RESEARCH ARTICLE

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# The Prognostic Evaluation of West Syndrome Patients: A Retrospective Observational Study

**ABSTRACT**
**Objective:** To determine neurodevelopmental and seizure prognoses in our patients with West syndrome receiving adrenocorticotropic hormone (ACTH) therapy, and to identify the factors affecting these.
**Methods:** We determined the demographic factors, previous seizure histories, ACTH use and drug response times, and etiological reasons of 34 patients diagnosed with West syndrome in our clinic at 3-24 months old and receiving ACTH therapy. We also investigated their neurological development and its effect on seizure prognosis.
**Results:** We found a significant relationship between patients experiencing seizures before diagnosis and subsequent seizure prognosis. We also defined a later response to ACTH and poorer neurodevelopment and seizure prognoses in patients with symptomatic etiologies. Global developmental delay was identified in 76% of all cases, and seizures persisted despite antiepileptic drugs in 62%.
**Conclusions:** Symptomatic etiological factors in West syndrome adversely affect the neurodevelopmental process and subsequent seizure prognosis.

**Keywords:** West Syndrome, ACTH Therapy, Spasm, Neurodevelopmental Delay, Prognosis

# West Sendromlu Hastaların Prognostik Değerlendirilmesi: Retrospektif Gözlemsel Çalışma

**ÖZET**
**Amaç:** ACTH tedavisi alan West sendromlu hastalarımızın ileri dönemdeki nörogelişimsel prognozu ve nöbet prognozunun saptanması ve bunlara katkı sunan faktörlerin belirlenmesidir.
**Gereç ve Yöntem:** Kliniğimizde 3-24.aylarında West sendromu tanısı alarak ACTH tedavisi uygulanan 34 hastanın demografik faktörleri, nöbet şekilleri, öncesindeki nöbet öyküleri, ACTH kullanımı ve yanıt süreleri, etyolojik faktörlerini belirledik. Bunların nörolojik gelişim ve nöbet prognozuna etkisini araştırdık.
**Bulgular:** Hastaların tanı öncesinde nöbeti olmasının ilerideki nöbet prognozu ile ilişkisini anlamlı bulduk. Ayrıca semptomatik etyolojili hastalarda ACTH yanıtını daha geç; nörogelişim ve nöbet prognozunu ise daha kötü saptadık. Tüm hastaların %76' sında global gelişme geriliği, % 62'sinde antiepileptik ilaclara rağmen devam eden nöbetler belirledik.
**Sonuç:** West sendromunda semptomatik etyolojik faktörler nörogelişimsel süreci ve ileriki dönemdeki nöbet prognozunu olumsuz etkilemektedir.

**Anahtar Kelimeler:** West Sendromu, ACTH Tedavisi, Spazm, Nörogelişimsel Gerilik, Prognoz

## INTRODUCTION

West syndrome (WS) is the most common infantile devastating epileptic encephalopathy, with an incidence of 3-4.5/100,000. It is characterized by hypsarrhythmia on electroencephalograms (EEG), spasm seizures, and developmental arrest or delay (1,2). Epilepsy is difficult to treat due to various factors, including late recognition of spasms by both parents and physicians, and weak response to antiepileptic drugs. Although neurodevelopmental prognosis in children with WS can range from normal to severe neuromotor retardation, prognosis is generally poor (3-5). Treatment of spasms in the early period has been linked to good prognosis (6). The purpose of this study was to determine prognoses concerning subsequent neurodevelopment and persistence of seizures in our patients with West syndrome and the factors affecting these.

## MATERIAL AND METHODS

Thirty-four patients with WS diagnosed at 3-24 months in 2015-2018 in our university hospital's pediatric neurology clinic and receiving adrenocorticotropic hormone (ACTH) therapy were investigated retrospectively. WS was diagnosed in patients with clinical developmental arrest, spasm seizures, and hypsarrhythmia at EEG examination (1,2). Patients with inadequate attendance for clinical controls or exhibiting spasm but with no hypsarrhythmia determined at EEG were excluded from the study. Our patients were followed-up for a mean two years. Approval for the study was granted by our medical faculty ethical committee (No. 2020/138).

Patient age, sex, and age at diagnosis were determined. Patients were divided based on type of seizure, those with spasm and those with other seizure types. Patients with histories of seizure before WS were identified.

Complete blood count, blood biochemistry, lactate, pyruvate, ammonia, serum amino acids, urine organic acids, free and total carnitine analysis, plasma acylcarnitine analysis, uric acid, and biotinidase activity were investigated to determine etiology in all cases. Various genetic examinations were performed as required in case of dysmorphic findings and other data (chromosome analysis, CGH array, single-gene sequencing, etc.). Whole exome sequencing/whole genome analysis could not be performed due to unavailability. EEG examinations were carried out before and after ACTH therapy. Patients were classified at cryptogenic or symptomatic, depending on their etiology. Cryptogenic cases were defined as those with no previous history of convulsion, exhibiting normal development, with normal neuroimaging, and with no underlying disease. Patients with previous seizures, abnormal neurological development, with anomalies detected at neuroimaging, or with abnormality detected at other examinations were defined as symptomatic. Patients diagnosed with WS due to diagnosis of tuberous sclerosis were also excluded.

Our unit's standard ACTH (tetracosactide) therapy protocol was applied intramuscularly in the form of 1 mg for patients weighing >10 kg and 0.5 mg for those weighing <10 kg administered three times weekly in the first two weeks, twice weekly in the subsequent two weeks, and once weekly in the following four weeks. Patients were assessed in terms of ACTH response at the end of the first and second weeks and the first and second months. Times elapsing to reactions to ACTH were also determined. At the end of ACTH therapy, types of response were divided into four categories – patients exhibiting complete response (patients whose spasms disappeared and whose hypsarrhythmia patterns at EEG resolved with ACTH therapy alone), those exhibiting partial response (spasms decreasing by more than 50% with additional drug requirements), those with no response to ACTH, and patients with recurrence of spasms one month after ACTH therapy. All patients started on ACTH therapy were also given pyridoxine from the outset.

Seizure prognosis was assessed at one year. Patents were divided into four groups – seizure-free without medication (not using any antiepileptic drug (AED)), seizure-free with medication (using AEDs and without seizures), partial control (fewer than two seizures a month with AEDs), and uncontrolled (patients with refractory seizures).

Neurological prognosis was assessed after one year using Denver II developmental tests and clinical examinations (7). Patients were divided into three groups - normal neurological development, isolated speech delay (delay in a single area), and global developmental delay (GDD).

Age, sex, age at diagnosis, time elapsed between diagnosis and spasms, presence of seizure prior to spasms, type of seizure, effects of etiology of seizure prognosis and neurological prognosis, and type of response to ACTH were determined.

**Statistical Analysis:** The general characteristics of the participants were summarized using descriptive statistics. Continuous variables were calculated as mean ± standard deviation and median (range). Categorical variables were expressed as frequency (n) and percentages (%). Categorical variables were analyzed using Fisher's exact test. The Wallis and Mann Whitney U tests were applied to compare continuous variables between groups due to non-normality of distribution. Spearman's correlation coefficient was calculated to assess correlations between continuous variables. Significance was set at $p<0.05$, and all analyses were performed on Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA) software.

**RESULTS**

The patients consisted of 15 girls and 19 boys. Median age at start of treatment was nine months (2-36). The mean time elapsing to response to ACTH therapy was 12 days. Treatment lasted between two and eight weeks, depending on the response (Table 1).

**Table 1.** Descriptive Statistics

| | |
|---|---|
| ***Age at onset (months)*** | |
| Mean ± SD | 14.03 ± 11.26 |
| Median (range) | 9.0 (2-36) |
| ***Length of follow-up (years)*** | |
| Mean ± SD | 1.92 ± 1.58 |
| Median (range) | 2 (0.2-9) |
| ***Presence of seizure before infantile spasm n(%)*** | 15 (44.1) |
| ***Seizure types n(%)*** | |
| Spasm | 21 (61.8) |
| Generalized tonic seizure | 3 (8.8) |
| Multiple seizure types | 10 (29.4) |
| ***Cryptogenic/symptomatic n(%)*** | |
| Cryptogenic | 10 (29.4) |
| Symptomatic | 24 (70.6) |
| ***Response to treatment(days)*** | |
| Mean ± SD | 11.70 ± 6.51 |
| Median (range) | 12 (3-28) |
| ***Length of treatment (weeks)*** | |
| Mean ± SD | 5.5 ± 2.11 |
| Median (range) | 4 (2-8) |
| ***Etiology n(%)*** | |
| Unknown | 10 (29.4) |
| Prenatal | 11 (32.3) |
| Perinatal | 8(23.5) |
| Postnatal | 5(14.7) |

Treatment was discontinued at the end of two weeks in two patients with no response. Twenty patients exhibited complete response to ACTH therapy, eight exhibited partial response, and two exhibited no response, while recurrence was observed in four. Time between diagnosis of WS and onset of spasms ranged between two and 90 days. No relationships were determined between type of response to ACTH therapy and age, sex, age at diagnosis, time between diagnosis and spasms, time to response to ACTH therapy, or type of response to ACTH. These parameters exhibited no correlation with prognosis (Table 2).

**Table 2.** Parameters compared in terms of responses

| **Time(days)** | **Recurrence(n=4).** | **Partial (n=8)** | **Full(n=20)** | **Absent(n=2)** | **p** |
|---|---|---|---|---|---|
| *Diagnosis time* | 8 (3-12) | 12 (5-36) | 8 (4-36) | 19 (2-36) | 0.596 |
| *Lag time* | 44 (3-60) | 30 (7-90) | 14 (2-90) | 52 (14-90) | 0.354 |
| *Day of response* | 7 (6-10) | 14 (7-28) | 14(3-28) | | 0.202 |

Data are expressed as median (range). The Kruskal-Wallis test was performed.

Twenty-one patients presented with spasm only, three with generalized tonic seizure, and 10 with multiple seizures. Fifteen (44%) patients had seizures prior to spasms. No relationship was observed between presence of preceding seizure and type of response to ACTH, duration of response, and neurological prognosis. However, it was correlated with seizure prognosis (p=0.04). No correlation was also observed between type of seizure and type of response to ACTH, duration of response, neurological prognosis, and seizure prognosis.

Ten patients were cryptogenic, and 24 were symptomatic. Later response to ACTH was determined in the symptomatic group (p=0.04). Seizure prognosis (p=0.01) and neurological prognosis (p<0.01) were also markedly worse in this group. Neurodevelopmental delay was also more severe in the symptomatic group. Twenty-three of the 24 symptomatic patients exhibited moderate or severe developmental delay. However, neurodevelopmental delay was not observed in the cryptogenic group. No relationship was determined between type of response and etiology (Table 3).

Underlying etiological diagnoses in the 24 patients (70.5%) were Dandy-Walker in one, genetic syndromes (Kleefstra, Down, and Aicardi) in three, cortical dysplasia in four, congenital metabolic disease in two, meningomyelocele in one, perinatal hypoxia in eight, and postnatal events in five. The remaining 10 patients (29.5%) were in the cryptogenic group.

**Table 3.** Response and prognosis by etiology

| Category | Cryptogenic (n=10) | Symptomatic (n=24) | p |
|---|---|---|---|
| ***Response type*** | | | 0.063 |
| Recurrence | 1 (10.0) | 3 (12.5) | |
| Partial | 0 (0) | 8 (33.3) | |
| Full | 9 (90.0) | 11 (45.8) | |
| Absent | 0 (0) | 2 (8.3) | |
| ***Day of response*** | 7.0 (3-14 | 14(5-28) | **0.040** |
| ***Neurodev prognosis*** | | | **<0.001** |
| Normal | 4 (40.0) | 1 (4.2) | |
| Speech delay | 3 (30.0) | 0 (0) | |
| Mild neuromotor retardation | 3 (30.0) | 3 (12.5) | |
| Moderate neuromotor retardation | 0 (0) | 7 (29.2) | |
| Severe neuromotor retardation | 0 (0) | 13 (54.2) | |
| ***Seizure prognosis*** | | | **0.001** |
| Seizure-free without medication | 3 (30.0) | 0 (0) | |
| Seizure-free with medication | 6 (60.0) | 4 (16.7) | |
| Controlled seizure with medication | 0 (0) | 6 (25.0) | |
| Partially controlled seizure | 0 (0) | 1 (4.2) | |
| No control | 1 (10.0) | 13 (54.1) | |

Data are expressed as n(%) and median (range). The Mann–Whitney U test and Fisher's exact test were applied, and p values < 0.05 were significant

In terms of seizure prognosis, three patients were seizure-free without medication, 10 were seizure-free with medication, six were under control with medication, one was under partial control, and 14 were uncontrolled. Generally, prospective prognosis was poorer in WS. The number of seizure-free patients with or without medication was only 13 (38%) (Table 4). A single AED had been used in addition to ACTH by 12 patients, two AEDs by two, and multiple AEDs by 17. The most frequently used single AED was phenobarbital, employed in five patients, followed by vigabatrin in four, and valproic acid in three. Other additionally employed multiple AEDS included levetiracetam, clobazam, and sultiame.

No association was observed between these and seizure prognosis or neurological development. When patients were divided in terms of neurological prognosis, normal neurological development was present in five (15%), isolated speech delay in three (9%), and GDD in 26 (76%). Delay in more than three developmental areas was present in 13 patients with global developmental delay.

Our patients generally exhibited more than one side-effect due to ACTH use, the most common being irritability, weight gain, and infection. No statistical comparison was possible due to the retrospective nature of the data.

**Table 4.** Response and prognosis by presence of seizure before infantile spasm

| Seizure history | No (n=19) | Yes (n=15) | p |
|---|---|---|---|
| ***Response type*** | | | 0.154 |
| Recurrence | 2 (10.5) | 2 (13.3) | |
| Partial | 3 (15.8) | 5 (33.3) | |
| Full | 14 (73.7) | 6 (40) | |
| Absent | 0 (0) | 2 (13.3) | |
| ***Day of response*** | 10.0 (3-28) | 14(6-28) | **0.363** |
| ***Neurological Prognosis*** | | | **0.063** |
| Normal | 4 (21.1) | 1 (6.7) | |
| Speech delay | 3 (15.8) | 0 (0) | |
| Mild neuromotor retardation | 5 (26.3) | 1 (6.7) | |
| Moderate neuromotor retardation | 3 (15.8) | 4 (26.7) | |
| Severe neuromotor retardation | 4 (21.1) | 9 (60.0) | |
| ***Seizure Prognosis*** | | | **0.042** |
| Seizure-free without medication | 3 (15.8) | 0 (0) | |
| Seizure-free with medication | 6 (31.6) | 4 (26.7) | |
| Controlled seizure with medication | 5 (26.3) | 1 (6.7) | |
| Partially controlled seizure | 1 (5.3) | 0 (0) | |
| No control | 4 (21.1) | 10 (66.7) | |

Data are expressed as n(%) and median (range). The Mann–Whitney U test and Fisher's exact test were applied, and p values < 0.05 were considered significant.

**DISCUSSION**

The most important aim in the treatment of infantile spasm is to achieve good cognitive development. Unfortunately, however, neurological development is significantly affected in a large proportion of patients, depending on the etiology (8). The present study identified factors associated with neurodevelopmental and subsequent seizure prognosis in patients diagnosed with infantile spasm receiving ACTH. The male:female ratio in this study was 56/44, a figure compatible with the previous literature (9). Consistent with the present research, many previous studies have found no effect of gender on prognosis (6,10,11). There are also studies suggesting that male gender leads to poorer prognosis (12). Mean age at diagnosis was nine months. WS emerges in infancy, peaking between four and 10 months (8). We attribute the higher value in the present study compared to previous research to late recognition of the disease by both physicians and families due to low awareness concerning it, particularly in developing countries (5).

Analysis of responses to ACTH therapy revealed that the time elapsing between onset and diagnosis of spasms ranged between two and 90 days. Times ranging between 25 and 45 days have been reported in the previous literature (13). The pronounced difference between these figures and our findings may be due to our patient population being from various different provinces since ours is the only pediatric neurology center in the Western Black Sea region of Turkey. The mean response time to ACTH therapy was 12 days, with differing figures being reported depending on patient evaluation times in previous studies (14). Fifty-seven percent (20 patients) of our patients exhibited complete response to ACTH therapy. While figures consistent with those of the present study have been reported, rates as high as 76% have also been observed (15,16). No correlation was observed in the present study between time elapsing between onset and diagnosis of spasms and type of response to ACTH. Times between onset and treatment in the literature have generally been compared with neurodevelopmental prognosis, and a time less than four weeks has been linked to better neurological prognosis (17). A longer period has been associated with poor neurological development (14,18). As in the present research, this period has been associated with prognosis in some studies (10).

Seizure was present before spasms in 44% (15 patients) of patients. Previous seizure was also associated with subsequent seizure prognosis ($p=0.04$). In contrast to the previous literature, we observed no relationship between neurological prognosis and seizures prior to WS. However, several studies have reported that the presence of seizures before WS is associated with poor neurodevelopmental prognosis and also seizure prognosis (6,10,18).

Etiology has been identified as the most important factor affecting prognosis (14). Under the current classification, known etiology is described as symptomatic, and unknown etiology as cryptogenic (19). In the present study, the etiology was cryptogenic in 29% of cases and symptomatic in 71%. The proportion of WS cases classified as symptomatic has gradually risen with the use of improved metabolic and genetic neuroimaging techniques. Underlying disorder has been reported in approximately 60% of surviving patients and 90% of autopsy cases (20,21). Prenatal causes such as central nervous system malformations, intrauterine events, tuberosclerous complex (TSC), metabolic disorders, or genetic syndromes are present in approximately 50% of cases. Hypoxic-ischemic encephalopathy is one of the neonatal causes, while postnatal causes include trauma, infection, and rarely tumors (4). TSC is an important cause of WS (22). Patients with TSC were not included in the present study. Our patients' diagnoses were prenatal in 11 cases, perinatal in eight, postnatal in five, and unknown in 10. Consistent with previous research, the rate of hypoxia-related etiology in the present study was 24%. Rates between 6% and 69% have been reported in the literature (11-12,23-25).

Later responses to ACTH were observed in our symptomatic patient group ($p=0.04$), and subsequent seizure prognosis and neurodevelopmental prognosis were both poorer ($p<0.01$). We encountered no data in the literature concerning later responses to ACTH in symptomatic groups. Symptomatic etiology is known to worsen subsequent seizure prognosis and neurodevelopmental prognosis (10,26,27).

Eighty percent of the cases in the cryptogenic group with normal development prior to onset of spasm seizures also exhibited almost normal neurological development in the subsequent period (14). All three of our seizure-free patients, and four of the five with normal neurological development, were in the cryptogenic group. Close to normal development may be observed in 20% of patients in the symptomatic group (9,14,28). Hypoglycemia was determined in the etiology of our sole patient with normal neurological development and controlled seizures in the symptomatic group. Etiological factors exhibiting good prognosis with symptomatic etiology in previous studies include neonatal hypoglycemia, Down syndrome, stroke, periventricular leukomalacia, and neurofibromatosis (14).

Generally, and irrespective of etiology, 76% of all our patients had poor neurological development, and seizures other than spams were present in the subsequent period in 21 patients. Riikonen showed similar rates in several studies in a review article from 2020 (14). Despite advances

in treatment, WS still has a poor reputation from that perspective.

The limitations of this study include its retrospective nature and the low patient numbers. ACTH was used as the first-choice treatment in all our patients. Medications such as vigabatrin, phenobarbital, valproic acid, levetiracetam, clobazam, and sultiame were employed in cases with insufficient responses to ACTH. However, these data could not be subjected to statistical comparison due to our low patient numbers. Vigabatrin is the most commonly used agent in the treatment of tuberous sclerosis-related WS, and the second most common in WS associated with other etiological factors (2,8). However, despite being an effective option, vigabatrin is not frequently used in our clinic since it is not produced in Turkey, and is difficult to obtain. The most common side-effects of ACTH in our patients were irritability, weight gain, and infection, and the majority exhibited more than one symptom. Since data on this subject were insufficient in some patients, it was not subjected to statistical analysis.

**CONCLUSIONS**

The presence of seizure before diagnosis of WS and symptomatic etiological factors were found to be related to unfavorable prognosis. Consistent with previous studies, response to ACTH therapy was achieved later in WS patients with symptomatic etiologies. The prevention of diseases such and infection, which occupy an important place in the etiology, the early diagnosis of treatable metabolic diseases, and prenatal counseling management in patients at genetic are at least as important as treatment. Forms of treatment supported by new studies are needed for a promising diagnosis in WS.

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