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The evaluation of the neurocognitive development of the symptomatic West Syndrome patients

Semptomatik West Sendromu olan hastaların nörokognitif gelişimlerinin değerlendirilmesi

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ABSTRACT

Aim: Our study was aimed to determine both demographic and clinical data of patients with symptomatic West Syndrome (WS) and to monitor their neurocognitive development with Bayley Scales of Infant and Toddler Development Screening Test, third edition (Bayley-III) test.

Materials and Methods: Fourteen symptomatic WS patients were included in our study. Clinical and demographic data, electroencephalogram (EEG) findings, treatment response, Bayley III developmental test results were recorded before starting the treatment (T0) and in the 12th months of the treatment (T1 and T12).

Results: Patients had a significant increase in Bayley-III test scores in all areas at the end of one year (**p <0.05**). As the patients' EEGs improved, a statistically significant increase was observed in Bayley-III test scores in all areas (p <0.05). However, when the correlation between seizure control and the Bayley-III test scores were evaluated, there was an improvement only in the language area (p< 0,05); but there was no statistically significant difference in other brain areas (p> 0.05).

Conclusion: It has been shown that the neurocognitive level gradually improves even in symptomatic type WS with effective treatment during the follow-up of the disease or with the improvement of the EEG findings and seizure control.

Keywords: West syndrome, bayley III test, EEG, treatment, neurodevelopment.

ÖZ

Amaç: *Çalışmamız semptomatik West Sendromu tanısı olan hastaların hem demografik hem de klinik profillerinin belirlenmesini ve nörokognitif gelişimlerinin Bayley III gelişim testi ile takip edilmesini amaçladı.*

Gereç ve Yöntem: *14 semptomatik West Sendromu tanısı olan hasta çalışmaya dahil edildi. Klinik ve demografik verileri, elektroensefelogram (EEG) bulguları, tedavi yanıtları, Bayley III gelişimsel test sonuçları tedaviye başlamadan önce (T0) ve 12.ayda (T12) değerlendirildi.*

Bulgular: *Hastaların Bayley III test skorlarında bir yılın sonunda anlamlı bir artış gösterildi (p<0,05). Hastaların EEG'leri düzeldiği zaman Bayley III test sonuçlarında bütün alanlarda anlamlı bir değişim olduğu görüldü (p<0,05). Ancak nöbet kontrolü ve Bayley III test skorları değerlendirildiğinde sadece dil alanında gelişme olduğu görüldü (p<0,05); ancak diğer alanlarda anlamlı bir değişim görülmedi (p>0,05).*

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Sonuç: *Uygun tedavi ve nöbet kontrolü ile nörokognitif düzeyin semptomatik west sendromu olan hastalarda bile giderek gelişebildiği gösterildi.*

Anahtar Sözcükler: *West sendromu, bayley III test, EEG, tedavi, nörogelişim.*

INTRODUCTION

West Syndrome (WS) is the most common reason for the epileptic encephalopathy of infants and it was described in 1841 firstly by Dr. William West. The incidence is reported as 2.5-6/10000. Diagnosis of WS is defined as seizures in the form of infantile spasm (IS), hypsarrhythmia pattern on electroencephalography (EEG), and neurodevelopmental delay (1). IS attacks are sudden symmetrical flexion or contraction in the arms, extremities and neck. If there is an underlying etiological cause (such as prenatal, natal, postnatal reasons, hypoxic-ischemic encephalopathy, metabolic or cortical anomalies) it is called as a symptomatic type; if there is an underlying genetic cause it's called as a genetic type. However, an underlying cause cannot be found and if magnetic resonance imaging (MRI) is normal, it is defined as cryptogenic type WS (2, 3). If the seizures started before 4 months of age or there are other seizure types before IS attacks and if there is an underlying symptomatic etiology, the prognosis is poor. However, if it is the cryptogenic type, the prognosis is better (4). In our study, 14 patients diagnosed with WS were evaluated with the Bayley Scales of Infant and Toddler Development Screening Test, third edition (Bayley-III). Our study was aimed to examine both demographic and clinical data of patients diagnosed with symptomatic WS and to monitor their neurocognitive development with Bayley-III tests. It is crucial to control of the seizures as soon as and follow-up a neurocognitive prognosis of the patients who were diagnosed with WS.

MATERIALS and METHODS

This was a retrospective study. The etiological diagnoses of the patients were evaluated with gender, consanguinity, a history of birth, treatments and Bayley-III developmental tests were performed before starting treatment (T0) and in the 12^{th} months (T12). Treatment responses and EEG controls were recorded at the same time. The Bayley-III tests were performed by the same development specialist. Fourteen patients diagnosed with symptomatic WS between September 2016 and August 2020 from Mersin University Pediatric Neurology Outpatient Clinic were included in the study. Ethics committee approval was taken from Mersin University.

Inclusion criteria; It was determined that the ages between 6 and 18 months, diagnosis of WS according to the "International League Against Epilepsy" (ILAE) classification, presence of hypsarrhythmia or modified hypsarrhythmia in EEG, presence of an underlying cause in the etiology, deterioration in neuromotor development and presence of complete patient file data.

Exclusion criteria; It was determined that the ages less than 6 months-older than 18 months, being not supporting the diagnosis of WS clinically and with EEG, being in the cryptogenic WS group, and lacking of the patient data.

The neurocognitive development of children aged 1- 42 months is most commonly assessed by the Bayley-III test. The cognitive, language and motor developments are assessed in this test. Language area is defined by receptive and expressive language skills; the motor area is subdivided into fine and gross motor. The scores for the five subdivided are converted into composite scores. Normal development (≥85) within 1 SD of the mean, mild delay in any of the three subscale -1 to -2 SD (≥70 and <85), moderate developmental delay is among with -2 to -3 SD (≥55 and <70), and severe developmental delay is above than -3 SD (< 55) (5, 6).

Statistical Analyses

The SPSS (Statistical Package for the Social Sciences) 23.0 software has been utilized for statistical analyses. The Shapiro-Wilk test was applied to evaluate the suitability of normal distribution. Chi-square and Fisher exact tests were used for comparison of categorical data. Comparisons for continuous variables were carried out by the Mann-Whitney test or independent sample t test according to normality assumption. Continuous data was summarized as mean [standard deviation] or median (Percentiles) in dependent to distribution assumption. Categorical data was evaluated as count and percentage. P value of <0.05 was considered to be significant.

RESULTS

14 patients were evaluated in the study. The demographic and clinical features of the patients were shown in Table-1. Bayley III descriptive test results at the end of one year were shown in the (Table-2).

There was a statistically significant increase in the Bayley-III test scores at the end of one year (T12) in all areas compared to the baseline period (T0) ($p < 0.005$) (Table-3).

As the patients' EEGs improved at the end of one year, a statistically significant increase was observed in Bayley-III test scores in all areas (**$p < 0.05$**) (Table-4).

However, when the correlation between seizure control and Bayley-III test scores was examined, it was seen that only the language area improved (**$p < 0.05$**); However, there was no statistically significant relation in other areas ($p > 0.05$) (Table-5).

Table-1. Demographic and clinical features of the patients.

	Number (n)	%
Gender (girl / boy)	10/4	71/78
Week of birth		
<28 Gw	2	14
28-32 Gw	2	14
>36 Gw	10	71
Postnatal history		
Hypoxia	3	21
Mechanical Ventilator	3	21
Intubated patients	6	42
Etiology		
Premature birth	4	28
Cortical defect	3	21
Hypoxic birth	2	14
Tuberous sclerosis	2	14
Down syndrome	1	7
Hypoglycemia	2	14
A history of seizures before the diagnosis		
Yes	10	71
No	4	19
Consanguinity		
Yes	5	35
No	9	65
First started treatment		
ACTH	12	85
Vigabatrin	2	14
Control EEG at the end of one year		
Normal	6	42
Focal epileptiform	3	21
Secondary generalized	3	21
Hypsarrhythmia	2	12
Seizure control after one year		
Seizure free	11	78
Have a seizure	3	21
Number of antiepileptic drug after one year		
Single treatment	6	42
One more treatment	8	57
Antiepileptic used		
Lev	4	28
Vgbt	2	21
Lev+Vgbt	5	35
Tpx+Lev	2	21
Lev+Clnz	1	7

Gw: gestational week, ACTH: corticotrophin, Lev: levetiracetam, Vgbt: vigabatrin, tpx: topiramate, clnz: clonazepam

Table-2. Bayley-III descriptive test results at the end of one year.

Patients	Etiology	Cognitive descriptive	Language descriptive	Motor Descriptive
1	PM	Ext low	Ext low	Ext low
2	TSC	Average	Average	Average
3	Cort defect	Ext low	Ext low	Ext low
4	Cort defect	Ext low	Ext low	Ext low
5	Down syndrome	Ext low	Ext low	Ext low
6	PM	Ext low	Ext low	Ext low
7	Hypoxia	Ext low	Ext low	Ext low
8	PM	Ext low	Ext low	Ext low
9	TSC	Average	Average	Average
10	Cort defect	Ext low	Ext low	Ext low
11	PM	Ext low	Border	Ext low
12	Hypoglycemia	Ext low	Ext low	Ext low
13	Hypoglycemia	Average	Average	Average
14	Hypoxia	Ext low	Ext low	Ext low

PM: premature, TSC: tuberous sclerosis, Cort defect: cortical defect, Ext low: extremely low

Table-3. Increase in Bayley-III test scores of patients at the end of one year and p value.

Bayley-III scores		T0	T12	P
		Mean±std	Mean±std	
Cognitive				
	Raw	8.43±7.61	23.86±14.64	**0.006***
	Scale	1.57±2.14	2.86±2.85	0.105
	Composito	57.86±10.69	64.29±14.26	0.105
Language (recept+exp)				
	Scale	4.64±7.43	7.43±6.43	0.120
	Composito	54.93±11.68	63.14±19.0	0.120
Receptive language				
	Raw	5.36±2.34	12.36±5.33	**0.001***
	Scale	2.29±2.64	4.29±3.60	0.076
Expressive language				
	Raw	2.93±1.44	10.14±5.70	**0.001***
	Scale	2.36±1.69	3.86±3.98	0.126
Motor (fine+gross)				
	Scale	4.07±3.85	6.07±7.31	0.227
	Composito	52.21±11.56	56.14±24.69	0.481
Fine motor				
	Raw	6.29±5.01	18.43±11.31	**0.001***
	Scale	1.50±1.87	3.29±4.23	0.088
Gross motor				
	Raw	13.86±6.09	28.14±15.30	**0.002***
	Scale	2.57±2.56	2.79±3.12	0.782

Table-4. The association between the EEG control and Bayley III test scores at the end of one year (T12).

T12- Bayley-III results		EEG control			p
Cognitive	**Hypsarrhythmia Med (Min-Maks)**	**Sec gen Med (Min-Maks)**	**Focal ep Med (Min-Maks)**	**Normal Med (Min-Maks)**	
Raw	12.5 (10-15)	9 (4-22)	25 (7-28)	38.5 (18-48)	0.064
Scale	1 (1-1)	1 (1-1)	1 (1-1)	6 (1-8)	**0.028***
Composite	55 (55-55)	55 (55-55)	55 (55-55)	80 (55-90)	**0.028***
Language (recept+exp)					
Scale	8 (5-11)	7 (5-10)	11 (9-15)	18 (11-22)	**0.032***
Composite	1.5 (1-2)	1 (1-1)	3 (1-7)	7 (3-12)	**0.030***
Receptive Language					
Raw	5.5 (5-6)	5 (4-7)	10 (8-10)	17 (6-20)	**0.042***
Scale	1 (1-1)	1 (1-1)	2 (1-13)	5.5 (2-9)	**0.042***
Expressive Language					
Raw	2.5 (2-3)	2 (2-2)	4 (3-10)	12 (5-21)	**0.017***
Scale	48.5 (47-50)	47 (47-47)	53 (50-71)	77 (56-103)	**0.017***
Motor (fine + gross)					
Scale	9 (7-11)	6 (4-15)	16 (6-20)	31.5 (19-36)	**0.025***
Composite	1 (1-1)	1 (1-1)	1 (1-1)	6.5 (1-12)	0.082
Fine motor	22.5 (18-27)	5 (4-26)	22 (15-43)	43,5 (24-50)	0.132
Raw	1(1-1)	1 (1-1)	1 (1-3)	4.5 (1-10)	0.170
Scale	2 (2-2)	2 (2-2)	2 (2-4)	11 (2-22)	0.139
Gross motor	46 (46-46)	46 (46-46)	46 (16-52)	73 (46-107)	0.156
Raw	22.5 (18-27)	5 (4-26)	22 (15-43)	43.5 (24-50)	0.132
Scale	1(1-1)	1 (1-1)	1 (1-3)	4.5 (1-10)	0.170

PSS: Personal social scale, GM: Gross motor, Lang: Language, FM: Fine motor, Sec gen: secondary generalized, Focal ep: focal epilepsy

Table-5: Correlation between seizure control with Bayley-III test scores at the end of one year.

T12- Bayley-III results	Seizure control		
Cognitive	**Yes Med (Min-Max)**	**No Med (Min-Max)**	**P**
Raw	10 (4-15)	25 (7-48)	0.051
Scale	1 (1-1)	1 (1-8)	0.173
Composite	55 (55-55)	55 (55-90)	0.173
Language (recept+exp)			
Scale	5 (5-11)	12 (7-22)	**0.050***
Composite	1 (1-2)	5 (1-12)	0.094
Receptive Language			
Raw	5 (4-6)	10 (5-20)	**0.023***
Scale	1 (1-1)	2 (1-13)	**0.050***
Expressive Language			
Raw	2 (2-3)	8 (2-21)	0.059
Scale	47 (47-50)	65 (47-103)	0.059
Motor (fine + gross)			
Scale	2 (2-2)	2 (2-22)	0.174
Composite	46 (46-46)	46 (16-107)	0.301
Fine motor			
Raw	7 (4-11)	20 (6-36)	0.051
Scale	1 (1-1)	1 (1-12)	0.242
Gross motor	46 (46-46)	46 (46-46)	46 (16-52)
Raw	18 (5-27)	26 (4-50)	0.243
Scale	1 (1-1)	1 (1-0)	0.174

* p<0,05, Chi-squere and Fisher exact, Mann whitney U test, Min: Minimum, Max: Maximum

DISCUSSION

WS is an extremely rare epileptic syndrome that usually progresses with neurodevelopmental destruction. Although the prognosis of the disease is stated to depend on various factors (such as cryptogenic/symptomatic type, degree of EEG abnormality, continuation of seizures, pre-existing seizures), the disease generally

causes a delay in neuromotor development (7, 8). Our patient group was completely symptomatic type WS, and 71% of patients had a history of seizures before the diagnosis. In our study, the neurocognitive development was evaluated at the beginning of the treatment (T0) and at the twelfth time (T12). As the patients' EEGs improved, a statistically significant increase was shown in Bayley-III test scores in all areas ($p < 0.05$). When the correlation between seizure control with the Bayley-III test scores were evaluated, there was an improvement in the language area ($p<0.05$; and there was no statistically significant relationship in other areas ($p> 0.05$).

WS is an epileptic encephalopathy of the infant that affects to the neurocognitive development. Nasiri et al. (9) stated in their study that the neurocognitive development of all WS patients (criptogenic and symptomatic type) was quite low; however, we couldn't show such a like difference due to our study group occur from only symptomatic WS. Widjaja et al. (10) similarly reported that the symptomatic type WS had a worse prognosis than the cryptogenic type. In our study, the included patient group was only symptomatic type and all patients' neurocognitive development was completely retarded at the baseline (T0).

The following-up of the EEG is very important in WS patients. In our study, all the patients had hypsarrhythmia at the beginning, but at the end of one year, only 12% of patients had hypsarrhythmia findings on the EEG, and 42% were normal, 21% were focal, and 21% were seconder generalized epileptiform discharges. Also, significant increase was found in the Bayley-III test scores as the EEG findings improved at the end of one year ($p < 0.005$). It was considered that the improvement of EEG findings depends on the rapid diagnosis and initiation of treatment and the correct follow-up in the maintenance treatment. In our study, ACTH was started at the treatment to all patients immediately excluding the two tuberous sclerosis patients. On the other hand, maintenance treatment was arranged according to the patient's clinical and treatment responses and EEG findings. It was observed that as the EEG findings of the patients improved, their neurocognitive developments were also faster.

Guzzettaa et al. (11) followed 21 patients for two years in their study and showed that the continuation of the background activity disorder or the presence of ictal or interictal findings in the EEG during the follow-up of the patients associated with the neurodevelopmental retardation. In our study, the neurological development of the patients at T0 and T12 was evaluated with Bayley-III tests. At the end of one year, there was a significant increase in Bayley-III test scores in all areas ($p < 0.005$). Spennera et al. (12) stated that the continuity of sleep shuttles on EEG was associated with good prognosis only in patients with cryptogenic type WS, but this situation was not similar in symptomatic type WS. However, although Bayley-III test scores increased, the final neurodevelopment results of the patients were considerably poor. It was estimated that this situation was depends on to the natural course of the disease, the underlying cause, and the duration of the seizure period before treatment was initiated. At the end of one year, the best neurodevelopmental outcome was obtained with tuberous sclerosis patients. It was considered that this situation arises as a result of rapid and good response to vigabatrin treatment after detailed skin examinations of every patient with suspected WS are performed and tuberos sclerosis is considered.

Lux et al. (13) also stated in their study that the long-term prognosis depends on the length of the diagnosis period and the starting time of the treatment from the time of diagnosis. In our patient group 71% of the patients had a history of seizures before the diagnosis.

In addition, 78% of the patients were followed up without seizures at the end of one year, and 42% were followed only with a single antiepileptic drug. When the seizure control at the end of one year, Bayley-III test score results were examined, it was found that there was only a significant improvement in the language area. The reason of this could be due to the symptomatic type of the patient group, the fact that 71% had seizures before the diagnosis, and also the insufficient number of patients. Pavone et al. (14) reported that the course of the disease varies according to the etiological causes, the presence of seizures before, the initiation of appropriate treatment, and the response of the treatment.

Gupta et al. (15) stated in their study that the neurocognitive development of patients diagnosed with WS was quite retarded, only 21% of them had normalized EEG with treatment, and the rest of them had severe EEG disorders. They attributed this to the difficulty of finding drugs such as ACTH and vigabatrin immediately. In our study, 41% of the patients' EEG returned to normal and 21% had focal abnormalities in the

EEG. It was considered that this situation was due to fast and appropriate treatment. Sharma et al. (16) stated that ACTH and vigabatrin should be started first in the WS patients, and other antiepileptic drugs such as topiramate, sodium valproate, or clobazam did not show a rapid effect and did not improve the EEG findings.

CONCLUSION

Our study evaluated of the WS patients which is quite rare and causes neurodevelopmental retardation in children, at the beginning of the disease and in the twelfth month using Bayley-III test. It has been shown that the neurocognitive level gradually improves even in symptomatic type WS with effective treatment applied in the follow-up of the disease or with the improvement of EEG findings. As a result, it was found that the development of symptomatic type WS patients was much lower than their peers. We believe that supporting the patients as soon as possible with rapid diagnosis and treatment, as well as supportive treatments such as physical therapy or special education, will be obtained further increase the development of patients.

Limitations

The number of the patients was not enough, and the diagnosis time was different from each other. Hence, this situation can create some differences in the content of the Bayley-III test. So, this may affect the scoring.

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