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Long-term outcomes in patients with West syndrome: An outpatient clinical study

Betül Tekin Güveli [a,*], Özlem Çokar [b], Nimet Dörtcan [c], Gülçin Benbir [d], Veysi Demirbilek [d], Ayşın Dervent [d,1]

[a] Bakirkoy Research and Training Hospital for Psychiatry, Neurology, Neurosurgery, Department of Neurology, Istanbul, Turkey
[b] Haseki Research and Training Hospital, Department of Neurology, Istanbul, Turkey
[c] Fatih Sultan Mehmet Research and Training Hospital, Department of Neurology, Istanbul, Turkey
[d] Istanbul University, Cerrahpasa Faculty of Medicine, Department of Neurology, Pediatric Neurology, Istanbul, Turkey

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ABSTRACT

Purpose: Nearly half of all patients with seizure onset in the first year of life suffer from West syndrome (WS). The prognosis of epilepsy and psychosocial outcomes in children with WS are variable. This study was performed to examine the factors influencing the outcome of this patient population.
Methods: A total of 109 patients with WS followed up regularly for at least 3 years were included in the study. Relevant clinical, laboratory, and imaging data were collected.
Results: The male/female ratio was 65/44 (59.6%/40.4%). The mean age at onset of infantile spasm (IS) was 6 ± 6 (1–36) months. With regard to neuro-developmental and social conditions during the final evaluation, 29.4% of the patients were socially dependent on caregivers, 61.8% needed assistance, and 8.8% were normal. Among the patients, 5.9% were free of epilepsy and antiepileptic drugs (AED) for at least 2 years, 49.0% had no seizures with AEDs, and 45.1% had uncontrollable seizures. Parameters with significant negative effects on the long-term outcomes included symptomatic etiology, presence of developmental retardation before the onset of IS, persistence of active epilepsy, and male gender.
Conclusion: In this study, 37 (33.9%) patients had severe consequences as a result of WS. The majority of the rest could cope with daily life with varying degrees of assistance. Eight percent of the patients had a normal development. These results draw attention to the two-thirds of patients with WS who have the chance of an acceptable quality of life (QoL) with early diagnosis and therapeutic measures.

1. Introduction

West syndrome (WS) is the most frequently occurring infantile epileptic encephalopathy with a yearly incidence of 2–4.5/10,000 and a prevalence of 1.5–2/10,000 at 10 years of age or older [1]. Approximately 50% of patients with seizure onset before 12 months of age, excluding the neonatal period, suffer from WS characterized by infantile spasm (IS), psychomotor arrest or retardation, and hypsarrhythmia on electroencephalograms (EEG) [2–4]. Epileptic spasms most often show a temporal relationship with hypsarrhythmia, which is the typical interictal EEG activity in WS. Both spasms and focal seizures in WS are frequently intractable to conventional antiepileptic drug (AED) treatment, and in such cases, either polypharmacy and/or steroids are applied to suppress epileptic phenomena, although this has only been partially successful. There have been relatively few reports regarding the long-term prognosis of epilepsy and its impact on the daily life of patients with WS [4,5]. Both the prognosis of epilepsy and cognitive outcomes of WS are related to the etiological characteristics of the syndrome, as cryptogenic WS (cWS) has a more favorable outcome than symptomatic WS (sWS) [6–9]. Normal or subnormal cognitive development has been reported in approximately 25% of adult patients with previous WS [5]. The prognostic consequences of WS have been causally related to various additional parameters, such as premorbid developmental status, age at onset of WS, time and type of management [10–13]. The present study was performed to examine the long-term consequences of epilepsy and the psychosocial impacts of WS in the patient population under long-term follow-up in our center.

* Corresponding author at: Bakirkoy Research and Training Hospital for Psychiatry, Neurology, Neurosurgery, Department of Neurology, Bakırköy, 34147 Istanbul, Turkey. Tel.: +90 532 7848273; fax: +90 212 5729595.
E-mail address: betultekin2013@gmail.com (B.T. Güveli).
[1] Retired.

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2. Methods

Data belonging to a total of 109 patients with WS recruited since 1991 and followed up for at least 3 years in our WS outpatient clinic were included in the study. Last controls were completed in 2013. Patients with lack of recent information were called back and reevaluated to collect the missing data. Diagnosis of WS was confirmed by interviews, clinical observations, and analyses of video-EEGs. Patients were examined at least once a year until 6–7 years of age; regular follow-ups were once in 1–3 years later, if epilepsy was stabilized by then. Almost all patients underwent cranial magnetic resonance imaging (cMRI) and laboratory tests, including biochemical screening and tests for inborn metabolic diseases. Etiologically, patients were grouped as sWS, cWS, or idiopathic WS (iWS) according to the proposed ILAE classification scheme [14]. According to the neuro-developmental and social conditions during the final evaluation, the patients were divided into three categories: Group A, the "normal living group", patients with normal or subnormal motor and intellectual outcomes with favorable social status; Group B, the "assisted living group", ambulatory patients receiving special academic and/or physical support to cope with social needs; Group C, the "dependent living group", patients with severe motor and/or mental impairment with solely supervised living. Those groups were determined based on our neurological evaluations, interviews with the parents and on consultation reports of child-psychiatrists. Patients were grouped according to the status of epilepsy as follows: Group in remission, no epilepsy or treatment for at least 2 years; Group under control, epilepsy under control for a minimum of 2 years with AED treatment; Group active, persistent seizures despite AED treatment. The cMRI findings were classified as normal, diffuse cortical and/or subcortical involvement, or unilateral cortical and/or subcortical involvement.

The following parameters were included in the statistical evaluation: the age of onset of spasms and partial seizures, gender, family history of seizures, presence of parental consanguinity, presence of developmental delay or neurological deficit prior to the onset of spasms, etiology, characteristics of cognitive and motor involvement during the active phase of WS and later follow-ups, response of epilepsy to treatment, and clinic status of epilepsy during follow-ups.

Continuous variables are expressed as means ± SD, and categorical variables are presented as frequencies and percentages. The chi-square test was used to compare the differences in categorical variables among the groups. SPSS 17.0 statistical software (SPSS, Chicago, IL, USA) was used for the statistical analysis. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

This study was approved by Ethics Committee of Cerrahpaşa Medical Faculty, University of Istanbul, Turkey.

3. Results

A total of 109 patients with WS were included in this study. The study population consisted of 65 male (59.6%) and 44 (40.4%) female with a mean follow-up duration of 8 years (3–16 years) (Table 1).

The number of patients as distributed to the groups with different neuro-developmental and social conditions was as follows: Group A, $n = 9$ (8.3%), Group B, $n = 63$ (57.8%), and Group C, $n = 30$ (27.5%). Seven deceased subjects were not included in these groups. Six patients (5.5%) free of epilepsy and AEDs were classified as the Group in remission. Epileptic seizures were under control by AEDs in 50 patients (45.9%, Group under control) and persisted despite AEDs in 46 (42.2%, Group active) (Table 2).

Table 1
Demographic and clinical features of the patients.

	$n = 109$[a]/%
Follow-up duration, years	8 (3–16)
Gender	65M/44F
Mean age at the last visit, years	9.5 ± 4 (3–19)
Age at onset of IS, months	6 ± 6 (1–36)
Type of IS	
Symmetrical	104/95.4
Asymmetrical	5/4.6
Patients with pre-spasm partial seizures	35/31.2
Patients with pre-spasm neuro-developmental involvement	79/72.5
Etiological groups	
Symptomatic	99/90.8
Hypoxic injury	44
CNS infections	9
Chromosomal anomaly	8
Cortical dysplasia	6
Cerebrovasculer diseases	4
Tuberosclerosis	3
Metabolic diseases	3
Others	22
Cryptogenic	9/8.3
Idiopathic	1/0.9
Patients with parental consanguinity	30/27.5
Patients having relatives with epilepsy and/or febrile seizures	17/15.6
Patients with inborn metabolic diseases	3/2.7
Cranial MRI results	
Normal	29/26.6
Diffuse cortical and/or subcortical involvement	57/52.3
Unilateral cortical and/or subcortical involvement	16/14.7
Others	2/1.8

IS: infantile spasm. CNS: central nervous system.
[a] Seven deceased patients were included.

Valproic acid (p53) (30–50 mg/kg/day), vigabatrin (p26) (50–100 mg/kg/day), and ACTH (p21) (0.5–1 mg/day) are the first-line drugs for WS (Table 3).

The number of females ($n = 7$) versus males ($n = 2$) in Group A was compared with the number of females ($n = 34$) versus males ($n = 59$) in groups B and C combined, and a statistically significant difference was found in favor of females. Females showed better long-term performance in neuro-developmental and social outcomes ($P = 0.04$).

Patients were divided into three groups according to the age at onset of IS: 0–3, 4–9, and ≥10 months. There were no correlations among prognostic variables, such as neuro-developmental and social performances and severity of epilepsy, among the types of IS, the age at onset of IS, and the presence or absence of neuro-developmental deficits before the onset of IS. Interestingly, the presence of partial seizures showed an inverse relationship with the age at onset of IS, as partial seizures were present before IS in 81.3%, 24.5%, and 21.2% of patients with spasm onset at ≥10, 4–9, and 0–3 months, respectively ($P < 0.001$) (Table 4).

Seventy of 74 (94.6%) patients with pre-IS neuro-developmental involvement and 23 of 28 (82.1%) patients with normal pre-IS development were present in Group C, and this was significant ($P = 0.03$).

The presence of pre-spasm focal seizures and the type of spasm did not show a significant relationship with clinical outcome with regard to the neuro-developmental and social performances of the patients. Of 93 patients in Groups B and C, 85 (91.3%) showed sWS.

Eighty-five of 92 patients (91.3%) with sWS were in Groups B and C, and only 7 (7.6%) were in Group A. One of nine patients in the cWS group and a single patient in the iWS groups were in Group A. Symptomatic etiology was significantly related to poor prognosis ($P = 0.01$).

The presence of active epilepsy was significantly related to the neuro-developmental and social performances of the patients. All

Table 2
Characteristics of epilepsy and neuro-developmental/social outcomes.

Neuro-developmental and social outcomes	Group A ($n=9$)	Group B ($n=63$)	Group C ($n=30$)	P
Follow-up period, months	128 ± 47 (48–180)	100 ± 46 (36–192)	90 ± 43 (36–180)	0.98
Gender (F/M)	7/2	22/41	12/18	**0.04**
Age at onset of IS	6.7 ± 5 (1–17)	6.4 ± 5 (1–30)	5.4 ± 6 (1–36)	0.73
Neuro-developmental deficit pre-IS				
Absent	5	19	4	**0.03**
Present	4	44	26	
Focal seizures pre-IS				
Present	8	41	20	0.35
Absent	1	22	10	
Type of IS				
Symmetric	9	58	13	0.19
Asymmetric	–	5	–	
Etiology				
Idiopathic	1	–	–	
Cryptogenic	1	7	1	**0.01**
Symptomatic	7	56	29	
Parental consanguinity				
Absent	8	49	19	0.19
Present	1	14	11	
Epilepsy/FS in relatives				
Absent	9	55	24	0.28
Present	–	8	6	
Response to AEDs				
Group in remission	2	3	1	**0.02**
Group under control	7	30	13	
Group active	–	30[a]	16[a]	

Group A: normal living group; Group B: assisted living group; Group C: dependent living group.
Group in remission: No AED, no seizures; Group under control: AED + no seizures; Group active: AED + seizures + IS: Infantile spasm; AED: Antiepileptic drug; FS: Febrile seizure.
If p value is <0.05, this is significant result.
[a] Patients with sWS.

patients in Group A were seizure-free, and two did not undergo AED treatment. The proportions of seizure-free patients were 33/63 (52.4%) in Group B and 14/30 (46.6%) in Group C ($P=0.02$). All 46 patients with active epilepsy were in the sWS group.

4. Discussion

Although WS is a major type of infantile epilepsy, there is a paucity of data regarding the prognostic consequences of this syndrome. Special efforts may be needed to closely follow-up patients after they grow out of childhood, or to be informed if death occurs in another hospital setting or at home. In many countries, there are insufficient institutions for chronically disabled patients and a lack of interdisciplinary and interinstitutional communication, which may exacerbate this issue. In the present study, we examined the long-term outcomes of our patients with WS and searched for early variables that may have an impact on their quality of life (QoL) later in life. Various studies have indicated that age at onset of epileptic spasms is related to poor prognosis in WS. In a group of patients with cWS, the onset of spasms during the first month of life was reported to be a factor indicating poor outcome, while that after age 4 months indicated a better outcome [8,15]. The age at onset of spasms in the present study did not seem to influence either the neuro-developmental outcome or the prognosis of epilepsy later in life. However, the presence of early focal seizures was shown to be positively related to late onset (i.e., ≥10 months) of spasms. This may be because epileptic seizures with marked motor manifestations are alarming for the parents, and spasms may go unnoticed or misdiagnosed during the early stages. Although this may be valid in some cases, the majority of the focal seizures prior to spasms had subtle clinical manifestations in these patients. Another question is whether focal seizures produce some competitive inhibitory effect on the development of epileptic spasms for a limited time during the early postnatal stage. Epileptic spasms can be related to focal lesions in the brain as well as to diffuse anatomical or functional disturbances [16]. However, the EEG correlates of these spasms, despite variable morphological characteristics, are almost always a generalized paroxysmal discharge, even in patients with hemihypsarrhythmia [17]. A delayed effect of generalized epilepsy on the onset of experimental focal seizures in some studies on adult rats with genetically determined deficiencies was reported previously [18,19]. Here, the situation was the opposite, suggesting that the focal firing can produce a delayed effect on the maturational processes including myelination, which are necessary for generalization of epileptic discharges.

In our study, boys had a slightly less ($P=0.04$) favorable course with regard to neuro-developmental and social performances compared with girls. A study on rat pups showed that sex hormones can affect epileptogenesis in the developing brain, and that the immature brain of males is more vulnerable to the insult than the female brain [20]. This may provide some support for the

Table 3
Treatment of WS.

	N:109	%
Valproic acid	53	48.6
Vigabatrin	26	23.9
ACTH	21	19.3
Phenobarbital	9	8.2

Table 4
Relationship between the age at onset of IS and the presence/absence of pre-IS focal seizures.

Age at onset of IS	Pre-IS focal seizures		P
	Present ($n=69$/%)	Absent ($n=33$/%)	
0–3 months ($n=33$)	26/78.8	7/21.2	
4–9 months ($n=53$)	40/75.5	13/24.5	
≥10 months ($n=16$)	3/18.8	13/81.3	<0.001

IS: infantile spasm.

male/female discrepancy in later QoL observed in the present study.

Neuro-developmental involvement prior to IS, a feature that mostly indicates the pre- or perinatal etiology, was a poor prognostic variable in the present study. Riikonen [4,5] reported that patients of WS with a favorable outcome had normal neuro-development before the onset of the spasms. Nearly all previous studies on this variable reported similar results [3,7,10,21–26]. The presence of parental consanguinity and epilepsy in near relatives showed no significant effect on prognosis in this study. The results of a study on a heterogeneous epileptic population including WS patients in Saudi Arabia where the consanguinity rate was 53% did not indicate this parameter as a major factor affecting the genetics of the study group [27]. A study on a heterogeneous group of children with progressive encephalopathy with autosomal recessive (AR) involvement, however, revealed an 11-fold increased risk in consanguineous Pakistani patients compared with a non-consanguineous Norwegian cohort [28]. Evidence suggests that although many genetic disorders may lead to WS in infants, AR disorders do not play a major role among the diverse etiologies. The presence of epilepsy within family members also had no effect on the outcome of our patients.

Epilepsy was stabilized, with or without AED treatment, in more than half (54.9%) of our patients at the latest visit. The remaining patients had intractable seizures. All patients with ongoing epilepsy at the latest visit had sWS. At the end of 5 years, the rate of epilepsy remission was 28% in a group of WS patients within a cohort with symptomatic epilepsies in a previous study, [29] whereas it was considerably higher (52%) in the present study.

Some aspects regarding the details of the clinical and EEG characteristics of epilepsy and the therapeutic and neuro-developmental outcome measures of our patient population will be discussed in later reports.

In this study, during the follow-up period, 37 of 109 (33.9%) patients (including those deceased) had developed severe consequences from WS. The majority of the remaining patients were able to cope with daily life with varying degrees of assistance. Eight percent of the patients had a normal QoL. The limitations of our study are that the data is retrospective and it does not include treatment of patients.

5. Conclusion

The results of the present study suggest that in patients with WS symptomatic etiology, the presence of focal seizures, neuro-developmental involvement before the onset of spasms, and poor response to AEDs are indicators of poor prognosis with future disability. Thus, early etiological diagnosis and treatment are required to minimize the effects later in life in these patients.

Conflict of interest statement
There are no conflicts of interest.

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