

Autistic spectrum in West syndrome

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Summary

Aim: Children with early-onset and severe epilepsies are known to carry a risk for autism. Considering that association of West syndrome (WS) and autism has not been sufficiently investigated, we aimed to examine autistic features using Autism Behaviour Checklist (ABC) in West syndrome.

Material and Method: Data of 267 infants with WS were examined retrospectively and Autism Behavior Checklist (ABC) was used in 90 cases who could be reached. Patients with a high probability of autism were determined.

Results: Mean age of 90 cases was 56.2±38 months. In 80% of the patients seizures started in the first 6 months and in 26.5% spasms stopped after 12 months of follow-up. The mortality rate was 16.1% and rate of psychomotor retardation was 86%. Seventeen cases (18.9%) who had a total score of 67 or above on ABC were considered to have autism with a high probability. When 14 cases who had a score between 54 and 67 were added, the ratio was found to increase to 34.5%. Ninetyfour point one percent of cases with a high probability of autism were in the symptomatic group.

Conclusions: Autistic disorder is found with a unignorable high ratio in West syndrome. Therefore, cases with West syndrome should be scanned for autistic disorder during their follow-up. (*Turk Arch Ped* 2011; 46: 67-73)

Key words: West syndrome, autistic disorder, Autism Behavior Checklist

Introductin

West syndrome (WS) is an epileptic encephalopathy observed with a frequency of 4-10% among epilepsies occurring in childhood and constituting 25% of all epilepsies occurring in the first year of life. The three main features of West syndrome are as follows: 1. infantile spasms, 2. an arrest or regression in psychomotor development, 3. finding of hypsarythmia on electroencephalogram (EEG).

Prognosis is predominantly related to the etiology. Cryptogenic/idiopathic etiology, late onset and quick response to treatment are associated with good prognosis. In 50% of all cases, spasms disappear before the age of two. In 70% of cases, severe mental retardation,

autism, behavioral disorder (hyperactivity), all other epilepsies and in 25-50% Lennox-Gastaut syndrome (LSG) develop. Only 5-10% of cases can display normal or near-normal mental development (5,6). The cause/effect relationship between epilepsy and autism has been investigated for a long time. It is known that severe epileptic encephalopathies including early myoclonic encephalopathy, Ohtahara syndrome, WS and Dravet syndrome cause regression or slowing in cognitive functions and development of language and behaviour (7). This regression is more severe in cases with onset of epilepsy before the age of two.

Autism Behavior Checklist (ABC) (Attachment 1) developed by Krug et al. (8) is one of the scales frequently referred to for scanning and evaluation of education in

autism in many countries. There are 57 items defining autistic symptoms in Autism Behavior Checklist.

Yılmaz et al. (9) showed in 2007 that Autism Behavior Checklist is an appropriate scanning tool for Turkey. In a study in which Autism Behavior Checklist was adapted to Turkish and validity, confidentiality and threshold score for our country were determined, its easy and quick application, its ability to evaluate different areas of development and its use as a valid and confidential evaluation tool suggested that ABC can be preferred for investigations about autism.

Although the number of investigations about autism has increased recently, studies about the association of WS and autism are limited. This study was performed with the aim of investigating the prevalence of autistic disorder in WS and presenting accumulated data about WS. Autistic Behavior Checklist was used for scanning autism in patients with West syndrome and patients considered to have autism with a high probability were referred to pediatric psychiatry outpatient clinics.

Material and Method

Two hundred sixty seven WS cases (165 male and 102 female) who presented to Istanbul University Istanbul Medical Faculty Department of Pediatrics, Division of Pediatric Neurology between 1995 and 2007 were recruited to the study.

Patient files were examined retrospectively. The diagnosis was made by the age of the patient, definition of seizures by the families and/or observation of seizures during examination and observation of hysparythmia on EEG.

Electroencephalograms were taken using Micromed 18 channel digital video EEG device with international 18-20 electrode system. EEG's were evaluated by instructors of Division of Pediatric Neurology.

On the first presentation, age, gender, age on presentation, follow-up period, prenatal and postnatal histories, phases of psychomotor development, physical and neurologic examination, forms of spasm, cranial imaging and laboratory findings were evaluated. Metabolic screening tests (Tandem MS, organic acids in urine using thin layer chromatography, biotinidase screening test) and biochemical tests (thyroid hormones, serum ammonia and lactate levels..) were performed among laboratory investigations. Cranial imaging methods including computerized tomography and/or magnetic resonance imaging (CT/MRI) were performed. Psychomotor development was evaluated clinically and using Denver screening test.

Subgroups of West syndrome were determined by 1991 ILAE (International League Against Epilepsy) classification. Cases with normal psychomotor development, percentiles of head circumference within normal limits, normal neurologic examination, normal laboratory findings and normal radiologic findings before the beginning of spasms were assigned to cryptogenic WS group. The others were assigned to symptomatic WS group. Cases in

the symptomatic group were divided into prenatal and postnatal subgroups according to the period of affection after history taking, physical examination, neurologic examination and laboratory and radiology tests.

Autism Behavior Checklist is a scale composed of 57 items which are marked as "yes" or "no". The number of the statement describing the child most accurately is circled. If the statement does not describe the child it is left blank. The test is composed of 5 scales; scoring for sensory status, relationship with others, use of body and objects, language abilities, social care and self-care is performed between 0 and 158. In individuals with a score of 54-67 extensive features specific for autism may be found or these individuals may be high-functional and need further investigation. A score of 67 or higher suggests autism with a high probability.

It was understood that 43 of 267 patients with West syndrome who were examined retrospectively died. Among 224 patients, a total of 90 patients who could be reached and presented to our clinics and who were older than 3 years were assessed by ABC after receiving consent from their families (Attachment 3). The mother and/or father of these patients were asked 57 items by the same person (the associate investigator).

Data determined as high probability on ABC with the findings examined were analysed on SPSS 12.0 for Windows package program. Variants were expressed as mean \pm standard deviation, standard error and percent. For comparison of data, Student's t-test was used for continuous variants and Chi-square test was used for specified variants.

Ethics committee approval: Approval was given by Istanbul Medical Faculty Deanery Local Ethics Committee (project number: 2007/1289).

Results

Age, gender distribution, age at seizure onset, etiology distribution, prognosis of 267 patients examined are given in Table 1. In our study, 242 (91%) patients were in the symptomatic group. Perinatal factors were involved with a rate of 38.2% (the leading factor being hypoxic ischemic encephalopathy), prenatal factors were involved with a rate of 24.3%, unknown factors were involved with a rate of 24.3% and postnatal factors were involved with a rate of 14.9%. Hypoxic ischemic encephalopathy and premature birth constituted most of the perinatal factors. When we examined the patients after a mean follow-up period of 12 months (1 month-180 months, median 12 months), we found that spasms stopped in 71 patients, spasms and/or other seizures continued in 149 patients and 43 patients died.

Autistic disorder and ABC screening

There was no patient with hearing and/or vision defect among 90 patients who were assessed by Autism Behavior Checklist. The youngest of the patients who were assessed with ABC was 36 months old and the oldest was 192 months old; mean age was 85.6 \pm 55.7 months.

Autism with a high probability was considered in 17 patients with West syndrome (18.9%) who had a score of 67 or higher (Table 2). These patients were compared with the WS patients who had a score of ≤67 in terms of gender, age at seizure onset, etiology, cranial imaging, response to treatment and prognosis.

In the group with a high probability of autism, 9 patients were (52.9%) male and 8 patients (47.1%) were female. Gender distribution was statistically insignificant (p=0.56, p>0.05). When we added the patients with a score between 54 and 67, male/female ratio was found to be 1.3/1.

When patients with a high probability of autism were examined in terms of etiology, 59% were found to be in the cryptogenic group and 94.1% were found to be in the symptomatic group. In the symptomatic group, perinatal factors were involved with the highest rate (53%) (Figure 1). Distribution of factors in the symptomatic group was statistically insignificant (p=0.78, p>0.05).

When age at seizure onset was evaluated, it was found that spasms in 16 patients started at or before the age of 12 months. This was statistically insignificant when compared to our WS patients (t=0.36, p=0.72) (Table 3).

On cranial imaging performed by CT and /or MRI, brain atrophy (8 patients), delay in myelinization (2 patients), findings compatible with tuberous sclerosis (2 patients), agenesis of the corpus callosum (2 patients) and lissencephaly (2 patients) were found and only one patient out of 17 patients was found to be normal. When these data were compared with the patients who had a lower score, the difference was statistically insignificant (p=0.20, p>0.05).

Psychomotor retardation was found in 78 (87%) of 90 patients assessed by Denver Developmental Screening

Test. 100% of our patients with a high probability of autism had a score of >67. However, this finding was statistically insignificant (p:0.08, p>0.05).

When our patients were evaluated in terms of response to treatment, it was found that valproic acid was started as a first-line drug in 71% and the rate of patients whose spasms stopped after the first-line drug was found to be 11.8%.

On follow-up of the patients with a high probability of autism, it was found that spasms stopped in 4 patients (23.5%) and spasms and/or other seizures types continued in 13 patients (76.5%). When these findings were compared with the patients who had a lower score, the difference was statistically insignificant (p=0.20, p>0.05).

When 57 items in Autism Behavior Checklist were compared between the patients with a high probability of autism and the patients who had a score below 54, it was found that three items were commonly observed with the highest rate. These findings were found to be statistically significant. These items were item 41: "Difficulties with toilet training", item 45 : " Does not dress self without help", item 55: " A developmental delay was identified at or before 30 months of age". In patients with a high probability of autism, the frequency of item 3 and item 22 was found to be statistically significant. These items were as follows: item 3: " Frequently does not attend to social/environmental cues", item 22: "flaps hands aimlessly". Items determined with a high rate on ABC are shown in Table 4.

Discussion

In West syndrome, prognosis is predominantly related to etiology. It is known that cryptogenic cases have a good prognosis (1,5). When 267 patients were evaluated after follow-up (one month-180 months, mean: 12 months), it was found that spasms stopped in 27.3%, spasms and/or other seizure types continued in 56.5% and 16.1% died. Mortality rate was found to be 8% in cryptogenic cases and 16.8% in symptomatic cases.

Psychomotor development is poor in West syndrome (4,6). In our study, the patients were evaluated using Denver Developmental Screening Test and psychomotor retardation was found in 232 patient (86%) and normal psychomotor development was found in 32 patients (2%). Considering the fact that 91% of our patients were symp-

Table 1. Examination of patients with WS

	Distribution	mean±SD
Age (months)	5-180 Female	56.2± 38.8 Male
Gender (n/ %)	102/ 38.3 1-≤12 months	165/ 61.7 above 12 months
Age at seizure onset (n/ %)	265/ 99.3 Cryptogenic	2/ 0.7 Symptomatic
Etiology distribution (n/ %)	24/ 8.9 Full seizure control	243/ 91.1 Seizures continue Death
Prognosis (n/ %)	73/ 27.4	151/ 56.5 43/ 16.1

Table 2. Patients assessed with Autism Behavior Checklist (n:90)

	Number of patients	%
High probability (≥67)	17	18.9
A score of 54-67	14	15.6
A score of ≤54	59	65.5

Table 3. Distribution of patients according to age at seizure onset (n:90)

Age at seizure onset	Patients with a score of >67		Patients with a score of ≤67	
	N	%	N	%
1-≤3 months	9	53	38	52.1
3-≤6 months	4	23.5	18	24.6
6-≤9 months	2	11.8	9	12.3
9-≤12 months	1	5.9	4	5.4
>12 months	1	5.9	4	5.4
Total	17	100	73	100

tomatic, these data are compatible with the literature.

The association between epilepsy and autism has been investigated in various studies in recent years (7, 10-13). Tuberous sclerosis constitutes an important example for epilepsy and autism (14). In recent studies, it has been reported that along with tubers in the temporal lobe, local epileptic activity is also associated with autism. In our study, highly probable autism was found in one of our two tuberous sclerosis cases. In both of our cases, diffuse tubers involving the temporal lobes were present on cranial imaging.

In the study performed by Aşan İ. et al (14), the prevalence of autism in tuberous sclerosis was found to be 35,3%. In this study, infantile spasms were observed with a markedly higher rate in the group with autism compared with the group without autism, but this finding was found to be statistically insignificant.

Chugani at al.(15) found slowing in metabolism in the temporal lobes in 18 of 110 WS patients in a study conducted with PET (Positron emission tomography). At a mean follow-up period of 3 years, autistic disorder was found in 14 of these patients.

Although there is no specific EEG finding, various EEG abnormalities are observed in 17-60% of autistic children. Findings are frequently observed in frontal, temporal, parietotemporal and centrottemporal lobes. Kayaalp et al. (11) compared video-EEG's and ages of WS patients with autism and without autism. In this study, it was suggested that hypsarhythmia continuing at advanced ages and spike-wave findings predominant in the frontal lobes in 28

patients caused the development of autism. It was concluded that hypsarhythmia caused permanent damage to cognitive functions and behavioral abilities. Other studies about autism and WS are shown in Table 5. Saemundsen et al. (12) investigated the prevalence of autism in 20 patients with infantile spasms diagnosed between 1981 and 1998 in Iceland. Three of these patients died during the study and 17 patients were evaluated using Social Communication Questionnaire after receiving consent from the families and evaluation was performed by a psychiatrist. Four of the patients were reported to be in the cryptogenic group. In the symptomatic group, hypoxic ischemic encephalopathy, tuberous sclerosis, hypertensive encephalopathy, subdural hemorrhage, Down syndrome and Aicardi syndrome were found as causative factors. In 6 of the patients (35.3%), autistic disorder was observed. When age limit was considered as 24 months and older, this rate was calculated to be 17.6%.

In our study, autism with a high probability was considered in 17 (18.9%) patients who had a score of 68 and above among 90 patients who were tested. When we added 14 patients with a score between 54 and 67 to these patients, we reached a rate of 34.5% which is higher. However, it is known that a part of the individuals with a score of 54-67 may have extensive findings specific for autism or may be high-functional. In clinical evaluation, test results, developmental history and observational data should be assessed together for the diagnosis. Evaluation should be repeated at certain intervals especially for chil-

Table 4. Examination of items contained in Autism Behavior Checklist (n:90)

Item (%)	55	45	41	38	24	23	22	3
Rate in patients with a score of >67 (n)	100 (17)	83 (14)	76 (13)	58 (10)	70 (12)	47 (8)	83 (14)	76 (13)
Rate in patients with a score of 54-67 (n)	85 (12)	92 (13)	85 (12)	71 (10)	57 (8)	50 (7)	50 (7)	50 (7)
Rate in patients with a score of <54 (n)	68 (37)	48 (26)	40 (22)	37 (20)	40 (22)	38 (21)	40 (22)	25 (14)
Rate in patients in all patients (n)	77 (66)	62 (53)	55 (47)	47 (40)	49 (42)	42 (36)	50 (43)	40 (34)
p value	0.01	0.00	0.00	-	-	-	0.02	0.00

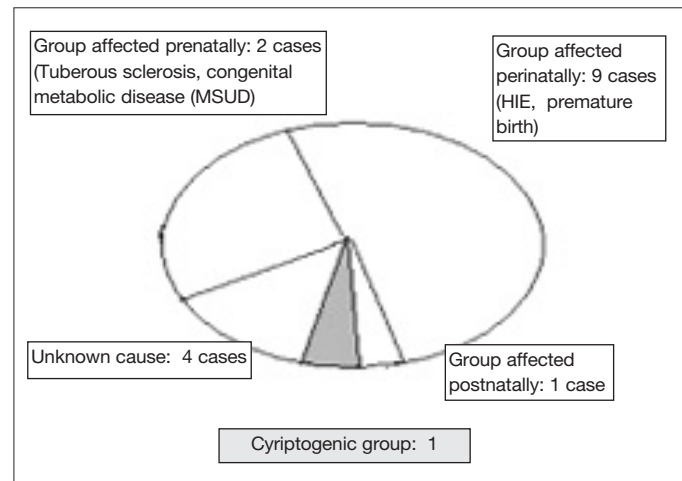


Figure 1. Etiology distribution in our patients (n:17)

Table 5. Studies about WS- autism

Investigator	Country	Number of cases with infantile spasms (n)	(Autistic disorder) (%)	Test performed
Saemundsen E. (2007)	Iceland	20	17.6 Questionnaire	Social Communication
Riikonen R. (1982)	Finland	192	12.5	13-point scale
Our study	Turkey	90	18,9 (high probability)	Autism Behavior Checklist

dren with borderline scores. These children who needed further investigation were referred to pediatric psychiatry outpatient clinics.

In the study performed by Yılmaz et al.(9), it was investigated if ABC could differentiate between the groups with autism and without autism and 53 items out of 57 items were found to differentiate the groups with autism and mental retardation. Items which were not considered to be differentiative were as follows: item 34: "Often will not blink when a bright light is directed toward eyes", item 41: "Difficulties with toilet training", item 54: "Is very destructive (toys and household items are quickly broken)", item 56: "Uses less than 30 spontaneous phrases daily to communicate". When these items were examined, they were found to indicate problems faced both in autism and in severe mental retardation. In our study, when the patients with a high probability of autism and the patients who had a score below 54 were compared, it was found that three items were commonly observed with the highest rate. These items were as follows: item 41: "Difficulties with toilet training", item 45: "Does not dress self without help", item 55: "A developmental delay was identified at or before 30 months of age". As behaviors expected to be observed both in WS and in autistic disorder, these items were considered to be determined with a similar rate in our study.

Autistic disorder is seen in boys 3-5 times more than in girls (16-18). In our study, this ratio was 1.2/1. When the patients with a score of 54-67 were added, male/female ratio was found to be 1.3/1.

When the patients with a high probability of autism were examined in terms of etiology, 5.9% (n=1) of the patients were found to be in the cryptogenic group and 94,1% (n=16) of the patients were found to be in the symptomatic group. In the symptomatic group, the leading cause was perinatal factors. In the study performed by Saemundsen (12), 83% of autistic patients were symptomatic. This finding was compatible with the literature.

Mental retardation is present in 75% of autistic patients (19). Gilbert et al (20) found that autistic disorder is present in 27% of the patients with mental retardation. In our study, psychomotor retardation was found with a rate of 86% in WS patients and with a rate of 100% in the patients with a high probability of autism. Compatible with the literature, a high rate of association was found between psychomotor retardation and autism in our patients, but statistical significance was not found when compared with WS patients without autism. In the patients with a high probability of autism, response to treatment and prognosis were found to be similar to WS patients.

In West syndrome, autistic disorder is observed with an unignorable high rate. Since autism is a disorder continuing life-long, type of treatment varies according to age and development of the individual. According to the results of many studies about autism treatment, the best treatment was found to be education. Therefore, it is very important to start education at the youngest age possible. Thus, patients with West syndrome should be screened for autistic disorder during follow-up. Patients with a high probability of autism or patients on borderline should be

referred to pediatric psychiatry. In addition, more studies about neurologic diseases which accompany autism should be performed.

We need multi-center formations which are specifically bound to Divisions of Pediatric Neurology in medical faculties and which can offer guidance in any area needed by the children with West syndrome. Teams and assistants in these centers will provide medical care, education and rehabilitation for children.

Conflict of interest: None declared

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Attachment 1:					
AUTISM BEHAVIOR CHECKLIST RECORDING FORM					
Name Surname;					
Date of interview;	Physician who conducted the interview;				
INSTRUCTION: Circle the number for those items most accurately describing the child.					
	Sensory	Relationship with others	Use of body and objects	Language abilities	Social and self-care
1- Whirls self for long periods of time			4		
2- Learns a simple task but "forgets" quickly					2
3- Frequently does not attend to social/environmental cues		4			
4- Does not follow simple commands (sit down, come here, stand up) given once				1	
5- Does not use toys appropriately (spins wheels, etc.)			2		
6- Poor use of visual discrimination when learning (fixates on parts of objects such as size, color, position..)	2				
7- Lacks a social smile		2			
8- Exhibits pronoun reversal (you for I..)				3	
9- Insists on keeping certain objects with him/herself			3		
10- Seems not to hear(despite normal hearing tests)	3				
11-Speech is atonal and arrhythmic				4	
12-Rocks self for long periods of time			4		
13-Does not (or did not as a baby) reach out when reached for		2			
14-Strong reactions to minor changes in routine/environment					3
15-Does not respond to own name when called out among two or more other names				2	
16-Lunges and darts about, interrupted by spinning, toe walking, hand flapping...			4		
17-Not responsive to other people's facial expressions or feelings		3			
18-Seldom uses "yes" or "I"				2	
19-Has special abilities in one area-seems to rule out mental retardation					4
20-Does not follow simple prepositional commands (e.g., "put the ball in the box")				1	
21-Sometimes shows no "startle response" to a loud noise	3				
22-Flaps hands aimlessly			4		
23-Severe temper tantrums and/or frequent minor tantrums					3
24-Actively avoids eye contact		4			
25-Resists being touched or held		4			
26-Sometimes, painful stimuli (cuts, injections, bruises) evoke no reaction	3				
27-Is (or was as a baby) stiff and hard to hold		3			
28-Is flaccid (doesn't cling) when held in arms		2			
29-Gets desired objects by gesturing				2	
30-Walks on toes			2		
31-Hurts others by biting, hitting, kicking...					2

Attachment 1:					
32-Repeats phrases over and over again				3	
33-Does not imitate other children at play		3			
34-Often will not blink when a bright light is directed toward eyes	1				
35-Hurts self by biting hand, banging head...			3		
36-Does not wait for needs to be met (wants thing immediately)					2
37-Cannot point to more than five named objects				1	
38-Has not developed any friendships		4			
39-Covers ears at many sounds	4				
40-Twirls, spins, and bangs objects a lot			4		
41-Difficulties with toilet training					1
42-Uses 5 or less words per day spontaneously to communicate wants or needs				2	
43-Often frightened or very anxious		3			
44- Squints, frowns, or covers eyes when in the presence of natural light	3				
45- Does not dress self without help					1
46- Repeats sounds or word over and over again				3	
47-"Looks through" people		4			
48- Echoes questions or statements made by other people				4	
49- Frequently unaware of surroundings and may be oblivious to dangerous situations					2
50- Prefers to manipulate and be occupied with inanimate objects					4
51- Will feel, smell, or taste objects in the environment			3		
52- Frequently has no visual reaction to a "new" person	3				
53- Gets involved in complicated "rituals" such as lining things up			4		
54- Is very destructive (toys and household items are quickly broken)			2		
55- A developmental delay was identified at or before 30 months of age					1
56- Uses less than 30 spontaneous phrases daily to communicate				3	
57- Stares into space for long periods of time	4				
TOTAL :					