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PERINATAL BRAIN LESIONS AND EPILEPSY: PREMATURITY AND CEREBRAL HYPOXIA EVOLVING WITH WEST SYNDROME

LESÕES CEREBRAIS PERINATAIS E EPILEPSIA: PREMATURIDADE E HIPÓXIA CEREBRAL EVOLUINDO COM SÍNDROME DE WEST

LESIONES CEREBRALES PERINATALES Y EPILEPSIA: PREMATURIDAD E HIPOXIA CEREBRAL EVOLUCIONANDO CON SÍNDROME DE WEST

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ABSTRACT

Introduction: West syndrome (WS) is the most frequent epileptic encephalopathy in the first year of life and is strongly correlated with prenatal and perinatal brain injury. Objective: To analyze the relationship between prematurity and birth asphyxia (cerebral hypoxia) with WS. Methods: This is an observational and cross-sectional study. All the patients with WS treated at Pediatric Neurology Service of Pequeno Príncipe Children's Hospital from January 2010 to January 2015 were analyzed. The patients underwent magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG). Results: Thirty-eight patients with WS, 23 (60.53%) females; ages ranging from 9 to 27 months (±16.6 months). Twenty (52.63%) patients had a history of hypoxia/anoxia perinatal, 8 (21.05%) were premature, 8 (21.05%) had brain malformations, 4 (10.53%) had Down syndrome, 4 (10.53%) had tuberous sclerosis, and 2 (5.26%) had no comorbidities. MRI showed: 9 (23.68%) multi-cystic encephalomalacia, 4 (10.53%) periventricular leukomalacia, 4 (10.53%) periventricular leukomalacia with cerebral atrophy, 4 (10.53%) periventricular nodules, 3 (7.89%) brain atrophy, 2 (5.26%) pachygyria associated with agenesis of corpus callosum, one (2.63%) agenesis of the corpus callosum, one (2.63%) right frontal dysplasia, one (2.63%) left frontal dysplasia, one (2.63%) right frontoparietal dysplasia, one (2.63%) left frontoparietal dysplasia, and one (2.63%) pachygyria. Conclusion: The history of hypoxia/anoxia perinatal and prematurity is very frequent in WS. Improved care during pregnancy and childbirth is very important to reduce perinatal brain injury, premature birth, and neurological morbidity.

Keywords: West syndrome; Brain hypoxia; Infant, premature.

RESUMO

Introdução: A síndrome de West (SW) é a mais frequente encefalopatia epiléptica do primeiro ano de vida e está fortemente relacionada com lesões cerebrais pré-natais e perinatais. Objetivo: Analisar a relação entre prematuridade e asfixia perinatal (hipóxia cerebral) e SW. Métodos: Este é um estudo observacional e transversal. Todos os pacientes com SW tratados no Serviço de Neurologia Pediátrica do Hospital Infantil Pequeno Príncipe entre janeiro de 2010 e janeiro de 2015 foram analisados. Os pacientes foram submetidos a ressonância magnética (RM) do encéfalo e eletroencefalograma (EEG). Resultados: Trinta e oito pacientes com SW, 23 (60,53%) do sexo feminino; idade entre 9 a 27 meses (±16,6 meses). Vinte (52,63%) pacientes tinham história de hipóxia/anóxia perinatal, 8 (21,05%) eram prematuros, 8 (21,05%) tinham malformações cerebrais, 4 (10,53%) tinham síndrome de Down, 4 (10,53%) tinham esclerose tuberosa e 2 (5,26%) não apresentavam nenhuma comorbidade. A RM

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mostrou: 9 (23,68%) casos de encefalomalácia multicística, 4 (10,53%) leucomalácia periventricular, 4 (10,53%) leucomalácia periventricular com atrofia cerebral, 4 (10,53%) nódulos periventriculares, 3 (7,89%) atrofia cerebral, 2 (5,26%) paquigiria associada à atrofia de corpo caloso, um (2,63%) agenesia de corpo caloso, um (2,63%) displasia frontal direita, um (2,63%) displasia frontal esquerda, um (2,63%) displasia frontoparietal direita, um (2,63%) displasia frontoparietal esquerda e um (2,63%) paquigiria. Conclusão: A história de hipóxia/anóxia perinatal e prematuridade é muito frequente na SW. A melhora dos cuidados durante a gestação e o parto é muito importante para reduzir lesões cerebrais perinatais, nascimentos prematuros e consequentemente, a morbidade neurológica.

Palavras-chave: *Síndrome de West; Hipóxia cerebral; Prematuridade.*

RESUMEN

Introducción: El síndrome de West (SW) es la más frecuente encefalopatía epiléptica del primer año de vida y está fuertemente relacionado con lesiones cerebrales prenatales y perinatales. Objetivo: Analizar la relación entre prematuridad y asfixia perinatal (hipoxia cerebral) y SW. Métodos: Este es un estudio observacional y transversal. Fueron analizados todos los pacientes con SW tratados en el Servicio de Neurología Pediátrica del Hospital Infantil Pequeno Príncipe entre enero de 2010 y enero de 2015. Los pacientes fueron sometidos a resonancia magnética (RM) del encéfalo y electroencefalograma (EEG). Resultados: Treinta y ocho pacientes con SW, 23 (60,53%) del sexo femenino; edad entre 9 a 27 meses (±16,6 meses). Veinte (52,63%) pacientes tenían historia de hipoxia/anoxia perinatal, 8 (21,05%) eran prematuros, 8 (21,05%) tenían malformaciones cerebrales, 4 (10,53%) tenían síndrome de Down, 4 (10,53%) tenían esclerosis tuberosa y 2 (5,26%) no presentaban ninguna comorbilidad. La RM mostró: 9 (23,68%) casos de encefalomalacia multiquística, 4 (10,53%) con leucomalacia periventricular, 4 (10,53%) con leucomalacia periventricular con atrofia cerebral, 4 (10,53%) con nódulos periventriculares, 3 (7,89%) con atrofia cerebral, 2 (5,26%) con paquigiria asociada a la atrofia de cuerpo calloso, uno (2,63%) con agenesia de cuerpo calloso, uno (2,63%) con displasia frontal derecha, uno (2,63%) con displasia frontal izquierda, uno (2,63%) con displasia frontoparietal derecha, uno (2,63%) con displasia frontoparietal izquierda y uno (2,63%) con paquigiria. Conclusión: La historia de hipoxia/anoxia perinatal y prematuridad es muy frecuente en SW. La mejora de los cuidados durante la gestación y el parto es muy importante para reducir lesiones cerebrales perinatales, nacimientos prematuros y consiguientemente, la morbilidad neurológica.

Descriptores: *Síndrome de West; Hipoxia cerebral; Prematuridad.*

INTRODUCTION

Recent technological advances in medicine, particularly in the last decade, has allowed a higher survival rate among the newborns. Furthermore, this increased survival is directly related to increased neurological morbidity, especially with new cases of cerebral palsy, mental retardation, developmental delay and symptomatic epilepsy. Brain lesions in the neonatal period due to prematurity and hypoxia/ischemia are directly related to the development of epilepsies and epileptic syndromes.

West syndrome (WS) is the most frequent epileptic encephalopathy during 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, and characterized by epileptic spasms (flexor, extensor or mixed), a typical pattern in interictal electroencephalogram (EEG) denominated hypsarrhythmia and developmental delay at diagnosis or during the course is required[1].

The aim of this study was to analyze the relationship between prematurity and birth asphyxia (cerebral hypoxia) with WS.

METHODS

The Ethics Committee on Research Involving Human Subjects approved all aspects of this research at our institution (number 771.087).

This is an observational and cross-sectional study. Medical records of all patients with WS treated at the Neurology Department of the "Hospital Infantil Pequeno Príncipe, Brazil" from January 2010 and January 2015 were analyzed. The data collected included the following variables: current age, age at the first seizure, sex, first EEG, magnetic resonance imaging (MRI) and antiepileptic drugs. The history of asphyxia and perinatal hypoxia was investigated in all patients.

All EEG was performed with a minimum duration of 30 minutes, and with electrodes positioned according to the International 10-20 System. The digital equipment with 21 channels used was NEUROTEC EQSA260 (made in Brazil), NEUROVIRTUAL BRAIN WAVE II (made in Brazil) and NIHON-KODEN (made in Japan).

The diagnosis of WS was established by the presence of seizure of spasms, EEG with an abnormal interictal pattern of hypsarrhythmia and developmental delay. We adopted

the WHO definition of prematurity - children born less than 37 weeks gestational age (more than 196 but less than 259 full days of gestation) and the extreme prematurity – children born less than 28 weeks gestational age (less than 196 days of gestation)[2]. Brain hypoxia/anoxia perinatal was defined as an insufficient cerebral oxygenation that occurs around the time of birth.

RESULTS

Were included 38 patients with WS, 23 (60.53%) females and 15 (39.47%) males, ages ranging from 9 to 27 months (±16.6 months). The age at the first seizure was between 3 to 15 months (±6.58 months). All patients had developmental delay, six had spasms associated with tonic seizures and 32 had exclusively spasms seizures. All EEG scans showed classic hypsarrhythmia (Table 1).

Co-morbidities: 20 (52.63%) patients had a history of hypoxia/anoxia perinatal, 8 (21.05%) were premature, 8 (21.05%) had brain malformations, 4 (10.53%) with Down syndrome, 4 (10.53%) with tuberous sclerosis and 2 (5.26%) had no morbid history (Table 2).

MRI was performed in all children and showed: 9 (23.68%) multi-cystic encephalomalacia, 4 (10.53%) periventricular leukomalacia, 4 (10.53%) periventricular leukomalacia with cerebral atrophy, 4 (10.53%) periventricular nodules, 3 (7.89%) brain atrophy, 2 (5.26%) pachygyria associated with agenesis of corpus callosum, 1 (2.63%) agenesis of the corpus callosum, 1 (2.63%) right frontal dysplasia, 1 (2.63%) left frontal dysplasia, 1 (2.63%) right frontoparietal dysplasia, 1 (2.63%) left frontoparietal dysplasia, 1 (2.63%) pachygiria. Six (15.79%) MRI scans were normal (Table 2). Clinical treatment: antiepileptic drugs used were sodium valproate, vigabatrin, phenobarbital and benzodiazepines. Some children were treated with adrenocorticotropic hormone (Table 3).

DISCUSSION

Epileptic encephalopathies (EE) are severe brain disorders in which the epileptic electrical discharges may contribute to developmental delay, progressive psychomotor dysfunction, and motor/cognitive impairment. This neurological deterioration is caused by an excessive and continuous excitatory activity in the cerebral cortex. Several epileptic syndromes can cause stagnation and regression of psychomotor development, such as WS, infantile epileptic encephalopathy with burst-suppression, neonatal myoclonic encephalopathy, severe myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome, epilepsy with continuous spike-and-waves during slow-wave sleep and myoclonic status in non-progressive encephalopathies[3].

The EE is also known as "catastrophic epilepsies of childhood". However, the "catastrophic" term should be avoided because it has a strong negative connotation to the families.

Table 1. Demographic data and classification of seizures.

Patient	Gender	Current Age*	Age at first seizure*	Classification
1	Female	23	6	Spasms + tonic
2	Female	26	7	Spasms
3	Female	11	5	Spasms
4	Female	20	9	Spasms
5	Female	17	8	Spasms + tonic
6	Male	15	11	Spasms
7	Female	19	8	Spasms
8	Female	24	15	Spasms + tonic
9	Male	12	5	Spasms
10	Male	10	8	Spasms
11	Female	20	8	Spasms
12	Female	10	6	Spasms
13	Female	17	9	Spasms
14	Male	21	9	Spasms
15	Female	18	5	Spasms
16	Male	16	7	Spasms + tonic
17	Female	16	7	Spasms + tonic
18	Female	25	11	Spasms
19	Male	27	13	Spasms
20	Female	18	6	Spasms
21	Female	17	6	Spasms
22	Female	19	8	Spasms
23	Male	14	7	Spasms
24	Female	13	6	Spasms + tonic
25	Male	9	3	Spasms
26	Male	9	4	Spasms
27	Female	17	3	Spasms
28	Female	16	5	Spasms
29	Male	13	4	Spasms
30	Female	15	3	Spasms
31	Female	12	7	Spasms
32	Female	20	4	Spasms
33	Male	16	4	Spasms
34	Male	19	3	Spasms
35	Female	17	6	Spasms
36	Male	9	5	Spasms
37	Male	15	6	Spasms
38	Male	9	3	Spasms

Note: * values in months.

Table 2. Neuroimaging and clinical history.

Patient	Magnetic Resonance	Medical History
1	Multi-cystic encephalomalacia	Perinatal hypoxia
2	Normal	Down syndrome
3	Right frontal dysplasia	Cerebral malformation
4	Agenesis of the corpus callosum	Cerebral malformation
5	Multi-cystic encephalomalacia	Perinatal hypoxia
6	Cerebral atrophy	Perinatal hypoxia
7	Normal	Down syndrome
8	Cerebral atrophy	Perinatal hypoxia
9	Multi-cystic encephalomalacia	Perinatal hypoxia
10	Normal	No morbid history
11	Left dysplasia frontoparietal	Cerebral malformation
12	Multi-cystic encephalomalacia	Perinatal hypoxia
13	Normal	Down syndrome
14	Periventricular leukomalacia	Prematurity (32 gw)
15	Normal	Down syndrome
16	Periventricular leukomalacia	Prematurity (30 gw)
17	Multi-cystic encephalomalacia	Perinatal hypoxia
18	Periventricular Leukomalacia + atrophy	Prematurity (28 gw)
19	Cerebral atrophy	Perinatal hypoxia
20	Normal	No morbid history
21	Pachygiria + agenesis of the corpus callosum	Cerebral malformation
22	Multi-cystic encephalomalacia	Perinatal hypoxia
23	Periventricular nodules	Tuberous sclerosis
24	Periventricular nodules	Tuberous sclerosis
25	Periventricular leukomalacia	Prematurity (34 gw)
26	Periventricular Leukomalacia + atrophy	Prematurity (32 gw)
27	Periventricular Leukomalacia + atrophy	Prematurity (28 gw)
28	Periventricular Leukomalacia + atrophy	Prematurity (30 gw)
29	Periventricular leukomalacia	Prematurity (30 gw)
30	Multi-cystic encephalomalacia	Perinatal hyposia
31	Multi-cystic encephalomalacia	Perinatal hypoxia
32	Multi-cystic encephalomalacia	Perinatal hypoxia
33	Periventricular nodules	Tuberous sclerosis
34	Periventricular nodules	Tuberous sclerosis
35	Left frontal dysplasia	Cerebral malformation
36	Pachygiria + agenesis of the corpus callosum	Cerebral malformation
37	Pachygiria	Cerebral malformation
38	Right frontoparietal dysplasia	Cerebral malformation

Note: GW – gestation weeks.

Table 3. Clinical treatment-antiepileptic drugs.

Patient	Gender	Antiepileptic drugs
1	Female	adrenocorticotropic hormone + vigabatrin
2	Female	vigabatrin + clonazepam
3	Female	sodium valproate + clonazepam + phenobarbital
4	Female	sodium valproate + clonazepam
5	Female	sodium valproate + phenobarbital
6	Male	adrenocorticotropic hormone + sodium valproate + clonazepam
7	Female	sodium valproate + clonazepam
8	Female	adrenocorticotropic hormone + vigabatrin
9	Male	sodium valproate + clonazepam
10	Male	sodium valproate + clonazepam
11	Female	vigabatrin
12	Female	sodium valproate + phenobarbital
13	Female	sodium valproate
14	Male	sodium valproate
15	Female	vigabatrin + clonazepam
16	Male	adrenocorticotropic hormone + vigabatrin
17	Female	sodium valproate + clonazepam
18	Female	adrenocorticotropic hormone + vigabatrin
19	Male	sodium valproate + clonazepam + phenobarbital
20	Female	vigabatrin + phenobarbital
21	Female	vigabatrin
22	Female	sodium valproate + clonazepam + phenobarbital
23	Male	adrenocorticotropic hormone + vigabatrin
24	Female	vigabatrin
25	Male	sodium valproate + clonazepam
26	Male	sodium valproate
27	Female	sodium valproate + phenobarbital
28	Female	sodium valproate
29	Male	sodium valproate + clonazepam
30	Female	sodium valproate
31	Female	adrenocorticotropic hormone + sodium valproate
32	Female	sodium valproate
33	Male	sodium valproate + clonazepam
34	Male	sodium valproate + phenobarbital
35	Female	sodium valproate
36	Male	adrenocorticotropic hormone + sodium valproate
37	Male	sodium valproate + clonazepam
38	Male	sodium valproate + phenobarbital

The immaturity of the brain seems to be a decisive factor for the occurrence of EE. Therefore, this nosological condition is considered age-related. Clinical observation demonstrates that brain damage occurring in the first days of life increases the risk of developing an EE. In this study, we analyze the relationship between acquired brain injury in the neonatal period (related to prematurity and hypoxia/anoxia brain) and WS.

Prematurity, hypoxia and brain damage

Preterm newborns represent approximately 10% of all live births and are a high-risk population for brain damage, and injuries can occur in white matter and brain cortex. These children have several risk factors for developmental impairment and symptomatic epilepsy (caused by structural lesions of the brain tissue), involving the ischemic pathway, inflammatory pathway and genetic susceptibility. Research in animal models demonstrates that within minutes of hypoxia/anoxia, metabolic changes, reduction in protein synthesis and an increase in excitatory neurotransmitters cause permanent damage to neurons[4].

Cardiovascular and respiratory complications in premature infants are common and can cause the reduction of systemic and cerebral oxygenation. The reduction of cerebral blood flow causes metabolic changes in neurons, reduces glucose to the central nervous system, alters the permeability of neuronal membranes (calcium ion), increases excitatory neurotransmitter (glutamate), reduce the production of antioxidant molecules, and, finally triggers the activation of a series of lytic intraneuronal enzymes. If this sequence of pathological events is maintained for a long time the damage of neuronal cells is irreversible. Activation of mast cells in brain tissue causes increased production of histamine and serotonin. These substances together with free radicals and reactive oxygen species (ROS) aggravate the injury of neurons[5,6].

Researchers in animal models have shown that interleukin (IL)-9 (addition of free radicals, ROS and other toxic substances) is related to the final damage to neuronal cells due to destruction of vital cellular structures such as mitochondria and plasma membrane cytokines are polypeptides or glycoproteins extracellular, soluble, produced by various types of cells at the site of injury and immune cells. During the phenomena that generate brain injury, there is the formation of a cytokines-cascade (the production of a cytokine triggers the production of various other cytokines)[6].

In preterm infants, some brain regions are more susceptible to injuries as around the occipital and frontal horns of the lateral ventricles (periventricular leukomalacia). Currently, it is known that prostaglandins and cytokines (particularly interleukin-9, interleukin-6 and tumor necrosis factor α) are associated with preterm labor. Cytokines may be directly or indirectly involved in the mechanisms of brain injury in premature infants. There appears to be the right relation between cytokine levels in the umbilical blood and the risk of central nervous system injury and future cerebral palsy[7].

Prematurity, brain damage and West syndrome

Although some epileptic encephalopathies have a genetic origin, most of these diseases are related to brain malformations or structural damage that are acquired early in life. Moreover, preterm infants have a greater risk of brain damage. There is a direct relationship between prematurity and neurological impairment.

The causes of WS appear to be extremely variable and little is known about the physiopathology[8]. Various types of brain injuries in early childhood can evolve with WS. Thus, it is possible that there is a common mechanism for all the cases. The "stress/corticotropin-releasing hormone theory" proposes that a common mechanism in all etiologies (regardless of the brain injury cause) provoke an increase in the release of stress-activated mediators in the specific brain structures (especially the neuropeptide CRH in brain stem and the limbic)[9].

Although there are prenatal disorders (neuronal migration disorders, schizencephaly, hydranencephaly, polymicrogyria, tuberous sclerosis, Sturge-Weber syndrome, incontinentia pigmenti, congenital infections, trisomy 21) and post-natal disorders (meningitis, encephalitis, pyridoxine dependency, biotinidase deficiency, mitochondrial encephalopathies, phenylketonuria, maple syrup urine disease, nonketotic hyperglycinemia, degenerative diseases, trauma) that evolve with WS, the perinatal etiologies (asphyxia, birth injury and complications of prematurity) are strongly related to EE and WS[1,3,4]. Mure *et al.*[10] showed that preterm infants with WS had better responses to treatment, especially oral medication, compared with those with prenatal and postnatal etiologies. Okumura *et al.*[11] analyzed the timing of brain insults in preterm infants who later developed WS. These authors showed that children of less than 29 weeks of gestation were more likely to suffer brain damage postnatally, and those of more than 28 weeks tended to have brain injury prenatally.

One of the most common brain injury in premature infants is the periventricular leukomalacia resulting in cerebral palsy and cognitive or attention deficit. The periventricular leukomalacia provokes focal necrosis in the periventricular white matter and can induce other cellular abnormalities (oligodendroglial precursors).

Kuzmaníc-Samija *et al.*[12] analyzed 37 infants diagnosed with WS caused by periventricular leukomalacia and concluded that these patients usually exhibit reduction in white matter volume, ventricular dilatation, impaired myelination, and changes in cortical gray matter. WS is a common complication of the severe periventricular leukomalacia and that it correlates strongly with epileptogenic paroxysms type polyspike-and-wave bursts.

CONCLUSIONS

Over 70% of the patients with WS analyzed in our study showed a history of hypoxia/anoxia perinatal and/or premature birth. These same data were reported in several other studies. A preterm newborn has a higher risk of hypoxic-ischemic damage due to the immaturity of the central nervous system.

Although the pathophysiological mechanisms involved in WS is not completely known; although acquired brain injury during the prenatal and perinatal period are closely related to this syndrome. Thus improving the quality of care for women during pregnancy and delivery reduce the risk of preterm birth and perinatal complications, and consequently decrease the neurological morbidity.

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