}\) In 2004, the American Academy of Neurology and Child Neurology Society concluded that ACTH is “probably effective” in the treatment of infantile spasms.\(^\text{26}\) The rates of cessation of spasms ranged from 42-87%,\(^\text{22-26}\) 2012 update of AAN suggested that low-dose ACTH is probably as effective as high-dose ACTH.\(^\text{27}\) In this study, complete spasm cessation was found in 6(54.5%) out 11 children with use of ACTH.

As per American Academy of Neurology guidelines, there is insufficient evidence to determine whether other forms of corticosteroids are as effective as adrenocorticotrophic hormone (ACTH) for short-term treatment of infantile spasms.\(^\text{27}\) Initially, studies suggested that corticosteroids were inferior to ACTH. Prednisolone was used in lower doses, ranging from 2-3 mg/kg/day, with response rates from 25-59%.\(^\text{22-26}\) In most cases, these were significantly lower than the response to ACTH. Multiple studies have subsequently used higher doses of prednisolone.\(^\text{25,26}\) These have shown rates of efficacy similar to ACTH, ranging from 67-80%. Relapse rate was also like ACTH or lower. Authors had used 4mg/kg/day dose of prednisolone in their patients. With oral prednisolone, (65.4%) out of 11 had complete cessation of spasms. Response rate was comparable with other studies with higher dose of prednisolone.

Vigabatrin is the preferred first-line therapy for patients with infantile spasms and tuberous sclerosis, with some studies showing efficacy of greater than 90% in patients with tuberous sclerosis.\(^\text{28}\) In general, vigabatrin has been thought to be less effective than ACTH in other patient populations.\(^\text{28}\) In this study, with vigabatrin, 3(33.33%) out of 9 had complete spasm cessation. All other drugs were used either as second line or third line drugs or were already in use because of the other seizure types. With nitrazepam, 3(50%) out of 6 had spasm cessation. This was higher than reported in literature.\(^\text{11}\) 01(12.5%) out of 8 responded with valproate, 2(40%) out of 5 with topiramate, 1(50%) out of 2 with clobazam and none of 5 with levetiracetam.

Favourable clinical response at 6 months follow up was found in 8 (47.06%) of the 17 children. Surprisingly, lag time and symptomatic etiology did not have any significant impact on favourable outcome. This is unlike other similar studies where longer lag time and symptomatic etiology were associated with poorer outcome.\(^\text{11,15,17}\) Mean age at onset, lag time, male gender, symptomatic etiology, developmental delay prior to spasms, microcephaly and birth asphyxia did not have any significant effect on favourable outcome at 6 months follow up.

Limitation of this study was that it was a single centre retrospective study, so sample size was relatively small. In addition, formal developmental assessment for developmental outcome was not carried out in this study.
Despite limitations, this study gives further insight into etiological profile of west syndrome in developing countries which is different than in developed countries. It also highlights the role of cheap and easily available drug like prednisolone especially in resource constrained settings, as it had good clinical response in this study. Authors recommend further prospective studies and preferably randomised controlled trials for the efficacy of prednisolone in treatment of west syndrome.

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