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RESEARCH ARTICLE

West Syndrome: A Spectrum Of Disorders With Diagnostic And Therapeutic Challenges

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Abstract

Introduction: West syndrome (WS) is a rare epileptic encephalopathy of multifactorial etiology, characterized by epileptic spasms, psychomotor delay, and hypsarrhythmia on electroencephalogram. Its prevalence is 1.5 to 2 per 10,000 children under 10 years, with an incidence of 1 per 2,000-4,000 live births. **Objective**: This article describes the clinical characteristics of a pediatric patient with WS in a developing country context. Materials and methods: With informed consent, the clinical history was performed, detecting psychomotor delay at 6 months, manifested by loss of social smile and gross motor skills. Physical examination revealed generalized hypotonia, desaturation, and bradycardia. Neuroimaging ruled out organic abnormalities however, the electroencephalogram (EEG) showed hypsarrhythmia, confirming the diagnosis of West syndrome by meeting the classic clinical triad. **Results and discussion**: Male patient of 6 months, firstborn, born by cesarean section at 39 weeks due to hypoxic encephalopathy, with negative STORCH and toxicological tests. He presented to the emergency room with four episodes of spastic movements in the upper limbs, which spontaneously resolved without loss of consciousness, during the previous month. Currently, at 12 years old, the patient is in remission, without seizure episodes for over 10 years. He shows adequate social and family adaptation, with academic performance appropriate for his age group. Cognitive tests indicate borderline performance, suggesting the presence of ADHD, with no evidence of underlying cognitive deficit.

INTRODUCTION

West syndrome (WS) is an epileptic encephalopathy which has been associated with multiple etiologies; among them are genetic factors such as aneuploidies and mutations, including the genes STXBP1, TSC1, TSC2, as well as brain injuries (prenatal, perinatal, and postnatal), neurocutaneous disorders, trauma, congenital infections, inborn errors of metabolism, and even cases without apparent etiology have been described [1,2].

The diagnosis of this syndrome is based on clinical manifestations, which include a characteristic triad (Figure 1).

Figure 1. Triad of clinical manifestations of West syndrome.

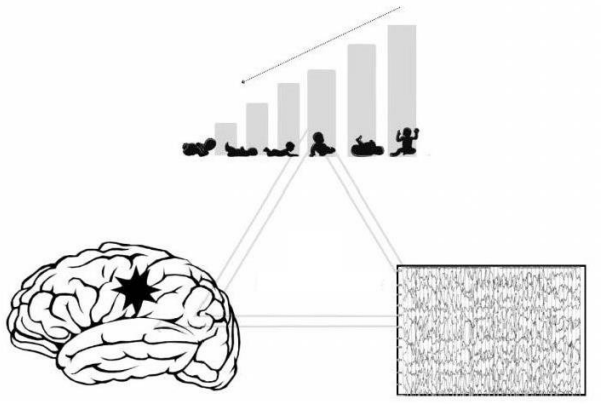

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Table 1. Classification of the Etiologies of West Syndrome.

Structural/Metabolic 50%	Displasia cerebral	
	Esclerosis tuberosa	
	Hypoxic-ischemic encephalopathy	
	Perinatal stroke	
	Prenatal brain infections	
	Leukomalacia Hemorragia periventricular	
Genetics 14.4%	ARX1	Featured Xp22
	CDKL5	Featured Xp22
	STK11	
	PAFAH1B1/LIS1	
	DCX	
	TUBA1A	
	KCNQ2	
	GRIN2B	
	GRIN2A	
	MAGI2	
	SPTAN	
	Microdeletions	2q24.3
		5q14.3
		9p34
	Microduplications	2q24.3
		Xp28.11.93
	Deletions	16p12.1
	Unknown cause - 35.6%	

Table prepared from West Syndrome: a comprehensive review [11].

First, there are clustered epileptic spasms, symmetrical, lasting approximately 5 to 10 minutes with a repetition every 5 to 10 seconds, predominantly axial in flexion, extension, or mixed, in some cases associated with ocular retroversion, mostly occurring upon awakening. Secondly, psychomotor delay consisting of loss of grip and visual contact and may even be accompanied by axial hypotonia. Lastly, the presence of an electroencephalographic trace equivalent to hypsarrhythmia, which predominates in wakefulness and non-REM sleep [3,1].

When diagnosing West syndrome, it is crucial to try to identify its etiology. In approximately 70% of cases, an underlying cause can be determined, often related to malformations or genetic alterations, including those linked to the X chromosome.

Regarding incidence, between 4.4% and 4.8% of patients with West syndrome have an alteration specifically associated with the X chromosome, while the remaining percentage corresponds to cases where a clear cause cannot be identified [4].
It is a rare disease, as it is estimated at 1 case per 4,000 – 6,000 live births and represents 2-10% of childhood epilepsies, with an incidence ranging from 1 case per 2,000-4,000 live births [5], with symptoms typically appearing between 3 to 7 months and even up to the first year of age [2].

The prognosis of pediatric patients with West syndrome is severe, as the majority develop cognitive deficits, which may be associated with motor deficits and/or behavioral disorders.

However, it is of great importance to mention the high percentages of patients who progress to Lennox-Gastaut syndrome and epilepsy with complex partial seizures, these being pathologies with poor life prognosis and difficult to manage [2].

Here is the case of a 12-year-old male pediatric patient, who is in remission after being diagnosed with SW, without presenting any degree of disability or convulsive episodes in a period of more than 10 years. Cognitive evaluations indicate an IQ of 79, suggesting the presence of attention deficit hyperactivity disorder (ADHD), with no evidence of underlying cognitive deficit.

The objective of this article is to describe and analyze a patient diagnosed with West Syndrome. His clinical presentation and comprehensive approach to the multidisciplinary treatment applied will be addressed.

METHODOLOGY

Informed consent of the mother of the underage patient is obtained before any procedure is carried out. Next, a thorough physical examination was performed and the patient's medical history was reviewed. The following paraclinical studies were requested: magnetic resonance imaging, simple cranial computed tomography, electroencephalogram, 24-hour holter monitor, echocardiogram, and video telemetry. The most relevant results were as follows: the electroencephalogram showed a pathognomonic pattern of hypsarrhythmia, electrocardiogram and echocardiogram ruled out structural or functional pathologies, and metabolic tests were within normal parameters.

RESULTS

Male patient, 6 months old, with a history of full-term pregnancy at 39 weeks, with negative STORCH studies and toxicological tests, born by cesarean section due to the identification of hypoxic encephalopathy.

At 6 months of age, the patient is taken to the emergency department, accompanied by his parents, due to a clinical picture of one month evolution characterized by four episodes of spastic movements in the upper extremities. These episodes resolve spontaneously and are not associated with loss of consciousness. However, there is observed loss of previously developed skills, such as palmar prehension and social smile. In addition, he presents generalized hypotonia, inadequate head control, and inability to achieve sitting position.

Given these findings, a brain tomography is indicated, which shows no intra or extra-axial lesions. An electroencephalogram is also performed, which reveals the presence of cerebral hypsarrhythmia. Based on the combination of infantile spasms, psychomotor developmental delay, and cerebral hypsarrhythmia, West syndrome is diagnosed.

During his hospital stay, he receives treatment with valproic acid, physical therapy, and occupational therapy. He shows an appropriate response to the treatment and is discharged. However, two months later, he is readmitted to the hospital with drowsi-

ness and bradycardia. A 24-hour Holter monitor and an echocardiogram are performed, which rule out structural or functional cardiac abnormalities, concluding that he has sinus bradycardia.

Due to the altered state of consciousness, the dose of valproic acid is reduced and a video telemetry is requested, which shows an increase in the frequency of epileptic seizures [1].

Given the low tolerance to valproic acid, it is decided to change the anticonvulsant to vigabatrin at a dose of 125 mg/day and initiate treatment with interdaily ACTH.

During the ACTH treatment, control tests are performed revealing severe hyperkalemia secondary to this treatment. Due to this, the patient is transferred to the ICU and receives treatment with enalapril and spironolactone [2].

The ACTH treatment is maintained for three months, while vigabatrin is administered for one year [3].

Since the end of the pharmacological treatment, the patient has been receiving only physical therapy, speech therapy, and occupational therapy. Currently, he is in remission of the disease, without epileptic seizures for over 10 years.

Currently, at 12 years of age, he presents adequate psychomotor development, with good academic and social performance, without evidence of cognitive deficit and with the only diagnosis of attention deficit.

DISCUSSION

Clinical manifestations

In this article, the case of a patient with West syndrome (WS) is presented, one of the most severe pediatric epileptic encephalopathies, characterized by epileptic spasms, psychomotor delay, and hypsarrhythmia in the electroencephalogram tracing. This syndrome, described by William West in 1841, affects approximately 1 in every 4,000 children, with a higher prevalence in the male population, in a ratio of 60:40 compared to the female population [6,7].

Clinical Diagnosis

SW diagnosis, according to the International League Against Epilepsy (ILAE) classification, is confirmed by the presence of epileptic spasms, hypsarrhythmia, and, in many cases, developmental delay [8,9]. 70-75% of cases have an identifiable cause, including brain malformations and genetic disorders.

Genetics and Molecular Diagnosis

It is essential to highlight among the possible etiologies mutations and genetic syndromes associated, such as those with an X-linked inheritance pattern which includes the ARX1 (Aristaless), CDKL5 (Cyclin-dependent Kinase-like 5) genes both located on Xp22 Additionally, gene impairments should be considered, such as STK11 (chromosome 9), PAFAH1B1/LIS1, DCX, TUBA1A, among others, as well as Sturge-Weber syndrome, incontinentiapigmenti, tuberous sclerosis, and Down syndrome [10,11,12].

International Classification

The etiologies can be classified according to the International Classification of Epilepsies and Epileptic Syndromes, [13] (See table 1), based on the identification of the origin of SW, which are grouped into genetic, metabolic/structural and/or unknown, replacing the previously used terms symptomatic, cryptogenic and idiopathic. Within the group of patients presenting SW related to a genetic etiology, it is characterized by a genetic alteration and the epileptic seizures are secondary to it. On the other hand, patients presenting SW due to metabolic/structural causes are characterized by the presence of a structural or metabolic disease related to the seizures. Likewise, a third group is proposed where the epileptic episodes have no established or identified cause yet, which may influence a better prognosis compared to a recognizable cause [10,14].

Etiology and prognosis

Identifying the underlying etiology of SW is crucial, especially when a genomic alteration is detected early, as this has a global impact on the patient's prognosis. Certain mutations are associated with better seizure control and management, but it should also be considered that some mutations may lead to a worse outcome due to predisposing a more severe course of the disease. However, it is important to emphasize that recognizing secondary SW due to a genetic alteration also helps prevent complications associated with it, provides genetic counseling, and opens up possibilities for initiating research on treatments based on corrections at the specific mutation level and/or biochemical signaling pathways.

Differential Diagnosis

Among the disorders that may present symptoms similar to SW are Lennox-Gastaut syndrome, which also involves multiple types of seizures and psychomotor development delay, and myoclonic spasms characterized by faster and less prolonged movements compared to infantile spasms [15]. In addition, Ohtahara syndrome and other epilepsies may show clinical and electroencephalographic characteristics that require a comprehensive differential diagnosis [16].

Regarding clinical manifestations, epileptic spasms are characterized by sudden and brief axial contractions affecting the neck, arms, and legs, and can occur in isolation or in clusters. These spasms may or may not be associated with eye rolling. Psychomotor regression is manifested by a loss of previously acquired motor and developmental skills, indicating a halt or regression in the child's psychomotor progress. The electroencephalogram should show a characteristic pattern known as hypsarrhythmia [17]. However, identifying hypsarrhythmia can be challenging, as some children with infantile spasms do not present this classic pattern, which can pose a significant diagnostic challenge [18].

In the case of the present patient, the diagnosis aligns with the criteria described in the literature for West syndrome (WS), which include the characteristic pattern of hypsarrhythmia in the EEG, the presence of multiple spasms, and the loss of motor skills such as palmar prehension and social smile, along with generalized hypotonia. Although these symptoms usually have a poor prognosis in terms of cognitive development, an early diagnosis has allowed to minimize complications, resulting in a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) instead of severe cognitive impairment, for the present case.

Future Considerations

Given that the diagnosis of West syndrome in the present patient has been based exclusively on clinical criteria [1] and the patient's outcome is atypical, it is necessary to consider genetic testing as the next step.

Associated Factors

Despite having an uncertain pathophysiology, the most accepted description for this syndrome was proposed by Baram in 1993, highlighting the crucial role of corticotropin-releasing hormone (CRH). Various factors contribute to this pathology, with cerebral stress being one of the main triggers that increases the release of secondary mediators, among which CRH is the most studied. It has been suggested that this hormone is responsible for the characteristic spasms in SW. During the neonatal period, the number of CRH receptors is significantly higher than in adults, which explains the predominance of clinical manifestations in childhood and their tendency to modulate or even disappear with the transition to adulthood. Additionally, studies in animal models have shown that CRH has excitatory properties in neurons, which could explain the electroencephalographic patterns observed during seizures in these patients [19].

Treatment

Based on the concepts previously described, two pharmacological approaches have been proposed, although they have been poorly studied. One of these approaches is the administration of corticotropin (ACTH), which, according to the physiological principles of the CRH-ACTH-cortisol axis, induces negative feedback that inhibits the secretion of CRH, thus reducing its action on neuronal stimulation. Similarly, the use of glucocorticoids, such as prednisone, generates a comparable inhibitory effect. Although studies have been conducted to compare the efficacy of these two treatments, no significant differences have been observed, except in the time required to achieve remission of symptoms, which could be shorter with the use of corticosteroids [18,19,20].

The dose and duration of treatment have not yet been fully established. However, the importance of early initiation of management has been emphasized as a significant improvement in the progression of child developmental milestones has been observed. Although the long-term effects on cognitive and developmental aspects have not been clearly defined due to inadequate patient follow-up in studies, it has been suggested that early treatment could prevent secondary complications, such as attention deficit hyperactivity disorder, associated with untreated seizure episodes [18,20].

Follow-up and prognosis

Due to limited research on the pathology and inadequate follow-up of patients throughout their lives, it

is difficult to establish an accurate prognosis for this disease. Most studies agree that the main determinant of a worse prognosis is late diagnosis and treatment. The term "late" has been vaguely defined, referring to interventions that occur after a month since the onset of clinical symptoms in cryptogenic cases, or after two months in cases associated with Down syndrome. Other factors, such as the short duration of spasms, biological indeterminacy, and the short duration of treatment (less than 6 weeks), have been linked to a more favorable prognosis. Likewise, most studies describe that the number of clinical manifestations is directly related to the severity of the disease and a poor prognosis [20,21,22].

CONCLUSIONS

In conclusion, West syndrome is a disease considered a major challenge due to the complexity of its diagnosis, given the multiple etiologies that generate it, not to mention its complications in case of a delayed suspicion, as a delay in its treatment is determined as a poor prognostic factor for patients.
Similarly, the difficulty of diagnosis and the difficult prognosis to establish for patients with this disease, allow opportunities to propose an early and targeted approach by the medical team, likewise generates possibilities in the area of research regarding therapies for SW, which could positively influence the clinical outcomes of patients, allowing for comprehensive and multidisciplinary treatment.

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