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Original Article

Clinical features and long-term follow-up of patients with West syndrome: 5-year developmental outcomes

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ABSTRACT

Objectives: West syndrome (WS) is an early childhood epileptic encephalopathy characterized by spasms, typically occurring within the first year of life. The International League Against Epilepsy reclassified WS as "infantile epileptic spasm syndrome" to enhance early diagnosis and treatment. It is marked by a triad of epileptic spasms, psychomotor retardation or regression, and hypsarrhythmia on EEG. The prognosis and response to classical anti-epileptic treatments are often poor, and factors influencing prognosis remain unclear.

Methods: This study retrospectively analyzed 75 patients with WS over five years, assessing etiology, MRI findings, and neurodevelopmental outcomes according to ILAE guidelines.

Results: The cohort comprised 35 females (46.7%) and 40 males (53.3%). The most common etiology was structural, observed in 41 patients (54.7%), followed by unknown causes in 19 patients (25.3%). Genetic, metabolic, and infectious causes were less common. Brain MRI findings were normal in 23 patients (30.7%). Treatment primarily involved Vigabatrin, which was used in 54.7% of cases, followed by Adrenocorticotropic hormone (ACTH) in 25.3%. Seizure control improved over time, with 24% of patients fully controlled at one year and 42.8% at five years. However, 28% showed no change in seizure frequency. The presence of structural abnormalities correlated with a poorer prognosis, while early and complete seizure control was associated with better outcomes. Mortality was 5.3%, with four patients passing away during the follow-up period.

Conclusion: The study highlights that while the etiology remains a significant factor in the prognosis of WS, early intervention and effective seizure management are crucial for improving long-term outcomes.

Keywords: west syndrome, long-term prognosis, development delay

INTRODUCTION

West syndrome (WS) is an early epileptic encephalopathy of childhood, which was first described by William West in 1841. This disease mostly affects infants in the first year of life, and its characteristic feature is spasms.[1] The terms infantile spasms, epileptic spasms, and infantile spasm syndrome (WS, IS, ES, and ISs) are still used interchangeably.[2] In 2022, The International League Against Epilepsy classified all patients with infantile spasm and epileptic activity on electroencephalography (EEG) as "infantile epileptic spasm syndrome (IESS)" in addition to typical WS patients for early diagnosis and treatment.[3]

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Infantile spasms have been evaluated for more than 170 years in terms of etiology, pathogenesis, clinical features, and diagnosis. It is a rare disease that occurs in 1.6% to 4.5% of 10,000 live births.[4-6] The clinical triad of WS is an epileptic spasm, psychomotor retardation or regression, and hypsarrhythmia pattern on EEG. It is one of the epileptic encephalopathy syndromes seen in early childhood.[7] The classical anti-epileptic treatment response and long-term prognosis are often poor.[8] The long-term overall prognosis for patients with infantile spasm is directly related to its etiology.[9] Although psychiatric problems such as autism and attention deficit are common, severe mental retardation is seen in 70% of patients together with psychiatric problems.[10] Current knowledge of the factors affecting the prognosis of WS is still limited. Therefore, the aim of this study was to determine the prognosis and factors affecting the prognosis of WS.

METHOD

A retrospective examination was conducted on the files of patients diagnosed with WS who were followed up for at least five years. The etiology of the patients was classified for the ILAE classification.[11] Magnetic resonance imaging (MRI) of the brain was performed in all patients. Chromosome analysis was performed. Urine and serum amino acid, organic acid in the urine, biotinidase, lactate, and pyruvate levels were examined. Psychomotor development steps were evaluated using the Denver II Developmental Screening Test, and the 5-year development milestones were examined.

Neurodevelopmental milestones were classified as normal, mild, moderate, or severe retardation. Developmental delay was categorized as mild for deficits less than 50%, moderate for deficits between 50% and 70%, and severe for deficits greater than 70%.

Patients with normal and mild retardation of neurodevelopmental milestones were classified as good prognosis, and those with moderate and severe retardation as poor prognosis. EEG hypsarrhythmia and modified hypsarrhythmia on admission were classified as normal or other. Hypsarrhythmia is an EEG pattern characterized by random, high-voltage spikes and slow waves. Key features include high-voltage slow waves of varying amplitude, multifocal spikes, and a lack of synchrony, resulting in a chaotic appearance. It is defined as random high-voltage (>200 µV) slow waves with intermixed multifocal spikes.[12] Modified hypsarrhythmia refers to variations of the classic hypsarrhythmia pattern seen on EEG that differ from the typical chaotic appearance. These variations may include more organized features, such as hemispheric synchronization, a consistent focal point, reduced overall voltage, or a lower frequency of spikes and sharp waves.[13]

The follow-up EEG findings were recorded in cases with normal EEG at the time of admission. The EEG findings were recorded after treatment per year. The efficacy of treatment and the factors affecting psychomotor retardation were investigated.

Approval for the study was granted by the Non-Pharmaceutical Clinical Research Ethics Committee of Dr. Behçet Uz Children's Health and Diseases Training and Research Hospital. (Date: 26.05.2021 Issue: E-13399118-799)

Statistical analysis

Data was analyzed using SPSS (Statistical Package for the Social Sciences) software. The Shapiro-Wilk test was used to determine whether the data followed a normal distribution. Mean and standard deviation were calculated for data that followed a normal distribution, whereas median and interquartile range were computed for data that did not follow a normal distribution.

The chi-square test or Fisher's exact test was used for categorical data. Independent samples t-test or Mann-Whitney U test was applied for differences between groups in continuous variables. For comparing more than two groups, ANOVA or Kruskal-Wallis test was utilized. Post-hoc tests were performed to identify differences between specific groups. Statistical significance was set at $p < 0.05$.

RESULTS

The records of 103 patients diagnosed with WS were retrospectively examined. A total of 28 patients who did not attend follow-up appointments regularly were excluded from the analyses. Evaluation was made of 75 patients, comprising 35 (46.7%) females and 40 (53.3%) males with a mean age of 5.5±3.6 months (median 5 months, min 0-max 20 months) at seizure onset. The age at seizure onset was 5.5±3.8 months in females and 5.6 ±3.4 months in males. No significant difference was found between the two groups ($p = 0.864$).

When the birth histories were examined, there was seen to be perinatal asphyxia in 13 patients (17.3%), premature birth in 14 (18.7%), hypoglycemia in 2 (2.7%), and intrauterine growth retardation in 2 (2.7%). There was a history of parental consanguinity in 12 (16%) patients. According to the ILAE, the etiology of WS was classified as genetic in 10 patients, structural in 41 patients, metabolic in 2 patients, infectious in 3 patients, and unknown cause in 19 patients (Table 1). All patients diagnosed with tuberous sclerosis complex (TSC) were genetically confirmed. All patients had mutations in the TSC1 gene.

Table 1. Etiology of West syndrome	
	n (%)
Genetics	10 (13.3)
MTHFR mutation	1 (1.3)
Merosin-deficient congenital muscular dystrophy	1 (1.3)
Rett syndrome	1 (1.3)
Prader Willi syndrome	1 (1.3)
TSC	6 (8.0)
Structural	41 (54.7)
Hypoxic ischemic encephalopathy	13 (17.3)
Periventricular leukomalacia	14 (19.7)
Others	14 (19.7)
Metabolic	2 (2.7)
Nonketotic hyperglycinemia	1 (1.3)
Possible metabolic disease	1 (1.3)
Infectious	3 (4.0)
Congenital CMV infection	1 (1.3)
Meningococcal meningitis	1 (1.3)
Herpes encephalitis sequelae	1 (1.3)
Unknown	19 (25.3)
Total	75 (100)

MTHFR: Methylenetetrahydrofolate reductase, TSC: Tuberous sclerosis complex, CMV: Cytomegalovirus.

The most common type of spasm in patients was flexor spasm. Two patients with flexor spasms had focal spasms. All patients had a history of more than one type of seizure. Seizure types were classified according to the ILAE. One patient had a focal clonic seizure in which awareness was maintained, and all other types of additional seizures were generalized (Table 2).

Brain MRI examination was performed in all the patients, and the findings were normal in 23 patients. The MRI findings of the patients are summarized in Table 3.

In the analysis of the patients' EEGs, hypsarrhythmia was identified in follow-up EEGs within a median of 14 days (min 7 - max 21 days) in eight patients who did not exhibit hypsarrhythmia at the time of admission.

Hypsarrhythmia was detected in 33 patients (44%), and modified hypsarrhythmia was detected in 42 (56%) patients.

B6 (pyridoxine) treatment was started orally at 30 mg/kg/day (maximum 300 mg/day) in all patients and discontinued within 2 weeks in patients with no change in seizure frequency.

Table 2. Seizures types in West syndrome	
	n (%)
Epileptic spasm	
Flexor spasm	42 (56)
Extensor spasm	6 (8)
Mixed spasm	27 (36)
Generalized tonic-clonic	65 (86.6)
Generalized myoclonic	22 (29.3)
Generalized Tonic	11 (14.7)
Generalized clonic	5 (6.7)
Focal clonic	2 (2.7)

Table 3. MRI findings in West syndrome	
	n (%)
Normal	23 (30.7)
Periventricular leukomalacia	25 (33.3)
Cerebral atrophy	7 (9.3)
Cortical tubers	5 (6.7)
Encephalomalacia	5 (6.7)
Cortical dysplasia	3 (4)
Corpus callosum dysplasia	3 (4)
Lissencephaly	2 (2.7)
Congenital CMV infection-related findings	1 (1.3)
Neurometabolic disorders-related findings	1 (1.3)

CMV: Cytomegalovirus.

The most commonly used anti-epileptic drugs in the treatment were vigabatrin (VGB) in 41 (54.7%) patients and ACTH in 19 (25.3%) patients.

VGB treatment was started at a dose of 50 mg/kg/day. The VGB dose was gradually increased in patients whose spasms could not be controlled (max150mg/kg/day). Tetracosactide (ACTH) was used at a dose of 0.02 mg/kg daily for two weeks and tapered over 6 weeks. Other anti-epileptic drugs were used by 15 patients (20%). VGB was started as the first treatment in 6 patients with TSC. All patients receiving VGB were examined for visual evoked potential (VEP) at 6-month intervals. The first positive waveform (P100) was defined as delayed when it was above 115 ms. P100 wave latency was prolonged in 5 patients. In 13 of the 19 patients administered ACTH in the first treatment, there was a decrease in the frequency of seizures in the 1st year of follow-up, while there was no change in the frequency of seizures in 6 patients. Four patients in the first year and eight patients in the 5th year were seizure-free. During the follow-up

Table 4. Seizure frequency and number of anti-epileptic drugs					
	1st year	2nd year	3rd year	4th year	5th year
Seizure free	18 (24%)	13 (17.3%)	21 (28%)	28 (37.3%)	32 (42.8%)
50%-99% decrease in seizure frequency	2 (2.7%)	8 (10.7%)	10 (13.3%)	14 (18.7%)	14 (18.7%)
< 50% decrease in seizure frequency	13 (17.3%)	14 (18.7%)	7 (9.3%)	5 (6.7%)	4 (5.3%)
No change in seizure frequency	42 (55%)	38 (49.7%)	33 (44.4%)	24 (32%)	21 (28%)
Number of anti-epileptic drugs	2±0.9	2.1±1	2.1±1.1	1.9±1.2	1.8±1.2

AEDs: anti-epileptic drugs

period, 65 patients (86.7%) required two or more anti-epileptic therapies. When the patients' seizure frequency was examined, 18 (24%) patients were fully controlled in year 1 and 32 (42.8%) in year 5. There was no change in the frequency of seizures in 21 (28%) patients (Table 4).

The most effective treatment for seizure control (50% or more decrease in seizure frequency and intensity) was VGB in 21 patients (28%), valproic acid in 13 patients (17.3%), clobazam in 11 patients (14.7%), and ketogenic diet in 7 patients (9.3%).

Mortality developed in 2 patients during the first year and in 2 patients during the second year of follow-up. The mortality rate was determined to be 5.3%. No statistically significant relationship was found between mortality and developmental delay (p=0.289).

The neuromotor development of the patients is summarized in Figure 1.

Complete remission was achieved in 7 patients (9.3%), with seizure freedom occurring after a median of 12 months (min 3– max 36 months) following seizure onset. EEG normalization was attained after a median of 36 months (min 12– max 60 months).

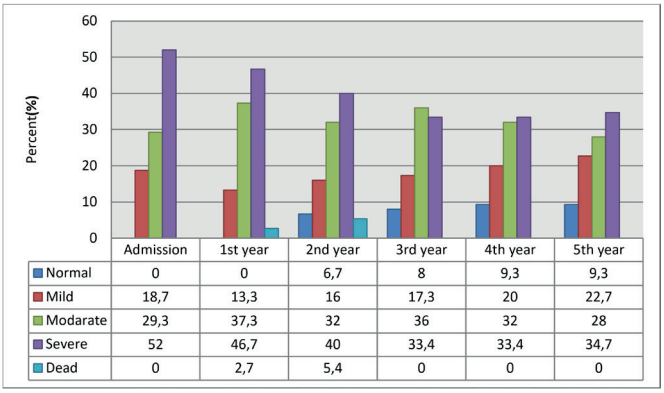

Figure 1. Neuromotor development from admission to 5 years

Age, gender, type of spasm, and choice of anti-epileptic treatment did not affect prognosis. The prognosis was worse in patients with structural etiology. In particular, complete seizure control was found to be associated with a good prognosis (Table 5).

In this study, in which the results of a 5-year follow-up were evaluated, important findings were obtained about the long-term prognosis of patients with WS.

Of the patients included in this study, 53% were male, which is consistent with the literature, which has shown mild male predominance.[7] WS is an age-related epileptic encephalopathy that typically begins around 6 months of age.[14] In the current study, the median age of seizure onset was 5 months, similar to the literature.[4,5] All patients had neuromotor growth retardation at the time of diagnosis.

In a 1993 study by Ohtahara et al.[15], 42.8% of patients had a prenatal history, while Osborne et al.[16] reported prenatal history in 36 of 208 patients. HIE is known to be one of the most common causes of WS etiology. In the UK Infantile Spasm study, the most common etiology of WS was HIE (10%), followed by chromosomal abnormalities (8%), complex malformation syndromes (8%), perinatal stroke (8%), TSC (7%), periventricular leukomalacia (5%), and intracranial hemorrhage (5%).[16]

In a cohort followed up in China, 70 of 541 patients were reported with HIE in the etiology.[17] In another study of 208 patients with HIE, Inoue et al. reported that 8 (4.9%) patients were diagnosed with WS.[18] Similarly, in the current study, HIE was determined in 13 (17.3%) patients as one of the most common causes.

In 5-35% of patients, the underlying cause cannot be determined.[4,19] It is thought that this rate will decrease with the widespread use of imaging examinations and advances in genetics and metabolism analyses.[20-22] In the current study, no cause could be determined in 19 patients (25.3%).

Table 5. Factors affecting the prognosis of WS			
	Good Prognosis (n=24)	**Poor Prognosis (n=51)**	**p**
The first month of the seizure			
Age (<3 months)	5 (20.8%)	20 (39.2%)	0.115
Gender (female)	11 (45.8%)	24 (47.1)	0.921
Etiology			
Genetic	6 (25%)	4 (7.8%)	0.049
Structural	8 (19.8%)	33 (64.7%)	0.011
Metabolic	1 (2%)	1 (1.9%)	0.593
Infectious	-	3 (5.9%)	0.123
Unknown	9 (19.6%)	10 (37.5%)	0.097
Type of spasm			
Flexor spasm	14	28	0.083
Extensor spasm	-	6	
Mixed type	10	17	
Cranial MRI (Normal)	11 (45.8%)	12 (23.5%)	0.051
First treatment			
ACTH	5	11	0.541
Vigabatrin	16	24	
Seizure Free			
1st year	9 (37.5%)	9 (17.6%)	0.060
2nd year	8 (33.3%)	5 (10.2%)	**0.015**
3rd year	14 (58.3%)	7 (14.9%)	**0.001**
4th year	17 (70.8%)	11 (23.4%)	**0.001**
5th year	17 (70.8%)	15 (31.9%)	**0.002**

MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone.

TSC is an autosomal dominant inherited disease that affects multiple organs.[23] Due to TSC-specific MRI findings, patients can be divided into both structural and genetic categories.[24] Of the 6 TSC patients included in the genetic etiology group in the current study, 5 had cortical tubers. These five patients can also be classified in a structural subcategory due to genetic disease, as in the study by Peng et al.[17]

Spasms may be flexor, extensor, or mixed axial jerks, and crying or screaming attacks may be seen before or after. The spasms often occur in a rapid sequence and commonly occur just before sleep or upon waking. In the most severe ictal phenotypes, spasms may also be noticed during sleep. Deviation in the eyes may occur during attacks, and cardiac and respiratory involvement may occur.[4,7] Flexor spasm was determined to be present in 56% of the current study patients, extensor spasm in 8%, and mixed-type spasms in the remaining patients.

Hypsarrhythmia, first described by Gibbs in 1953, is a chaotic interictal pattern in which normal background rhythm elements are not observed, involving a diffuse, irregular, high-voltage multifocal spike and multiple spike activity discharges.[25] Hypsarrhythmia with increased interhemispheric synchrony, asymmetric hypsarrhythmia, hypsarrhythmia with abnormal focal focus, hypsarrhythmia with generalized, focal, or localized voltage attenuations, and hypsarrhythmia including bilateral asynchronous slow activity with high voltage are considered modified hypsarrhythmia.[26] Of the patients in the current study, 56% had signs of modified hypsarrhythmia.

MRI is recommended for all patients to clarify the etiology of WS. Early imaging is essential for etiological differential diagnosis.[27] In addition, if the patient does not respond to treatment or does not follow the expected course associated with the etiological diagnosis and there is clinical deterioration, MRI repetition is recommended. In infants with incomplete myelination, some abnormalities, such as focal cortical dysplasia, may be overlooked.[28] In a study by Aydinli et al. in 1998, the findings of 14 of 78 children who underwent MRI were normal.[29] Brain MRIs were performed on all patients included in the current study, and the MRI findings of 24 patients (32%) were normal. No correlation was found between MRI findings and prognosis (p=0.051) (Table 5). It was thought that this might be due to the small number of patients.

Data on the treatment of infantile spasms are limited, as most studies are retrospective or small prospective studies. ACTH, corticosteroids, and VGB are the main recommended drugs in the treatment.[30,31]

While VGB is the first choice in patients with tuberous sclerosis, hormonal therapy is the first treatment option for other patients.[32] In the current study, 41 (54.7%) of the patients were started with VGB, and 19 (25.3%) with ACTH anti-epileptic as the first option.

One of the most well-known side effects of VGB is visual field defects[33], which manifests as visual field loss in 34% of children treated with VGB.[34] Visual field test follow-up is required at regular intervals before and after treatment. In a study conducted in 2014, retinal toxicity was detected in 21% of 146 patients using VGB.[35] Since a visual field test was not performed in our center, a VEP examination was performed on the patients. An abnormal finding was detected in the VEP test in 12% of the patients. VGB use for more than 6 months is thought to increase retinal toxicity.[35] In the current study, abnormality in VEP examination was observed in the median 1st year. At the end of 5 years of follow-up, there was no clinical vision loss in any patient.

In line with the literature, 8 of the 19 patients (42.1%) who underwent ACTH treatment achieved complete seizure control in the 5th year.[32]

In the current study, VGB was identified as the most effective anti-epileptic drug for seizure control, aside from ACTH therapy. This finding has been attributed to the initiation of treatment tailored to the underlying etiology.

While ketogenic diet therapy (KDT) is the first treatment option for GLUT-1 deficiency, it is also one of the alternative treatment methods that can be used in nonketotic hyperglycinemia (NKH) and drug-resistant epilepsy, and there have been reports that it is effective in infantile spasm.[36–39] The most effective treatment method in the current study was seen to be KDT in a total of 7 patients, one of whom was NKH.

The long-term prognosis of WS is poor, and prognostic outcomes and data are still limited. Etiology is recognized as the most important prognostic factor.[40] Generally, the prognosis is better in patients of unknown etiology than in patients of known etiology.[41,42] Similarly, the prognosis was found to be poor in patients with structural etiology and good in patients with unknown etiology. The developmental delay occurs in the majority of patients with infantile spasms, and the rate of complete remission is generally low.[40,43] In a study conducted by Güveli et al. 8 of 109 patients had complete remission.[44] This rate was 15% in a study by Yuskaitis et al.[22] and 28% in a study by Camfield et al.[45] In the current study, complete remission was obtained in 7 (9.3%) patients. It was thought that this difference may be related to the underlying etiology. Early initiation of treatment and good treatment response in WS is also known to affect the prognosis positively.[46] In the current study, it was seen that patients who were seizure-free in year 2 and later had better neuromotor development (Table 5). Mortality in WS ranges from 3-30%.[47–49] In the current study, the mortality rate was 5.4%, similar to the literature.

In conclusion, although the underlying etiology is the most important determinant in the long-term prognosis of WS, early and complete seizure control is just as important. Therefore, etiological diagnosis and treatment are necessary.

Ethical approval

This study has been approved by the Non-Pharmaceutical Clinical Research Ethics Committee of Dr. Behçet Uz Children's Health and Diseases Training and Research Hospital (approval date 26.05.2021, number E-13399118-799).

Author contribution

Study conception and design: YG, PK, and SP; data collection: YG, MY, and HHK; analysis and interpretation of results: İBPİ and ÜY; draft manuscript preparation: YG, AÜ and ÜY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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