

Short Communication

West Syndrome among Down Syndrome Patients

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Abstract

Down syndrome is the most common chromosome disorder. One constant concern is the care to improve development and quality of life that may be affected by the onset of West syndrome. The aim of this retrospective study is analyze the prevalence and evolution of West syndrome in patients seen at a Down syndrome outpatient clinic. Data was gathered from the medical files of 1,212 patients with Down syndrome, among whom 22 (1.9%) had been diagnosed with West syndrome. The data was analyzed using StatisticaR software. Among the 22 patients with West syndrome, 11 (50%) were male. The onset of spasms occurred at a median of 7 months (3-57). Patients received vigabatrin as first treatment with total control of spasms in 81.8%. Five patients (22.7%) developed epilepsy. A higher frequency of autistic spectrum disorder (29.4% versus 5.9%, $p < 0.001$) and seizures (17.6% versus 2.8%, $p < 0.001$) was observed. Pediatricians should promptly request an electroencephalogram when faced with a child with spasms. If hypsarrhythmia is detected, it is West syndrome, improving the prognosis when early treated. Development is recovered after seizure control with the specific treatment (vigabatrin or ACTH) instituted early.

ABBREVIATIONS

DS: Down Syndrome; WS: West Syndrome; EEG: Electroencephalogram; ASD: Autistic Spectrum Disorder; ACTH: Adrenocorticotropic Hormone; DSMV: Diagnostic and Statistical Manual of Mental Disorders; NMR: Nuclear Magnetic Resonance; NPD: Neuropsychomotor Development

INTRODUCTION

Down syndrome (DS) is the most common chromosome disorder, caused by regular trisomy 21 in 95% of people and by translocation and mosaicism in 5% [1-4]. DS has a universal distribution affecting the entire population equally, regardless of geographic location, ethnicity or socioeconomic level. The prevalence of patients with DS is 1 in 600 to 800 live births, with an average of 8,000 new cases per year [3].

Down syndrome patients may present not only specific physical characteristics but also intellectual impairment and anatomical and physiological alterations that may affect their physical and cognitive development in varied ways and intensities [5]. Epilepsy affects a significant portion of DS patients at some point in life [3]. The prevalence of epilepsy is 6.4-8.1% and of West syndrome (WS) 0.6-13% [6-8]. The pooled incidence was 0.249 cases/1000 live births. The pooled prevalence was 0.015 cases/1000 population.

West syndrome, characterized by the onset of epileptic spasms, occurs typically in the first year of life, between 3 and 12 months of age, although later onset may occur. Infants may have had no antecedent history, or the antecedent history may reflect the underlying cause such as chromosomal abnormalities, DS or Miller-Dieker syndrome, gene abnormalities include ARX, CDKL5, SPTAN1, STXBP1 or metabolic etiologies [6]. Global developmental impairment (with or without regression) is typically seen at onset of epileptic spasms. The background EEG is typically abnormal with high voltage irregular slowing. The background EEG is often highly disorganized with high voltage irregular slow waves intermixed with multifocal spikes and poly spikes. This is termed 'hypsarrhythmia' [9]. In the literature there is a doubt about which is the best treatment for WS among DS patients.

The objective of this study was to analyze the prevalence and evolution of West syndrome in patients seen at a Down syndrome outpatient clinic. We also wanted to compare the efficacies of treatments with antiepileptic drugs and ACTH and to evaluate the neuropsychological outcome after 24 months.

MATERIALS AND METHODS

This was a retrospective, observational, descriptive and cross-sectional study using data gathered from 1,212 patients' medical

records at the Down syndrome clinic covering the period from January 2015 until December 2017. These patients comprised 670 males (55.3%) and 542 females (44.7%), with a median age at first visit of 2 months, ranging from first week of life to 11 months (95% CI: 0-9). 59.1% started early intervention until the third month of age and 92.2% until the sixth month. The study was conducted in a public referral center for people with Down syndrome that was created in 1997 with the purpose of ensuring full health care for these people, with an interdisciplinary team and family support.

Medical records of West syndrome patients were analyzed looking for information regarding gender, age of onset of spasms, gestational and neonatal interurrences, etiology, use of medications, medication efficacy, spasms and electroencephalogram (EEG) control, relapse, neuroimaging and progression to epilepsy or autistic spectrum disorder (ASD), and comparing these records with records of DS patients without associated WS. IS was defined as a clinical history of spasms and an EEG demonstrating hypsarrhythmia, modified hypsarrhythmia, or electroclinical spasms captured on EEG.

"Age of spasm onset" was determined based on parental report of onset of clinical spasms. "Age at diagnosis" was based on EEG confirmation of IS: hypsarrhythmia, modified hypsarrhythmia, or electroclinical spasms captured on EEG. "Clinical resolution" of spasms was determined by parental report. "EEG resolution" was defined as resolution of clinical spasms and an EEG showing resolution of hypsarrhythmia. Relapse of infantile spasms was defined as 4 weeks without reported clinical spasms followed by return of clinical infantile spasms or a return of hypsarrhythmia after resolution.

"Etiology" was defined according to the classification proposed by the West Delphi Group (idiopathic-unknown etiology without other neurologic signs or symptoms, cryptogenic-unknown etiology but suspected symptomatic and symptomatic-an identifiable cause of IS present or an unequivocal developmental delay precedes IS) [10]. Vigabatrin was the treatment of first choice; ACTH was used when first-line drugs proved ineffective and subsequently randomized trials described in the literature (topiramate, valproic acid). The authors considered treatment response as 4 weeks without a reported clinical spasms and resolution of hypsarrhythmia in the EEG [11]. Development was recovered after seizure control with the specific treatment (Vigabatrin or ACTH) instituted early. Neurodevelopment was assessed with the Vineland Adaptive Behavior Scales, which measures adaptive levels of functioning from birth to adulthood. The presence of an autistic spectrum disorder was determined with the Modified Checklist for Autism in Toddlers in children aged 16-30 months, or with the Social Communication Questionnaire for children more than 4 years old.

This study was approved by the Clinical Hospital of the Federal University of Parana's Research Ethics Committee (Brazil Platform No. 04542712.3.0000.0096).

For the statistical analysis, Student's t-tests, Mann-Whitney, Fisher's exact test and Pearson's chi-square were used, with a significance level of 5% (Statistica®/Statsoft).

RESULTS AND DISCUSSION

In this series of 1,212 SD patients studied, 50 (4.1%) presented seizures, 22 of them (44%) represented by WS. In a similar study, the prevalence of seizures was more than twice as high in this study (9.2%) as in WS (66.7%) of the 130 patients with DS at Antwerp University Hospital, Belgium [4].

Down syndrome is determined by genetic alterations that may result from chromosome translocation (3-4%), mosaicism (1-2%), or trisomy 21 (95%). Mosaicism may appear with two distinct cell lines: trisomic and with 46 chromosomes [2-4,12], observed a frequency of mosaicism of 8.3%, whereas this genotype was significantly more frequent among patients with DS associated with WS (11.8% vs. 2.2%, $p = 0.02$). It was curious to find a higher frequency of WS in patients with a karyotype of mosaicism and to observe this reported in other studies.

The gender distribution among patients with DS was 1:1, the same proportion found in patients with WS associated, with 11 cases of each sex. Studies have a higher prevalence in males [2,8].

The age of spasms onset ranged from three to 57 months, with a median of 7 months. Although 45.5% of our patients started with infantile spasms from the age of 3 to 6 months and 45.5% patients from seven to 10 months, two patients had late onset of the disease, with 36 and 57 months, reported only in older studies [13,14].

Among them, 18% had previous seizures (focal complex) and 31.8% had a family history of epilepsy [4], observed the onset of crises varying from one to 56 days, variation not found in the present study.

There were no contributions of the gestational and neonatal complications and alterations in the Nuclear Magnetic Resonance image in development of WS in our study (Table 1). Of 12 patients submitted to neuroimaging, 5 (22.7%) had non-specific structural abnormalities.

Fourteen patients received Vigabatrin as first medication and eleven gained control with it. Three others needed to associate adrenocorticotrophic hormone (ACTH) as a second drug, two with complete resolution of clinical spasms. Five patients started treatment with valproate. One was treated with phenobarbital and another with prednisone. Others received no treatment because parents refused it and spasms resolved spontaneously.

Total resolution of spasms occurred in 81.8% of patients and partial in 18.2%. The percentage of recurrence was 13.6% and 22.7% progressed to epilepsy.

Higher frequency of autism spectrum disorder (29.4% versus 5.9%, $p < 0.001$) and seizures (17.6% versus 2.8%, $p < 0.001$) were observed. Two evolved to Lennox-Gastaut. One of the patients did not receive the correct treatment, used nitrazepam; and the other had started delayed treatment.

Seventeen of these 22 patients were followed up at the outpatient clinic and compared to the 1,190 patients with DS. No significant difference was observed in the general and neonatal characteristics of the two groups of patients. Also, there was no significant difference between the groups regarding the phenotypic signs of DS. There was a higher frequency of

Table 1: Characteristics of patients with Down Syndrome and West Syndrome.

Characteristics	DS/WS (n = 22)
Gender (M/F)	11/11
Spasms onset (months)	3-57
Previous crisis	4 (18,2%)
Gestacional complications	6 (27,3%)
Neonatal complications	8 (36,4%)
Family history	7 (31,8%)
Altered neurological examination	22 (100,0%)
Effective Treatment	
Vigabatrin	8 (36,4%)
Depakene	7 (31,8%)
ACTH	3 (13,6%)
Nitrazepam	2 (9,1%)
Topiramate	1 (4,5%)
Homeopathy	1 (4,5%)
Spasms control	
Total	18 (81,8%)
Partial	4 (18,2%)
Side effects	6 (27,3%)
Relapse	3 (13,6%)
RNM altered (n = 12)	5 (41,7%)
Evolution for epilepsy	5 (22,7%)
Altered neurological examination	21 (95,4%)
NPD Delaied	22 (100,0%)

Abbreviations: M: Male; F: Female; NMR: Nuclear Magnetic Resonance; NPD: Neuro Psicomotor Development

mosaicism among patients with associated WS ($p = 0.02$) (Table 2).

There was no significant difference in the prevalence of clinical or surgical diseases between groups. The frequency of ASD was significantly higher among patients with associated West syndrome (29.4% versus 5.9%, $p < 0.001$). The same was observed for the occurrence of epilepsy (17.6% versus 2.8%, $p < 0.001$).

Although they are not part of the description of DS, it is known that convulsive manifestations, are more frequent than in the general population (0.3% -1%) and less frequent than in patients with other types of mental retardation, varying of 1.5% to 15% [2,4,6]; being attributed to structural abnormalities of the brain or associated with medical complications such as infections and heart diseases, alterations in ion channels, and neurotransmitter dysfunction [4,14]. Infantile spasms is the most common type of seizures in DS patients, comprising about 4.5% to 45% of seizures, and were observed in 1.9% of the cases in this study [4] (Table 3).

This study was able to assess the neurodevelopmental outcome of the children. Given the altered developmental trajectory of those children with T21, it would be necessary to have structured neurodevelopmental assessment to address

this issue and given the retrospective nature of this study it was possible.

Regardless of the diagnosis and early initiation of treatment, WS is associated with delayed neuro psychomotor development [2,4,12,15,16]. Despite total spasm control in 81.8% of the patients studied here, 100% evolved with neuro psychomotor development delay and five of them had autistic features.

The clinical follow-up of DS is of fundamental importance for the evolution of the disease. However, in this or other studies, there were no typical phenotypic characteristics among DS patients associated with WS, which could be predictive of the diagnosis [2-4,16,17]. Children with DS and WS are recognized as being particularly responsive to the treatment of infantile spasms, reaching 90% of therapeutic success [17], response rate that varies according to the established response criteria. Considering the disappearance of hypsarrhythmia and spasms with 3 months of treatment [12]. Recorded 75% success, similar to that observed in this series. The same authors observed a high relapse the present study (13.6%).

In our service we had 33.3% patients in which the effective medication was Vigabatrin (80-200 mg/kg/day) for 4-12 months, 9.5% ACTH (30-50 UI/day) for 2-3 weeks, 23.8% Depakene (30 mg/kg/day) for 12-36 months. One patient responded to Nitrazepam and one patient had total control when given Topiramate (1.3 mg/kg/day). Vigabatrin and ACTH are the drugs of choice for seizure control, as first and second line of treatment, respectively. Other antiepileptic drugs have also been considered such as topiramate, levetiracetam, valproate [2,4,16,17] and variations in the choice of drugs depend on the expertise of the neurologists involved, evolution and characteristics of the patients [8], reported similarities about the onset of infantile spasms and EEG response among idiopathic WS and with DS children, but those with DS appeared to be less likely to have recurrence of spasms following treatment and to develop epilepsy after resolution of infantile spasms. They also had a better responsiveness to ACTH [12]. In this sample, Vigabatrin and Vigabatrin associated with ACTH was the best treatment (89%) with development recovery without difference with our DS population without WS.

Attention should be maintained even after treatment, since relapse can occur in up to 50% of cases [17-19].

CONCLUSION

Pediatricians, parents and caregivers should be vigilant and able to identify signs of childhood spasms, as these events may result in significant regression of neuropsychomotor development in DS patients [20].

Table 2: Karyotype of patients with Down Syndrome isolated and with associated West Syndrome.

Characteristics	DS/WS (n = 17)	DS (n = 1146)
Simple Trisomy	15 (88,3%)	1089 (94,4%)
Translocation	0 (0,0%)	32 (2,7%)
Mosaicism	2 (11,8%)	25 (2,2%)

Note: Pearson's chi-square/Yates tests: $p = 0,02$

Table 3: Treatment of West Syndrome among 21 patients with Down Syndrome.

	Gender	First drug	Associated drugs	Seizure Outcome
1	Male	Valproate	Valproate (30mg/Kg/d)	Seizure free
2	Male	Nitrazepam	Nitrazepam (0.4mg/Kg/d)	Lennox-Gastaut
3	Male	Prednisone	Vigabatrin (100mg/Kg/d)	Seizure free
4	Male	Valproate	Nitrazepam (0.25mg/Kg/d)	Seizure free
5	Male	Vigabatrin	Vigabatrin (110mg/Kg/d)	Infrequent seizures
6	Male	Vigabatrin	ACTH (30UI/d during 2 weeks)	Intractable seizures
7	Male	Vigabatrin	ACTH (50UI/d during 3 weeks)	Seizure free
8	Male	Vigabatrin	ACTH (40UI/d during 3 weeks)	Seizure free
9	Male	Vigabatrin	Valproate	Seizure free
10	Male	Vigabatrin	Vigabatrin (80mg/Kg/d)	Seizure free
11	Male	Anticonv	Valproate (40mg 2x/d)	Intractable seizures
12	Female	Phenobarbital	Valproate (30mg/Kg/d)	Seizure free
13	Female	Vigabatrin	Valproate (30mg/Kg/d)	Seizure free
14	Female	Vigabatrin	Vigabatrin (100mg/Kg/d)	Seizure free
15	Female	Vigabatrin	Valproate+Nitrazepam	Seizure free
16	Female	Vigabatrin	Vigabatrin (90mg/Kg/dia)	Seizure free
17	Female	Not treated	Not treated	Seizure free
18	Female	Vigabatrin	Vigabatrin (80mg/Kg/d)	Seizure free
19	Female	Nitrazepam	Vigabatrin (100mg/Kg/d)	Seizure free
20	Female	Nitrazepam	Topiramato (1,3mg/Kg/d)	Seizure free
21	Female	Vigabatrin	Vigabatrin (90mg/Kg/d)	Seizure free

The current spectrum of disorders associated to clinical spasms with onset in infancy is wider than previously thought; accordingly, its terminology has changed. Nowadays, the term Infantile spasms syndrome (ISs) defines an epileptic syndrome occurring in children younger than 1 year (rarely older than 2 years), with clinical (epileptic: i.e., associated to an epileptiform EEG) spasms usually occurring in clusters whose most characteristic EEG finding is hypsarrhythmia [the spasms are often associated with developmental arrest or regression]. The term West syndrome (WS) refers to a form (a subset) of ISs, characterized by the combination of clustered spasms and hypsarrhythmia on an EEG and delayed brain development or regression [currently, it is no longer required that delayed development occur before the onset of spasms]. Less usually, spasms may occur singly rather than in clusters [infantile spasms single-spasm variant (ISSV)], hypsarrhythmia can be (incidentally) recorded without any evidence of clinical spasms [hypsarrhythmia without infantile spasms (HWIS)] or typical clinical spasms may manifest in absence of hypsarrhythmia [infantile spasms without hypsarrhythmia (ISW)]. There is a growing evidence that ISs and related phenotypes may result, besides from acquired events, from disturbances in key genetic pathways of brain development: specifically, in the gene regulatory network of GABAergic forebrain dorsal-ventral development, and abnormalities in molecules expressed at the synapse. Children with these genetic associations also have phenotypes beyond epilepsy, including dysmorphic features, autism, movement disorders and systemic malformations. The prognosis depends on: (a) the cause, which gives origin to the attacks (the complex malformation forms being more severe); (b) the EEG pattern(s); (c) the appearance of seizures prior to the spasms; and (d) the rapid response to treatment. Currently, the first-line treatment includes the adrenocorticotrophic hormone ACTH and vigabatrin. In the near future the gold standard

could be the development of new therapies that target specific pathways of pathogenesis [21].

In this a West syndrome hasn't been thoroughly investigated in Georgia. The purposes of our study were a) to assess the clinical and etiological peculiarities of West syndrome, based on MRI data and its relation to the long-term outcome; b) to assess the evolution of West syndrome and its relation to patient characteristics; c) to compare the efficacies of treatments with ACTH and antiepileptic drugs (AEDs); d) to evaluate the neuropsychological outcome after 12 and 24 months and their early predictors. We evaluated 31 patients (17 male, 14 female) with infantile spasms. Mean age of seizure onset was 6.3 months. Inclusion criteria were newly diagnosed patients with infantile spasms from 2 to 18 months, abnormal EEG and written informed consent of parents/ caregivers. We collected birth, family and seizure detailed history. All patients were examined neurologically, investigated with prolonged sleep and awake video - EEG, brain MRI, developmental screening tests (Ages & Stages Questionnaires®, Third Edition, ASQ-3™) at the time of admission. Spasm diary was given and filled by every parent/caregiver. The video-recording of seizures to study the detailed phenomenology of event was done in all cases as well. In 94% of patients (n=29) spasm were observed in clusters. EEG investigation revealed hypsarrhythmia in majority of cases (n=20; 65%). 19% (n=6) and 16% (n=5) patients had modified hypsarrhythmia and other types of EEG changes respectively. In 19 (61%) cases neurological examination was normal. 7 patients (22.6%) showed normal neuropsychological development. In remaining 12 (38.7%) and 12 (38.7%) cases moderate and severe delay of development was revealed accordingly. MRI investigation revealed no abnormality in 16% (n=5). 16 (52%) individuals were treated with ACTH only. In 12 (39%) cases ACTH and AED were used simultaneously and 2 (6.5%) cases

were treated with AED only. One year follow-up assessments were provided in 22 (74%) cases. One patient died during the study. Neuropsychological development was with no changes in 12 (55%) individuals. In 3 (9.7%) cases some improvement was detected and the deterioration of development was identified in 6 (19%) individuals. In all cases with developmental deterioration, seizures were started before seven month of age, this association was statistically significant (Pearson Chi-Square 6.3; df 1; $p=0.019$). There was no relationship between developmental changes and sex, birth from full term pregnancy, infantile spasm type, treatment, or EEG pattern, however. Despite the fact, that the number of included patients was small, preliminary findings are in accordance to the other published data. The current study is still in process. 12-24 months follow-up with clinical, EEG and neuropsychological monitoring is planned for all cases.

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