WALKER-WARBURG SYNDROME

REPORT OF TWO CASES

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ABSTRACT - The purpose of this study is to describe two infants that were diagnosed with Walker-Warburg syndrome (WWS), a rare form of congenital muscular dystrophy (CMD).They were studied in their clinical, laboratory, and neuroradiologic features. The index case had a brain magnetic resonance imaging (MRI) and the second patient had a head computerized tomography (CT). In addition, a literature review was performed to describe the main forms of CMD. The index case fulfilled all criteria for WWS. A brain MRI performed at age 4 months served to corroborate the clinical diagnosis, showing severe hydrocephalus, type II lissencephaly, cerebellar vermian aplasia, and a hypoplastic brain stem. The authors were able to establish a retrospective diagnosis of WWS in the index case's older sister, based upon her clinical picture and head CT report.

KEY WORDS: child, lissencephaly, hydrocephalus, congenital muscular dystrophy, Walker-Warburg syndrome.

Síndrome de Walker-Warburg: relato de dois casos

RESUMO - O objetivo deste estudo é descrever dois lactentes que receberam o diagnóstico de síndrome de Walker-Warburg (WWS), uma forma rara de distrofia muscular congênita (CMD). Investigamos as manifestações clínicas, laboratoriais e neurorradiológicas dos dois pacientes. O caso-índice submeteu-se a uma imagem de ressonância magnética (MRI) cerebral e o segundo paciente a tomografia computadorizada (CT) do crânio. Ademais, realizou-se revisão da literatura para descrever as principais formas de CMD. O caso-índice satisfez todos os critérios de WWS. Uma MRI cerebral realizada aos 4 meses de idade confirmou o diagnóstico clínico ao mostrar hidrocefalia acentuada, lissencefalia do tipo II, agenesia do corpo caloso, aplasia do vermis cerebelar e um tronco encefálico hipoplásico. O diagnóstico de WWS foi estabelecido retrospectivamente na irmã mais velha do caso-índice, com base nos achados clínicos e no laudo da CT do crânio.

PALAVRAS-CHAVE: criança, lissencefalia, hidrocefalia, distrofia muscular congênita, síndrome de Walker-Warburg.

Walker-Warburg syndrome (WWS) is described among the congenital muscular dystrophies (CMD), a heterogeneous group of disorders that are largely inherited as an autosomal recessive trait and that usually present at birth or shortly thereafter with muscle weakness, respiratory distress, muscle hypotonia, eye abnormalities, and/or multiple contractures (arthrogryposis).

The definition of CMD as a clinical entity began in 1908 with Howard's landmark description[1] of a neonate with muscular dystrophic changes. In 1960, Fukuyama et al.[2] reported on a group of 15

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patients from Japan showing CMD associated with central nervous system (CNS) abnormalities. Santavuori et al.[3] characterized in 1977 the Finnish type of muscle-eye-brain disease. In 1994, Tomé et al.4 described 13 patients affected by CMD who showed absence of merosin, the laminin α2 chain, which is connected to the muscle fiber plasma membrane cytoskeleton.

WWS was the eponym suggested by Dobyns et al.[5] after Walker's description[6] in 1942 of a child with hydrocephalus, lissencephaly, and eyes malformation, and Warburg's report[7] in 1978 of cases with retinal detachment associated with hydrocephalus. WWS has virtually replaced the previous acronym HARD ± E syndrome (hydrocephalus, agyria, and retinal dysplasia, with or without encephalocele), which had been suggested by Pagon et al.[8].

The purpose of this study is to describe two Brazilian cases of WWS. To the best of our knowledge, these are the first Brazilian patients with WWS to be reported.

CASE REPORTS

Case 1. This female infant is the third child of non-related parents and was diagnosed with hydrocephalus and polyhydramnios at 24 weeks gestation. She was delivered at term by cesarean section due to macrocephaly (head circumference [HC] at birth 43 cm). Apgar scores were 1/5/7 at 1, 5, and 10 minutes, and birth weight was 3.98 kg. She was noted to have eye abnormalities, hypotonia, contractures of both hip joints, and a fixed position of her fingers. She required respiratory support and vasopressor agents for 3 days. Cerebrospinal fluid (CSF) studies showed zero cells/mm3, a protein level of 181 mg/dL, a glucose level of 26 mg/dL, and a negative bacterial culture. A head CT at first week of age showed enlargement of all ventricles, predominantly of the right lateral ventricle, and an underdeveloped cerebellum. She was suspected to have a congenital infection, but all serologic tests were not diagnostic; toxoplasma IgG titer was 1/64 and rubella IgG titer was 143 IU/ml, but all IgM titers were negative. She had several episodes of apnea, one of which was followed by a cardiorespiratory arrest that responded promptly to resuscitation. A ventriculoperitoneal shunt (VPS) was placed at 26 days of age, when her HC had grown to 47 cm. Her hospital course was complicated by pneumonia and sepsis, which were treated with appropriate antibiotics. An ophthalmologic consult identified bilateral cataracts, iridocorneal adhesions leading to glaucoma, and enlarged corneas; retinae could not be examined. Those findings were consistent with Peters' anomaly. She was discharged from nursery at 2 ½ months of age.

Four weeks after discharge, she was brought to the emergency room with symptoms of VPS malfunction. She then developed facial automatisms and focal and generalized motor seizures, which responded promptly to phenobarbital. A brain MRI (Fig 1) showed findings that were considered consistent with a diagnosis of Walker-Warburg syndrome. Serum CK level was 1825 U/L. A nerve conduction velocity study/electromyography showed a normal nerve conduction, while needle study detected small amplitude polyphasic potentials and fibrillation, which suggested a myopathic disorder. At 6 months of age, she developed swallowing difficulties and has since been fed through a nasogastric tube. She currently has failure to thrive, profound developmental delay, and occasional seizures.

Case 2. This female infant was the index case's sister and was 6 ½ years her older. She displayed a remarkably similar clinical course and died at 10 months of age lacking a specific etiology for her neurologic syndrome. At 28 weeks gestation, an ultrasound detected hydrocephalus and polyhydramnios. She was delivered at term by cesarean section. Apgar scores were 3/4/6 at 1, 5, and 10 minutes. Birth weight was 4.13 kg and HC was 41 cm. She was hypoactive and was admitted to the intensive care nursery. She was noted to have micrognathia, small pupils that reacted to light, hypotonia, edema in lower limbs, and decreased movements, small low set ears, and hepatosplenomegaly. Serologic titers for congenital infections were negative, and serum CK was 3885 U/L. A transfontanel ultrasound (TFUS) at 7 days of age showed marked dilatation of lateral and third ventricles with compression of cerebral cortex. A head CT in the following week revealed, in addition to the TFUS findings, fused thalami, agenesis of cerebellar vermis, and a posterior fossa cyst. She received a VPS at 19 days of age. Post-operatively, she developed high-grade fever and generalized seizures, which were treated with phenobarbital. A diagnosis of infectious endocarditis was suspected, but two-dimension echocardiography was normal. She received antibiotics, although her fever remained unexplained, as all her diagnostic work-up turned out to be negative. An ophthalmologic consult was never obtained; her parents state that her eyes looked very similar to her younger sister's eyes and that she apparently was blind. She was discharged at age 3 ½ months in a stable condition, except of intermittent fever. At ten months of age, she died of a pneumonia. Parents declined an autopsy examination.
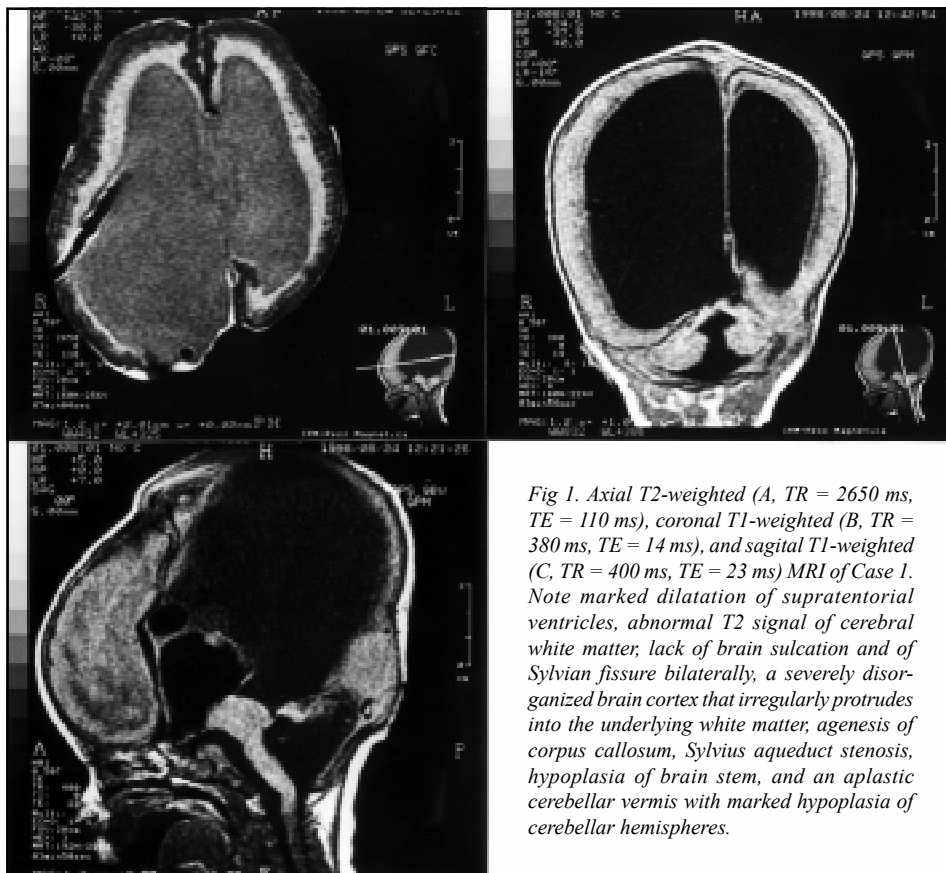
Fig 1. Axial T2-weighted (A, TR = 2650 ms, TE = 110 ms), coronal T1-weighted (B, TR = 380 ms, TE = 14 ms), and sagital T1-weighted (C, TR = 400 ms, TE = 23 ms) MRI of Case 1. Note marked dilatation of supratentorial ventricles, abnormal T2 signal of cerebral white matter, lack of brain sulcation and of Sylvian fissure bilaterally, a severely disorganized brain cortex that irregularly protrudes into the underlying white matter, agenesis of corpus callosum, Sylvius aqueduct stenosis, hypoplasia of brain stem, and an aplastic cerebellar vermis with marked hypoplasia of cerebellar hemispheres.

DISCUSSION

We describe two female siblings who presented in utero with severe hydrocephalus and who were noted to have diffuse weakness, muscle hypotonia, and joint contractures at birth. This clinical picture led to a suspicion of CMD in Case 1. Her eye abnormalities (Peters' anomaly) plus the brain MRI findings in the setting of CMD led to a diagnosis of WWS. Although we did not have access to brain imaging films obtained for her older sister, the radiological report is highly consistent with WWS. In view of the clinical similarities between the two siblings plus a definite diagnosis of WWS in the index case, we believe it is reasonable to make the same diagnosis in Case 2.

Although WWS is an extremely rare syndrome, the other CMDs are more common. Duggan et al.[9] recently reported an incidence of 69 cases of CMD (12.4%) among 556 patients presenting with a myopathy. One should consider a diagnosis of CMD in any neonate or infant who presents with generalized weakness (usually proximal greater than distal, and weakness greater in arms than in legs), respiratory distress, muscle hypotonia, eye abnormalities, and/or arthrogryposis. Given that presentation, the differential diagnosis should also include congenital myotonic dystrophy, congenital myopathies, and spinal muscular atrophy.

In reviewing 63 cases, Dobyns et al.[10] established the following diagnostic criteria for WWS: type II lissencephaly, cerebellar malformation, retinal malformation, and congenital muscular dystrophy. In addition, there are two frequent abnormalities, ventricular dilatation with or without hydrocephalus and anterior chamber malformation (Peters' anomaly), that are helpful, although not necessary to establish

a diagnosis. Posterior cephaloceles and cleft lip/palate were present in 25% and 14% in their series, respectively. Those authors proposed that WWS and MEBD are variations of a single clinical spectrum, i.e., allelic to a given gene, and there has been another study[11] claiming that WWS and FCMD could be assigned to the same locus on chromosome 9q31-33. However, both WWS and MEBD have been excluded from this locus. Although these three entities show clinical similarities and this issue is still controversial, the prevalent opinion[12-14] is that WWS, MEBD, and FCMD are different entities. In addition, recent studies have emphasized morphologic differences in muscle biopsy, i.e., there may be laminin α2 (merosin) deficiency in MEBD[14] whereas merosin is normal and laminin β2 chain may be deficient in WWS[15]. Nevertheless, muscle biopsy often shows a nonspecific dystrophic pattern only, including increased variability of fiber diameter, internal nuclei, fiber splitting, and fiber necrosis.

Classification of the CMDs has been debated in a series of international workshops under the guidance of Victor Dubowitz, the third of which occurred in March 1996[16]. Currently, most authors[12, 13] favor the categorization of five main types (Table 1), including classic or "pure" CMD, merosin-negative

Table 1. Main distinctive features of the congenital muscular dystrophies.

	Clinical course	Muscle biopsy	Ocular abnormalities	Inheritance gene mapping	Serum CK	Brain MRI findings
IA. "Pure" CMD	Developmental delay, IQ nl or subnormal, most sit up, death prior to adolescence	DP; Nl merosin	None	AR; ?	10-20 x Nl	Nl
IB. Merosin Negative CMD	More severe than above; seizures in 20%, dysmorphic features	DP; absent merosin	None	AR; 6q2	3-50 x Nl	Mild: Increased T2 signal in PV and subcortical WM
II. Fukuyama CMD	Normal IQ to severe MR, a few stand at age 4, seizures in 1/3, death by 10 yr.	DP; merosin may be deficient	Mild: Myopia, nystagmus, optic atrophy, choreoretinal degeneration	AR; 9q31	10-50 x Nl	Moderate: Delayed myelination in WM, micropolygyria, pachygyria, T2L, minor changes in cerebellar hemispheres
III. Muscle-Eye-Brain Disease (Finnish Type CMD)	MR (moderate-severe), seizures common, spasticity after age 5, long survival (10-30 yr.)	DP; merosin may be deficient	Moderate: Myopia, glaucoma, cataracts, Peters' anomaly, hipoplastic optic nerve, retinal changes	AR; 1p32-p34	Up to 10 x Nl	Moderate-severe: Abnl PV WM, micropolygyria, pachygyria, T2L, brain stem hypoplasia, cerebellar dysgenesis, hydrocephalus
IV. Walker-Warburg Syndrome	MR (severe), profound developmental delay (some sit), seizures common, mean survival 4 to 9 mo.	DP; Nl merosin; laminin β2 chain may be deficient	Severe: Glaucoma, cataracts, microphthalmia, megalocornea, Peters' anomaly retinal dysplasia and detachment	AR; ?	3-60 x Nl	Severe: Diffusely Abnl WM, micropolygyria, agyria, T2L,brain stem hypoplasia, cerebellar hypoplasia, hydrocephalus

Abnl, abnormal; AR, autosomal recessive; CMD, congenital muscular dystrophy; DP, dystrophic pattern; MR, mental retardation; Nl, normal; PV, periventricular; T2L, type II lissencephaly; WM, cerebral white matter.

CMD (MNCMD), Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain disease (MEBD, the Finnish type), and WWS. Identification of these types has been made possible by a combination of clinical, morphologic, and molecular studies. The advent of magnetic resonance imaging (MRI) over the past 15 years has helped to characterize the CMD types[17, 18]. Nevertheless, neuroimaging findings may not be enough to identify the CMD type[19], as for example type II (cobblestone) lissencephaly has been described in FCMD, MEBD, and WWS.

Differentiation of the five main types of CMD requires a thorough physical exam for associated malformations, serum CK determination, brain imaging (preferably with MRI), and an ophthalmologic examination (Table 1). This task is not always easy, as there is a great deal of overlap between clinical types and the parameters used to categorize a given patient may vary in a specific CMD type (e.g., ocular abnormalities) and even in a same patient over time (e.g., CK level). However, severity of clinical features[12], ocular defects[14,20], and radiologic findings[18] may be used as a diagnostic clue, since they tend to increase progressively from FCMD through MEBD to WWS. Considering that both FCMD and MEBD may be strongly linked to an ethnic group, a knowledge of the patient's ethnic background may also be helpful.

However, as stressed by Warburg[21], one can not identify genetic entities on clinical grounds only ("the phenotype does not predict the genotype"). Therefore, a more definitive classification of the several types of CMD must await localization and cloning of affected genes. A major step toward this goal may have been achieved by Cormand et al.[22], who recently reported localization of the MEBD gene to 1p32-p34.

Previous studies have shown that a prenatal diagnosis of WWS is possible through fetal ultrasonography, which may detect hydrocephalus[23] and/or retinal detachment[24] in an affected fetus. Had Case 2 been appropriately diagnosed based upon its clinical, laboratory, and radiological features, a prenatal diagnosis of WWS would have been possible for Case 1 when hydrocephalus was detected at 24 weeks gestation. Thus, accurate categorization of an infant with CMD is critical for appropriate parent counseling.

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