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Clinical Features and Treatment Outcome of West Syndrome Patients treated in a Tertiary Care Hospital: Bangladesh Perspective

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Abstract:

Purpose: *West syndrome (WS) is a catastrophic epilepsy syndrome with onset usually in the first year of life. A variety of drugs are currently being used for spasm control in WS. The purpose of this retrospective study was to compare the efficacy of ACTH , prednisolone and vigabatrin in the treatment of WS.*

Methods: *Children with WS were reviewed retrospectively for a period of 3 years. Inclusion criteria were clinical symptoms of infantile spasm and hypsarrhythmia or modified hypsarrhythmia on electroencephalography (EEG). Children treated with either ACTH , prednisolone or vigabatrin were enrolled into this study.*

Results: *Among 136 children who presented with infantile spasms, 100 children met the inclusion criteria as WS. Age ranged from 2 months to 3 years with a mean of 22.82±19.89 months . Most of them were male (62.3%). Mean ages of onset of seizure and first treatment were 4.97±3.94 and 5.03±3.80 months. Neonatal seizures, perinatal asphyxia, neonatal sepsis and focal neurological deficit were found in 26%, 31%, 6% and 4% children respectively. Motor delay prior to onset of symptoms was present in 56% children. No significant*

difference was found among these three drugs causing complete remission.

Conclusion: *ACTH, oral prednisolone and vigabatrin showed effective response among WS patients and there was no significant difference in the treatment response.*

Key words: West Syndrome, ACTH, Prednisolone, vigabatrin

INTRODUCTION:

West syndrome (WS), constitutes a devastating form of infantile epilepsy that is difficult to treat and is associated with a poor outcome.[1] The syndrome was the first described epileptic encephalopathy—a condition in which the epileptic activity itself contributes to cognitive and neurological decline.[2] This syndrome occur in roughly 2-3 per 10,000 live births, with peak incidence at 6 months of age and less than 10% of cases presenting after 12 months of age. [3, 4]

This syndrome is associated with neurodevelopmental stagnation or regression.[5,6] Unfortunately, due to the subtle and brief nature of spasms in some patients, there can be delay in diagnosis. There is evidence to suggest that earlier treatment (within one month of onset) is more effective in controlling spasms and may improve outcomes. Thus timely diagnosis is important for good prognosis.[6,7]

Identification of effective, swift acting treatments is important as well. There are limited data to guide the treatment of west syndrome. Most studies are retrospective or small prospective studies. [8,9,10]

The most recent practice guidelines from the American Academy of Neurology and the Child Neurology Society for the medical treatment of west syndrome, state that ACTH is probably effective and vigabatrin is possibly effective in the cessation of spasms.[8] When the practice guidelines were published, there was insufficient evidence to recommend oral corticosteroids or valproic acid as first-line treatments in WS; however, since then, high-dose oral prednisolone has been reported to possibly be effective.[11,12] This study therefore was done to compare the efficacy of hormonal

modalities (ACTH and prednisolone) and vigabatrin in treatment of WS in developmental country perspective.

METHOD AND MATERIAL:

Study setting: This study was carried out in the Institute of Paediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, a tertiary level teaching facility and Medical University in capital of Bangladesh.

Study design: Among 136 children who presented with infantile spasms, 100 children met the inclusion criteria as WS. The study was done from January 2013 to December 2015. Patient records were reviewed and data was collected on structured proformas especially prepared for this purpose.

Inclusion criteria**:** 1.Clinical symptomatology of infantile spasms as elicited by thorough physical examination and detailed history.2. Accompanying EEG findings at initial EEG (hypsarrythmia or modified hypsarrythmia).

Exclusion criteria**:** 1. Children who had already received any of the investigational drugs prior to their first encounter were excluded. 2. Children who were diagnosed to have tuberous sclerosis were excluded.

Children with Response to therapy**:** children were considered as a) **Seizure free (complete remission):** Either on the basis of clinical resolution of spasms or on the basis of both clinical resolution of spasms and EEG resolution of hypsarrythmia, b) **Partial remission**: When the number of spasms was reduced by at least ≥ 50% as compared to the baseline spasms at initial presentation before the administration of subsequent medication, c) **No response**: When there is no change in the number of spasms even after adequate period of therapy, 4) **Relapse:** Initial response both clinical and electro-physiological, but later on reappearance of clinical spasms.

***Categories based on etiology*:** All cases were grouped into three categories. **a)Symptomatic:** cases were considered as symptomatic when the infantile spasms resulted from an identifiable cause and who have evidence of neurologic injury at the time of onset or a known associated disorder, **b)Cryptogenic**: Patients who were suspected of being symptomatic but for whom an underlying structural or biochemical cause could not be identified**) Idiopathic:** Those cases in which infantile spasms occurred without any identifiable cause, other neurological signs or symptoms were normal.

Medication: The children who showed partial or no response to the initial therapy after the maintenance doses of any of the three medications for adequate time duration, were put on a second drug. For example, patients who were initially on vigabatrin but failed to show adequate response were put on ACTH. Similarly, patients who were initially on ACTH but failed to show adequate response were put on vigabatrin. Children who showed response to the initial drug were maintained on that therapeutic agent. Children were treated with following doses **a)**vigabatrin: 50-150 mg/kg/day 2 divided doses b) prednisolone: 2 mg/day for 4 weeks; then taper over 2 weeks c)ACTH:20-30 IU/day for 4 weeks then tapering over 2 weeks.

Data management and statistical analysis: The data was coded, entered and analyzed using Windows SPSS version 16.0. In descriptive analysis, the mean and standard deviations of the continuous variables and percentages of categorical variables were computed. A p-value of < 0.05 was considered statistically significant.

***Ethical considerations*:** Ethical clearance was taken from the Ethical Review Committee (ERC) of the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

RESULTS

Clinical profile of patient:

a. Baseline characteristics: The baseline characteristics of our children are presented in Table 1. Mean age was 22.82±19.89 months. The majority of the patients (68%) were male. Mean ages of onset of

seizure and first treatment were 4.97±3.94 and 5.03±3.80 months. Consanguinity was present in 8% children. Most of the child were (42%) delivered by LUCS followed by NVD at home (32%) and vaginal delivery at hospital (26%). Eighteen percent children were small for gestational age with a low birth weight (less than 2.5 kg). History of neonatal seizures, perinatal asphyxia, neonatal sepsis and focal neurological deficit were found in 26%, 31%, 6% and 4% children respectively. Developmental delay prior to onset of symptoms was motor 56% and speech 42%. Cognitive, visual and hearing impairment was present in 28%, 2% and 2% patients respectively. One patient had Sturge- weber syndrome and status epilepticus. All the patients received an initial EEG. Fifty two (92.8%) patients exhibited the classic hypsarrythmic pattern while modified hypsarrhythmia was less commonly seen (7.2%).

b. Etiology of west syndrome: In this study, 36 (64.3%) children were symptomatic, while 11 (19.6%) children were cryptogenic and the remaining 9 (16.1%) were idiopathic. Most of the causes of WS were structural (70%) followed by unknown 18%, metabolic 7% and genetic 5%. Nearly half of the children were diagnosed as cerebral atrophy (46%), 6% had multiple abnormalities, 3% had encephalomalacia, 4% had cerebral infraction. Lissencephaly and corpus callosal agenesis was present in 2% of patients. Among the symptomatic children, cerebral atrophy secondary to birth asphyxia was identified as the leading cause of WS (Table 3). It was seen that almost 31% patients had a history of perinatal asphyxia. APGAR scores were not available in most of the cases since the deliveries were performed outside our hospital.

Treatment outcomes

a. Initial therapy of west syndrome: All children were given one medication at any given time. Out of 100 patients, 39 received vigabatrin, 34 received prednisolone and 27 received ACTH as initial therapy. The results of initial therapy are presented in Table 4. Among the vigabatrin group (n=39), 23 children went to complete remission and 9 had partial remission. In oral prednisolone group (n= 34), 21 went to complete remission and 10 had partial remission.

Complete and partial remission occurred in 16 and 6 children among ACTH group (n=27).

b. Switch to second drug: After initial therapy, 15, 11 and 13 patients initially on vigabatrin, prednisolone and ACTH therapy showed partial/ no response even after adequate duration. They were then put on a second and different drug. The response of the second drug is shown in table 5. Complete remission occurred in 7/15(46.6%), 6/11(54.4%) and 8/13(61.5%) in vigabatrin, prednisolone and ACTH group.

c. Relapse: Thirty nine patients (2.6%) in vigabatrin group relapsed after initial therapy. However, no patients relapsed in oral prednisolone and ACTH group. During subsequent therapy one patient relapsed in oral prednisolone group.

d. Final outcome of patients: Final outcome was measured based on clinical presentation which was assessed by child neurologist combined with clinical psychologist by standard diagnostic tool (Table 7). Fourteen children developed cerebral palsy, 2 developed autism spectrum disorder(ASD), 3 attention deficit hyperactivity disorder (ADHD) and 2 developed behavioral problem .

DISCUSSION:

Since it has been first described by Dr William James West in 1841[13] different modalities of treatment have been tried in WS. Although a good number of studies have been done on treatment of WS, it is still one of the most distressing and difficult to treat epileptic syndrome. Till date there is debate which drug should be used as first line therapy. In a recent survey about 2/3 rd of the provider were using ACTH as first line treatment of WS with varying dose and duration.[14] While more providers are using prednisolone in WS as first line therapy. [15] Vigabatrin is the preferred first line therapy for patients with west syndrome and tuberous sclerosis. [9] In general, vigabatrin has been thought to be less effective than ACTH in other patient populations, although long-term outcomes may be similar. [12, 16, 17]

Our study provides a developing country perspective, clinical features and treatment outcomes of WS patients with particular reference to three drugs. Initially patients were treated with either vigabatrin or oral prednisolone or ACTH. A second drug was started if the patients showed partial or no response to the first agents. Subsequently a third drug was used when some of them showed partial or no response to the previous agents. At any given time, patients were put on not more than one drug.

The comparative analysis of the effectiveness of treatment as initial therapy with these three drugs showed no significant difference in complete remission. However, more number of children treated with ACTH as initial therapy showed no response to drug compared to other two drugs (ACTH 18.5% ,prednisolone 8.9% and vigabatrin 15%). Although previous Cochrane analysis of prospective studies comparing ACTH , hormonal treatment and vigabatrin indicate hormonal therapy leads to resolution of spasm three times more rapidly and in more infants than vigabatrin,[12] in our study we found minimal difference in cessation of spasm in these three drugs, rather, those who treated with ACTH showed more nonresponsiveness than the other groups. However, our study has similarity with one study which has been done in the neighboring country like Pakistan , where no significant difference was found in treatment with ACTH and vigabatrin (response rate 55% and 50% respectively).[18] This is an interesting finding and may highlight the future use of oral drugs rather ACTH which needs hospitalization.

In our study, children who showed no or partial response to initial therapy, a second line drug was added after 6 week trial. In the second line therapy, no significant difference was observed among the three groups. Nineteen children (19%) needed a third drug to control the spasm, among them 8 patients were treated with vigabatrin, 5 with prednisolone and 6 with ACTH. About half (50%) of the children who were treated with vigabatrin and ACTH as third line therapy achieved complete remission and none of them had relapse. We also observed that majority of the children who responded to drugs, the time of response was within first 2 weeks yet we continued the treatment for total 6 weeks.

Psychomotor outcome of this children were variable. Fourteen patients developed cerebral palsy in course of time. Apart

from cerebral palsy, 2 children presented with other types of movement disorders. Other psychiatric problems observed in these children were ASD (2) , ADHD (3), other behavioural problem (2). While comparing the three groups, children who were treated with ACTH developed ADHD more than the other groups (ACTH 7.4%, prednisolone 0%, vigabatrin 2.5%). the number of children who developed ASD were almost similar in vigabatrin and prednisolone group (3% and 2.5%) in comparison to ACTH group (none). In previous studies it has been seen that cognitive outcome was better after initial ACTH than vigabatrin in the unknown aetiology subgroup, but not in the identified aetiology subgroup.[11, 16] This might be explained by earlier cessation of the spasms in the ACTH/hormone group.

About sixty four percent of the children belonged to symptomatic group in this study and common underlying cause was perinatal asphyxia (31%), neonatal seizure (26%) and preterm low birth weight (LBW) (18%). Eleven children (19.6%) were cryptogenic and the remaining 9 (16.1%) were idiopathic. Thus majority of the children in this study group had structural defect (70%). Eighteen percent of the children had no identifiable etiology; this may be due to lack of comprehensive laboratory workup and neuroimaging studies. Our study results matches with the similar studies done in the regional areas where perinatal asphyxia (61.4%), neonatal sepsis/meningitis (10.6%), and postnatal meningitis (11.4%) were the predominant causes. The etiology could not be ascertained in 16.6% of children. [19]

Developmental delay prior to onset infantile spasm is a common feature of WS. In our study, we assessed the developmental milestones domain wise where we found 56% of children had motor delay, 42% speech delay, 28% cognitive delay. Visual and hearing impairment was present in 2% children . It is here to mention that neuro-developmental impairment in WS is a feature that mostly indicates the pre- or perinatal etiology and is a poor prognostic variable [20,21] reported that patients of WS with a favorable outcome had normal neurodevelopment before the onset of the spasms. Nearly all previous studies on this variable reported similar results. [8, 22]

Relapse after treatment completion is an important issue to address in WS. In our study, approximately 2.6% children who were treated with vigabatrin had seizure relapse during the initial therapy

while one patient relapsed in oral prednisolone group. In related studies the relapse rate was somewhat more. In one study by Hayashi 41.0% of children showed seizure relapse after ACTH administration in another study by Basheer Peer the response rate for steroid therapy was 61.1% and 42.5% for vigabatrin. [23] Cessation of spasms was achieved faster in the group receiving steroids. Both groups had similar relapse rates.[24]

CONCLUSION

Despite all the advances in understanding the various treatment options available, WS still remains an elusive childhood disease that is difficult to treat with the overall prognosis being dismal. Identification of the most appropriate therapeutic agent is a critical issue in treatment of west syndrome. In this study vigabatrin, oral prednisolone and ACTH showed no significant difference. This finding may change the trend of treatment of WS with easily accessible drugs with minimal side effect. However, larger studies are required to validate the therapeutic trends observed in our study.

REFERENCES:

1. Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M, Gaslini . Infantile spasms syndrome, West syndrome and related phenotypes: what we know in 2013. Brain Dev. 2014; 36: 739–751.
2. Engel J Jr and International League Against Epilepsy. A proposed diagnostic scheme for people with epileptic seizues and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001;42: 796-803.
3. Nordphysicianguides.org/Infantile-Spasms. Available online: http://nordphysicianguides.org/Infantile-Spasms/
4. Wang JC, Jonas R, Fu CM, Ng CY, Douglass L. Quality-of-care indicators for infantile spasms. J Child Neurol 2013;28:13–20.
5. Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S.Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia 2004; 45(3) :255-62.

6. O'Callaghan FJ, Lux AL, Darke K, Edwards SW, Hancock E, Johnson AL et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia 2011;52:1359-64.
7. Widjaja E, Go C, McCoy B, Snead OC et al. Neurodevelopmental outcome of infantile spasms: A systematic review and meta-analysis. Epilepsy Res 2015;109:155-62.
8. Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004;62:1668-81.
9. Go CY, Mackay MT, Weiss SK, Stephens D, Adams-Webber T, Ashwal S, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2012;78:1974-80.
10. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev 2013;6:CD001770.
11. Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Lux AL, et al: Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child 2010, 95:382–386.
12. Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, et al: The United Kingdom Infantile Spasms Study comparing vigabatrinwith prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 2004, 364:1773–1778.
13. West WJ. On a peculiar form of infantile convulsions. Lancet. 1841;1:724–725.
14. Mytinger JR, Joshi S; Pediatric Epilepsy Research Consortium, et al. The current evaluation and treatment of infantile spasms among members of the Child Neurology Society. J Child Neurol 2012;27:1289-94.
15. Kossoff EH, Hartman AL, Rubenstein JE, Vining EP . High-dose oral prednisolone for infantile spasms: an effective and less expensive alternative to ACTH. Epilepsy Behav 2009;14:674-6.

16. Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol 2005;4:712-7.
17. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997;38:1270-4.
18. Ibrahim S, Gulab S, Ishaque S, Saleem T. Clinical profile and treatment of infantile spasms using vigabatrin and ACTH: a developing country perspective. BMC Pediatr. 2010;10:1.
19. Kaushik JS, Patra B, Sharma S, Yadav D, Aneja S.Clinical spectrum and treatment outcome of West Syndrome in children from Northern India. Seizure 2013 Oct;22(8):617-21.
20. Guveli BT, Cokar O , Dortcan N , Benbir G , Demirbilek V , Dervent A. Long-term outcomes in patients with West syndrome: An outpatient clinical study . Seizure 2015:25; 68–71.
21. Riikonen R. Long-term outcome of West syndrome: a study of adults with a history of infantile spasms. Epilepsia 1996;37:367–72.
22. Lagae L, Verhelst H, Ceulemans B, Meirleir LD, Nassogne MC, Borchgrave VD, et al. Treatment and long term outcome in West syndrome: The clinical reality. A multicentre follow up study. Seizure 2010;19:159–64.
23. Hayashi Y, Yoshinaga H, Akiyama T, Endoh F, Ohtsuka Y, Kobayashi K. Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain Dev. 2016 Jan;38(1):32-9.
24. Mohamed BP , Scott RC ,Desai N ,Gutta P, Patil S. Seizure outcome in infantile spasms—A retrospective study. Epilepsia 2011: 52 (4);746-52.

Table 1: Baseline Characteristics of Children with West Syndrome

Baseline Characteristics		n- 100
Age in Months (Mean ± SD)		22.82±19.89
Gender	Male	68
	female	32
Age of onset of seizures in months (Mean ± SD)		4.97±3.94
Age at first treatment in months (Mean ± SD)		5.03±3.80
Status Epilepticus		1
Consanguinity of parents		8
Birth History	NVD at Home	32
	NVD at Hospital	26
	LUCS	42
Preterm/LBW/IUGR		18
History of neonatal seizures		26
PNA/HIE/Delayed cry		31
History of neonatal sepsis/meningitis		6
Focal neurological deficit		4
Developmental delay prior to onset of symptoms	Motor delay	56
	Speech delay	42
	Cognitive impairment	28
	Visual impairment	2
	Hearing impairment	2
Down Syndrome		3
Tuberous Sclerosis		1
Sturge Weber Syndrome		1
Cytomegalovirus Infection		3

Table 2: Underlying causes of West Syndrome

Cause of infantile spasm	**Vigabatrin n=39**	**Prednisolone n=34**	**ACTH n=27**	**Total n=100**
Genetic	1	2	2	5
Structural	30	23	17	70
Metabolic	3	2	2	7
Unknown	5	7	6	18

Table 3: Neuroimaging findings of patients with West Syndrome

Neuroimaging findings	**Total n=100 (%)**
Atrophy	46
Cerebral Infraction	2
Basal ganglia infraction	2
Lissencephaly	1
Corpus callosal agenesis	1
Encephalomalacia	3
Multiple abnormalities	6
Normal	39

Table 4: Clinical response to initial therapy

Response of patients	Vigabatrin n=39(%)	ACTH n=27(%) p value
Complete Remission	23(59)	16(59) >0.5
Partial Remission	9(23)	6(22)
No Response	6(15)	5(18.5)
Relapse	1	0

Table 5: Clinical response to initial therapy

Response of patients	Prednisolone n=34 (%)	ACTH n=27(%) p value
Complete Remission	21 (61)	16(59) >0.5
Partial Remission	10 (29)	6((22)
No Response	3 (8.9)	5(18.5)
Relapse	0	0

Table 6: Response to subsequent therapy *

Response of patients	Vigabatrin n=15(%)	Prednisolone n=11(%)	ACTH n=13(%)
Complete Remission	7(47)	6(55)	8(61)
Partial Remission	5(33)	3(27)	5(38)
No Response	3(20)	1(9)	1(8)
Relapse	0	1	0

***That was administered after 6 weeks in case of partial or no response to first drug**

Table 7: Response to third drug*

Response of patients	Vigabatrin n=8(%)	Prednisolone n=5(%)	ACTH n=6(%)
Complete Remission	4(50)	2(40)	3(50)
Partial Remission	1(12.5)	1(20)	1(17)
No Response	3(37.5)	2(40)	2(33)
Relapse	0	0	0

*** That was administered after 6 weeks in case of partial or no response to previous drugs.**

Table 8: Final outcome of patients with West syndrome

Response of patients	Vigabatrin n=39	Prednisolone n=34	ACTH n=27	Total
Autism Spectrum Disorder (ASD)	1(2.5)	1(3)	0	2
Cerebral Palsy (CP)	6(15)	5(15)	3(11)	14
Attention Deficit Hyper Activity Disorder (ADHD)	1(2.5)	0	2(7.4)	3
Behavioral Problem (BP)	1(2.5)	1(3)	0	2
Abnormal Movement (AM)	0	1(3)	1(3.7)	2