JECN Journal of Epilepsy and Clinical Neurophysiology

Original Article/Artigo Original/Artículo Original

WEST SYNDROME: ETIOLOGY AND EVOLUTION OF THE INTER-ICTAL EEG PATTERN IN A COHORT OF 24 PATIENTS

SÍNDROME DE WEST: ETIOLOGIA E EVOLUÇÃO DE PADRÃO INTERICTAL NO EEG EM UMA COORTE DE 24 PACIENTES

SÍNDROME DE WEST: ETIOLOGÍA Y EVOLUCIÓN DE ESTÁNDAR INTERICTAL EN EL EEG EN UNA COHORTE DE 24 PACIENTES

Natasha Santos Mata[1], Paulo Breno Noronha Liberalesso,[2] Jair Mendes Marques[2], Bianca Simone Zeigelboim[2], Eliana Garzon[3]

ABSTRACT

Objective: West syndrome (WS) is the most frequent epileptic encephalopathy in the first year of life. Diagnosis requires the presence of epileptic spasms, developmental delay, and hypsarrhythmia EEG pattern. Methods: A retrospective study on the etiology and evolution of inter-ictal electroencephalographic patterns in children with West syndrome referred to the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January 2008 to January 2014. All children underwent magnetic resonance imaging and EEG. Results: Eighteen (75%) children had spasms, and 6 (25%) had spasms and tonic seizures. MRI scans showed agenesis of the corpus callosum (1/4.17%), dysplasia in the right frontal lobe (1/4.17%), dysplasia in the left frontal and parietal lobes (1/4.17%), pachygyria associated with agenesis of the corpus callosum (1/4.17%), periventricular nodes (2/8.33%), periventricular leukomalacia (3/12.5%), cerebral atrophy (3/12.5%), and multicystic encephalomalacia (6/25%). EEG monitoring showed hypsarrhythmia in the first exam in all cases; 18 (75%) progressed to multifocal epileptiform discharges (more than three independent epileptogenic foci), and 6 (25%) developed generalized spike-wave and polyspike-wave. Conclusions: Symptomatic form is the most common in WS and most patients develop multifocal epileptiform discharges visible in EEG.

Keywords: Spasms, infantile; Electroencephalography; Seizures.

RESUMO

Objetivo: A síndrome de West (SW) é a encefalopatia epiléptica mais frequente no primeiro ano de vida. O diagnóstico requer a presença de espasmos epilépticos, retardo de desenvolvimento e EEG com padrão de hipsarritmia. Métodos: Estudo retrospectivo sobre a etiologia e a evolução dos padrões eletroencefalográficos interictais em crianças com síndrome de West encaminhadas para o Departamento de Neurologia Pediátrica do Hospital Pequeno Príncipe, de janeiro de 2008 a janeiro de 2014. Todas as crianças foram submetidas a exames de ressonância magnética e EEG. Resultados: Dezoito crianças (75%) tinham espasmos e 6 (25%) tinham espasmos e convulsões tônicas. As imagens por RM mostraram agenesia do corpo caloso (1/4,17%), displasia no lobo frontal direito (1/4,17%), displasia nos lobos frontal esquerdo e parietal (1/4,17%), paquigiria associada à agenesia do corpo caloso (1/4,17%), nódulos periventriculares (2/8,33%), leucomalácia periventricular (3/12,5%), atrofia cerebral (3/12,5%) e encefalomalácia multicística (6/25%). A monitoração EEG mostrou hipsarritmia no primeiro exame em todos os casos; 18 (75%) progrediram para descargas epileptiformes multifocais (mais de três focos epileptogênicos independentes) e 6 (25%) evoluíram com espícula-onda e poliespícula-onda generalizadas. Conclusões: A forma sintomática é a mais comum na SW e a maioria dos pacientes desenvolve descargas epileptiformes multifocais aparentes no EEG.

Descritores: *Espasmos infantis; Eletroencefalografia; Convulsões.*

RESUMEN

Objetivo: El síndrome de West (SW) es la encefalopatía epiléptica más frecuente en el primer año de vida. El diagnóstico requiere la presencia de espasmos epilépticos, retardo de desarrollo y EEG con estándar de hipsarritmia. Métodos: Estudio retrospectivo sobre la etio-

1. Pediatric Neurology Department, Pequeno Príncipe Children's Hospital. Curitiba, Paraná, Brazil.
2. Otoneurology Laboratory, Tuiuti University of Paraná. Curitiba, Paraná, Brazil.
3. Electroencephalograghy Section, Neurological Clinic of the Hospital das Clínicas of São Paulo, University of São Paulo Medical School. São Paulo, Brazil.

Correspondence: Paulo Breno Noronha Liberalesso. Hospital Infantil Pequeno Príncipe.
Avenida Iguaçu, 1472, Água Verde. CEP: 80250-060 Curitiba, Paraná, Brasil. paulo.neuroped@gmail.com

logía y la evolución de los estándares electroencefalográficos intericticales en niños con síndrome de West encaminados para el Departamento de Neurología Pediátrica del Hospital Infantil Pequeno Príncipe, desde enero de 2008 a enero de 2014. Todos los niños fueron sometidos a exámenes de resonancia magnética y EEG. Resultados: Dieciocho niños (75%) tenían espasmos y 6 (25%) tenían espasmos y convulsiones tónicas. Las imágenes por RM mostraron agenesia del cuerpo calloso (1/4,17%), displasia en el lóbulo frontal derecho (1/4,17%), displasia en los lóbulos frontal izquierdo y parietal (1/4,17%), paquigiria asociada a la agenesia del cuerpo calloso (1/4,17%), nódulos periventriculares (2/8,33%), leucomalacia periventricular (3/12,5%), atrofia cerebral (3/12,5%) y encefalomalacia multicística (6/25%). El monitoreo EEG mostró hipsarritmia en el primer examen en todos los casos; 18 (75%) avanzaron para descargas epileptiformes multifocales (más de tres focos epileptogénicos independientes) y 6 (25%) evolucionaron con espícula-onda y poliespícula-onda generalizadas. Conclusiones: La forma sintomática es la más común en la SW y la mayoría de los pacientes desarrolla descargas epileptiformes multifocales aparentes en el EEG.

Descriptores: *Espasmos infantiles; Electroencefalografía; Convulsiones.*

INTRODUCTION

West syndrome (WS) is the most frequent epileptic encephalopathy in the first year of life, with an incidence ranging between 2 and 3.5 / 10,000 live births, with a peak age of onset between three and seven months old.[1] This syndrome was originally described in 1841 in an article published in The Lancet, by an English physician named William James West in his own son, James Edwin West.[2]

Classically, for diagnosis the presence of (a) seizures classified as spasms (may be flexor, extensor or mixed), (b) a typical pattern in interictal electroencephalogram (EEG) denominated hypsarrhythmia and (c) developmental delay at diagnosis or during the course is required.[1]

Most cases of WS is classified as symptomatic and therefore related to structural or metabolic lesions of brain, especially malformations of cortical development, tuberous sclerosis, Aicardi and Down's syndrome, metabolic disorders, congenital infections, pre-natal hypoxia, among others. Less commonly, there are reports of cryptogenic cases in which neurological development that precedes the onset of symptoms is normal and the etiology is undetermined.[3]

Although hypsarrhythmia to be present in all patients with WS, this interictal pattern will always be replaced by another EEG pattern during the course of the disease. Thus, the main aim of this study is to analyze the evolution of EEG in a group of children with WS. All aspects of this research were approved by the Ethics Committee on Research Involving Human Subjects at our institution (number 771.087).

METHODS

This is a retrospective study about the etiology and evolution of interictal electroencephalographic patterns of WS children referred for the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January/2008 to January/2014. Twenty-four patients were selected, 13 (54.17%) female and 11 (45.83%) male, all showing hypsarrhythmia pattern in the first EEG and with developmental delay at diagnosis.

Seizures were classified according to their clinical symptoms. All children were submitted to magnetic resonance imaging (MRI) and etiology was determined in almost all cases.

All EEG were performed for a minimum duration of 30 minutes, with electrodes positioned according to the International 10-20 System, in digital EEG monitoring equipments with 21 channels (Nihon Koden®, Neurotec® and Neurovirtual Brain Wave II®). EEG exams were performed sequentially until the hypsarrhythmia be replaced by another pattern and all exams were analyzed by the same physician.

RESULTS

In the group of 24 children included in the study, the age of seizures onset ranged from 5-15 months (mean 7.92 ± 2.52 months).

Etiology investigated by MRI

Eighteen (75%) children had exclusively spasms, and 6 (25%) had spasms and tonic seizures. The MRI was abnormal in 18 cases, showing agenesis of the corpus callosum (1/4.17%), dysplasia in the right frontal lobe (1/4.17%), dysplasia in the left frontal and parietal lobes (1/4.17%), pachygyria associated with agenesis of the corpus callosum (1/4.17%), periventricular nodes (2/8.33%), periventricular leukomalacia (3/12.5%), cerebral atrophy (3/12.5%), and multicystic encephalomalacia (6/25%). Six (25%) MRI scans of the brain were normal. Data from neuroimaging studies associated with clinical and / or neurological diagnosis history of each patient is shown in Table 1.

Evolution of interictal electroencephalographic patterns

All EEGs records showed hypsarrhythmia in the first examination, 18 (75%) progressed to multifocal epileptiform discharges (more than three independent epileptogenic foci) and six (25%) evolved with generalized spike-wave and polyspike-wave (Table 2). In none of the cases analyzed, did the EEG become normal after the disappearance of hypsarrhythmia.

DISCUSSION

In most cases, the parents bring the child to a pediatrician or pediatric neurologist because they realize the onset of spasms. Initially, these spasms can be confused with abdominal colic or gastroesophageal reflux. However, after a careful medical history and a detailed neurological examination, the diagnosis of WS is relatively simple. The spasms can occur alone or associated with other types of seizures, especially generalized tonic seizures. Epileptic spasms can be classified into flexors, extensors and mixed (combination of both earlier), depending on the muscle groups involved, and generally predominate in moments of transition from wakefulness to drowsiness or upon awakening. The spasms are clinically characterized by sudden and rapid contractions of muscle groups of the neck, arms and thighs. Simultaneously, the eyes may have tonic upward deflection. The contraction is often followed by a cry. Sometimes, mainly in patients treated with antiepileptic drugs, spasms can occur only with deviation of the eyes upward. These seizures typically occur clustered and have very variable frequency, occurring a few times to hundreds of times a day.[4] In our study, all patients had developmental delay at diagnosis of WS. Most of our patients had only spasms. Only a third had spasms associated with tonic seizures.

Table 1. Magnetic resonance of brain and relationship with clinical history or neurological diagnosis.

P	Scans	Historical clinical / neurological diagnosis
1	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
2	Normal	Down syndrome
3	Right frontal dysplasia	Brain malformation
4	Agenesis of the corpus callosum	Brain malformation
5	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
6	Brain atrophy	Hypoxic-ischemic injury in childbirth
7	Normal	Down syndrome
8	Brain atrophy	Hypoxic-ischemic injury in childbirth
9	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
10	Normal	No clinical history of neurological diseases
11	Dysplasia frontal and parietal (left)	Brain malformation
12	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
13	Normal	Down syndrome
14	Periventricular leukomalacia	Prematurity
15	Normal	Down syndrome
16	Periventricular leukomalacia	Prematurity
17	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
18	Periventricular leukomalacia	Prematurity
19	Brain atrophy	Hypoxic-ischemic injury in childbirth
20	Normal	No clinical history of neurological diseases
21	Pachygiria and agenesis of the corpus callosum	Brain malformation
22	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
23	Periventricular nodules	Tuberous sclerosis
24	Periventricular nodules	Tuberous sclerosis

P=Patient

Etiology

The causes of WS appear to be extremely variable and its pathophysiology is not completely known. It is possible that in all patients with WS there is an increase in the release of stress -activated mediators in the brain (particularly the neuropeptide CRH) in the limbic and brain stem regions.[5] A malfunction in the regulation of the GABA transmission process may also occur in some cases.[6]

The WS can be classified as cryptogenic or probably symptomatic (etiology cannot be clearly determined) and a symptomatic form (etiology is clearly defined). There is controversy about the existence of an idiopathic form. A Brazilian study of 95 children with WS (62% male) with mean age of 4.9 (±5.0), concluded that 72.6% were symptomatic, 26.3% were cryptogenic and only 1.1% were idiopathic.[7]

Pre-natal asphyxia is a very frequent cause of WS in countries where care during pregnancy is inadequate.[8] Therefore, pregnancy and pre-natal complications are often related to WS in many regions of Brazil.

Brain lesions are present in 60-90 % of all children with WS, and almost half of these patients have radiological signs of cerebral atrophy. MRI has a high capacity to identify small cortical and subcortical lesions and should be performed in all cases. Brain malformations are identified in at least one third of patients with WS, including focal cortical dysplasia, polymicrogyria, pachygyria, schizencephaly, lissencephaly, and agenesis or dysgenesis of the corpus callosum, subcortical band heterotopias and double cortex syndrome.[8,9]

Patients with neuromesoectodermosis or neurocutaneous syndromes, particularly tuberous sclerosis, may also evolve with WS.[8] When the WS occurs in children with tuberous sclerosis, the evolution seems to be more benign.[10]

WS may also occur in children with genetic syndromes. It is considered one of the most frequent generalized epileptic

Table 2. Evolution of interictal electroencephalographic patterns in West syndrome.

Patient	EEG 1	EEG2	EEG 3	EEG 4	EEG 5	EEG 6
1	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
2	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
3	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
4	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---
5	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW
6	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---
7	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	Multifocal SW	---	---
8	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
9	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW.	---	---
10	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
11	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---	---
21	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
13	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---
14	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
15	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
16	Hypsarrhythmia	Multifocal SW	---	---	---	---
17	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
18	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---
19	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
20	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	Multifocal SW	---
21	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
22	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---	---
23	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---
24	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---

SW – sharp wave. G-SW/PSW – generalized spike-wave and polyspike-wave.

encephalopathies in children with Down's syndrome (DS). The mechanisms that explain the high incidence of epilepsy in DS are not completely known. However, structural brain abnormalities, persistent fetal dendritic morphology, underdeveloped synaptic profiles and high concentrations of carbonic anhydrase II occur in many individuals with epilepsy, WS and DS.[8,11,12]

Recently, two genes located in the human chromosome Xp22 region (ARX and CDKL5), have been found to be responsible for cryptogenic WS.[8,9]

Similarly to the medical literature,[8] most of our patients (75%) had some changes in MRI being classified as a symptomatic form of WS. In half of our cases the brain damage (cerebral atrophy or multicystic encephalomalacia) was caused by complications and hypoxic-ischemic injury in childbirth. Pre-maturity and periventricular leukomalacia are infrequent causes of WS. However, we found three cases in our study. As observed in other authors,[8,10,12] DS and tuberous sclerosis were frequent causes of WS in our patients, occurring in one third of cases.

Evolution of interictal electroencephalographic patterns

The presence of hypsarrhythmia is required for the diagnosis of the syndrome. The hypsarrhythmia was described by F.A. Gibbs and E.L. Gibbs consists of "random high-voltage slow waves and spikes, that vary from time to time, both in location and duration. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally, the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the *petit mal* variant type".[13]

Early in the disease, the hypsarrhythmia may be interspersed with periods of normal brain electrical activity. However, after a period of days or a few weeks, the hypsarrhythmia becomes constant in the EEG during wakefulness and sleep. This abnormal EEG activity is continuous and chaotic, but in sleep it can be fragmented. Several authors have described atypical hypsarrhythmia, also called modified hypsarrhythmia, including forms with increased interhemispheric synchronization, with a consistent focus of abnormal discharge, asymmetrical hypsarrhythmia, patterns with hypsarrhythmia with episodes of attenuation and forms with hypsarrhythmia comprising mainly high voltage slow activity (with little amount of spiky activity).[14] The hypsarrhythmia is usually easily recognized and this is very important because it has implications for the choice of the most appropriate antiepileptic drug. In our group of patients, all children had the hypsarrhythmia in classic form in the first EEG.

In our series, all patients showed the classic form of hypsarrhythmia. The hypsarrhythmia is an age-dependent EEG abnormality. Therefore after a few months or years it is always replaced by another pattern in the EEG.

There are few studies reporting on the evolution of interictal patterns in WS.

The classic studies of Gibbs et al.[15] showed that 75% of children with WS remained with focal discharges after the disappearance of hypsarrhythmia and this data corresponds exactly to what we found in our study.

In idiopathic WS would be possible that the EEG evolved to normality after the disappearance of hypsarrhythmia.[7] However, this form is considered very rare and was not observed in our study.

CONCLUSIONS

Our data show that most children with WS are classified as symptomatic forms (brain injury may be seen in scans) and that most also evolve with multifocal epileptiform discharges. Although WS has been analysed for over a century and a half, questions remain about its pathophysiology. Furthermore, it remains the most common form of epileptic encephalopathy in the first year of life, justifying further research on this topic.

REFERENCES

1. Hrachovy RA, Frost JD. Severe encephalopathic epilepsy in infants: infantile spasms (West syndrome). In. Pediatric Epilepsy: Diagnosis and Therapy. Edited by Pellock JM, Boorgeois BF, Dodson WE, Nordi DR Jr, Sankar R. New York, NY: Demos Medical Publishing. 2008:249-68.
2. West WJ. On a peculiar form of infantile convulsions. Lancet. 1841;1:724-5.
3. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia.1989;30:389-99.
4. Hrachovy RA, Frost JD Jr. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). J Clin Neurophysiol. 2003:20:408-25.
5. Baram TZ: Models for infantile spasms: an arduous journey to the Holy Grail. Ann Neurol. 2007;61:89-91.
6. Willmore LJ, Abelson MB, Ben-Menachem E, Pellock JM, Shields WD. Vigabatrin: 2008 update. Epilepsia. 2009;50:163-73.
7. Matta AP, Chiacchio SV, Leyser M. Possíveis etiologias da síndrome de West. Avaliação de 95 pacientes. Arq Neuropsiquiatr. 2007;65:659-62.
8. Dulac O, Tuxhorn I. (2002), "Infantile spasms and West syndrome", in Roger J, Bureau M (orgs). Epileptic Syndromes in Infancy, Childhood and Adolescence. United Kingdom: John Libbey & Co Ltd, 47-63.
9. Kato M. A new paradigm for West syndrome based on molecular and cell biology. Epilepsy Res. 2006;70 (S1): 87-95.
10. Fukushima K, Inoue Y, Fujiwara T, Yagi K. Long-term follow-up study of West syndrome associated with tuberous sclerosis. Brain Dev. 2001; 23(7):698-704.
11. Palminiello S, Kida E, Kaur K, Walus M, Wisniewski KE, Wierzba-Bobrowicz T, Rabe A, Albertini G, Golabek A. Increased levels of carbonic anhydrase II in the developing Down syndrome brain. Brain Res. 2008;1190:193-205.
12. Wisniewski KE. Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. Am J Med Genet. 1990; 37(S7):247-81.
13. Gibbs FA, Gibbs EL in: Atlas of electroencephalography. Vol. 2. Addison-Wesley, Cambridge, Mass. 1952:356–374.
14. Hrachovy RA, Frost JD Jr, Kellaway P. Hypsarrhythmia: variations on the theme. Epilepsia. 1984;25:317-25.
15. Gibbs EL, Fleming MM, Gibbs FA. Diagnosis and prognosis of hypsarrhythmia and infantile spams. Pediatrics. 1954;13:66-72.