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MEROSIN-POSITIVE CONGENITAL MUSCULAR DYSTROPHY

Neuroimaging findings

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ABSTRACT - Congenital muscle dystrophy (CMD) is a heterogeneous group of autosomal recessive myopathies. It is known that CMD may affect the central nervous system (CNS). Some authors have shown that merosin-negative CMD patients may have encephalic metabolic disturbances. In order to study metabolic changes within the brain, the authors performed a magnetic resonance spectroscopy (MRS) study in a 1-year-old girl with merosin-positive CMD (MP-CMD). MRS of brain demonstrated that NAA/Cr ratio was decreased (1.52), while Cho/Cr ratio was increased (1.78). These findings suggest that metabolic changes in CNS can also be found in patients with MP-CMD.

KEY WORDS: congenital muscle dystrophy, merosin, magnetic resonance.

Distrofia muscular congênita merosina-positiva: achados de neuroimagem

RESUMO - A distrofia muscular congênita (DMC) é um grupo heterogêneo de miopatias autossômicas recessivas que também podem afetar o sistema nervoso central (SNC). Alguns autores mostraram previamente que pacientes com DMC por deficiência da merosina podem apresentar alterações metabólicas no encéfalo. Com o objetivo de estudar as possíveis alterações metabólicas no SNC, os autores realizaram um estudo por ressonância magnética com espectroscopia em uma paciente de 1 ano com DMC sem deficiência da merosina. A razão NAA/Cr estava reduzida (1,52), enquanto que a razão Cho/Cr estava aumentada (1,78). Estes achados sugerem que alterações metabólicas no SNC também podem ser encontradas em pacientes com DMC merosina-positiva.

PALAVRAS-CHAVE: distrofia muscular congênita, merosina, ressonância magnética.

In June 2005, Aslan and co-workers published a case report of a 4-year-old girl with merosin-negative congenital muscular dystrophy (MN-CMD)[1]. The aim of that article was to report magnetic resonance spectroscopy (MRS) features of this entity. As they commented, CMD is essentially a heterogeneous group of muscular diseases with autosomal recessive inheritance[1,2]. Its main clinical presentation includes muscle weakness, hypotonia and dystrophic changes on skeletal muscle biopsy. All of them are present at birth or within the first 6 months of life[3]. It is also known that CMD may affect the central nervous system (CNS), as well[1,4-6]. Classically, CMD can be divided into the following sub-groups: merosin-negative and merosin-positive CMD, the Fukuyama CMD, the Ullrich syndrome, the Walker-Warburg syndrome, the muscle-eye-brain disease and CMD with spinal rigidity[2].

Merosin is found in skeletal muscle fibers, in basement membrane of Schwann cells and in blood vessels within the brain[1]. Thus, a patient with merosin deficiency can develop white matter abnormalities[5]. Surprisingly, some authors have recently reported some cases of white matter involvement among patients with merosin-positive CMD (MP-CMD). Their findings suggest that CNS can also be involved in MP-CMD[4,6].

In order to study possible metabolic changes within the brain, we performed a single voxel proton MRS in a 1-year-old Brazilian girl with proven MP-CMD and white matter involvement.

This study was undertaken with informed consent from parents in accordance with Sarah Network of Hospitals for Rehabilitation ethical guidelines.

CASE

A 1-year-old girl was admitted to our rehabilitation center with global development delay and hypotonia. There was no history of neurological diseases in her family and

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her parents were not consanguineous. Pregnancy and delivery were unremarkable. On physical examination, head balance was absent, and voluntary motor activity was globally reduced. There were also lower lip protrusion and facial weakness. Deep tendon reflexes were present, and Babisnki sign was absent. The optical discs were normal, and a convergent strabismus was found. There were no joint contractures or calf hypertrophy. Her weight was 6.8 Kg (<5 percentile), head circumference was 41.5 cm (<5 percentile), and length was 41 cm (<5 percentile). The rest of physical examination was normal. Cognition was assessed using the Bayley Scale of Infant Development (mental scale), which revealed a moderate impairment in executive functions and language. Creatinine phosphokinase (CPK) level was markedly raised (4990 UI/L). Muscle biopsy disclosed dystrophic changes (mild nuclear centralization, diffuse atrophy, focal necrosis and perimysial/endomysial fibrosis). Spectrin, emerin, and merosin staining were all positive. EMG showed myopathic features (polyphasic potentials of short duration and low amplitude), with normal nerve conduction. Auditory and visual evoked potentials were both bilaterally abnormal, suggesting a central demyelinating process.

Magnetic resonance imaging (MRI) and spectroscopy of the brain were performed on a 1.5-T system (Magneton Symphony, Siemens™). Cortical dysplasia, cerebellar hypoplasia, cerebellar cists and ventriculomegaly were not seen. Fluid-attenuated inversion recovery and T2 imaging showed diffuse and symmetric hyperintensity in white matter (Fig 1). Single voxel spectroscopy performed using a point-resolved spectroscopy sequence (TR: 1500, TE: 144 ms) with 130 averages; voxel sizes of 20x20x20 mm was used. Localized shimming and optimizations of the Gaussian pulse amplitude for maximum water suppression were adjusted prior to acquisition of the spectra. A spectral sweep width of 1000 Hz was used with data size of 1024 points. Analysis of the spectra was performed with spectroscopy software package of the MRI system supplied by the manufacturer. Voxels were placed in the frontal and posterior parietal white matter. The spectra were referenced to creatine (2.98 ppm). The signals from N-acetylaspartate (NAA), choline (Cho), and creatine (Cr) were integrated. Peak area metabolite ratios (NAA/Cr and Cho/Cr) were calculated. In our study, MRS of brain demonstrated that NAA/Cr ratio was decreased (1.52), while Cho/Cr ratio was increased (1.78) (Fig 2).

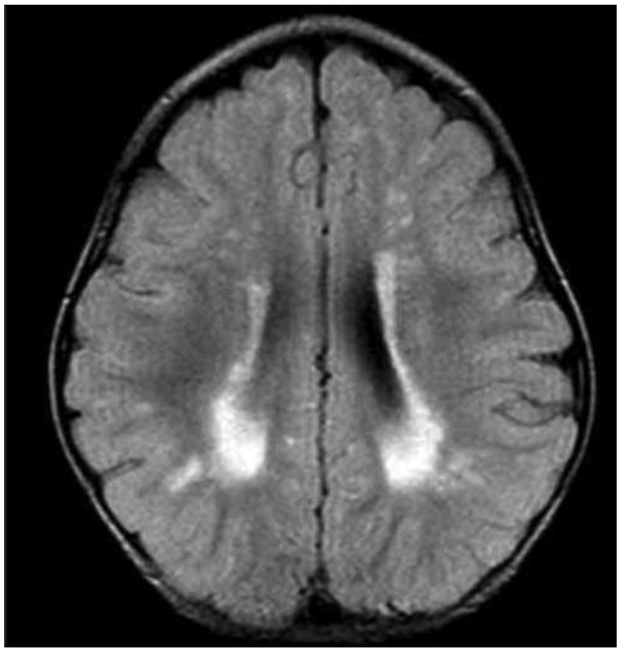

Fig 1. MRI FLAIR image showing diffuse and symmetric white matter hyperintensities.

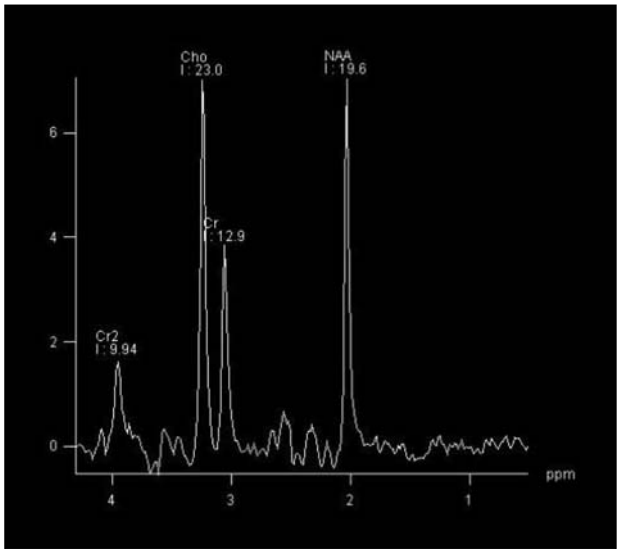

Fig 2. MRS of frontal white matter showing NAA, Cr and Cho peaks.

DISCUSSION

The phenotype described in our patient does not fulfill any of the diagnostic criteria for the known forms of CMD. According to Muntoni and Voit, there are many forms of CMD that cannot be classified based on clinical presentation or on pathological and molecular abnormalities[7]. Thus, the term MP-CMD can be generically used in this group.

As in the case described by Aslan and co-workers, diffuse white matter alterations could also be found in our patient`s MRI[1]. Curiously, in both cases, these changes were only detected in periventricular and subcortical areas (the last to be myelinated), while corpus callosum and internal capsule were spared. On the other hand, Ribeiro and co-workers reported a case of a MP-CMD woman with some different white matter alterations[4]. In their case, corpus callosum, posterior arms of internal capsules and the pyramidal tracts in brainstem were also affected. Thus, it seems that leucoencephalopathy can also be present among patients with MP-CMD, however, there

is still a need of a better characterization of the white matter involvement.

Some authors reported many structural encephalic malformations among patients with CMD, such as cortical dysplasia, cerebellar hypoplasia, cerebellar cists and ventriculomegaly[4,8-10]. For example, Topaloglu and co-workers reported two cases of CMD and cerebellar cysts on cranial MRI[9]. Belpaire-Delthiou and co-workers reported a case of a patient with CMD and cortical dysplasia, a thin corpus callosum, and diffuse ventriculomegaly[10]. In our patient, for an unknown reason, none of these alterations were detected on MRI. It is probably a consequence of genetic and clinical variability of CMD.

MRS is a non-invasive method that allows in vivo examination of brain metabolic changes and neuroaxonal integrity[11]. NAA is the most important neuroaxonal marker measured by MRS. Thus, a decrease in NAA/Cr ratio, seen in our patient, means that neuroaxonal damage may have occurred. Moreover, an increased Cho/Cr ratio, found in our patient, probably means that there is a disruption of normal myelin or that Cho-containing molecules are not being incorporated into myelin[1]. Aslan and co-workers also found this increased ratio in their MN-CMD patient. Thus, an elevated Cho/Cr ratio probably does not represent a specific feature of any known CMD subtypes. Besides, an increase in Cho/Cr ratio can also be seen among patients with other conditions, such as demyelinating lesions and brain gliomas.

During the recent years, MRS and MRI have been currently done in patients with CMD. It will probably help physicians in the elucidation of brain metabolic disturbances among these patients. Some authors believe that MRS and/or MRI should be present in the assessment of all patients with CMD[1,4]. It is important to note, however, that neuroimaging findings in CMD are almost always non-specific and one must be aware of the potential risks of sedation of a myopathic infant during the neuroimaging exam.

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