CASO CLÍNICO/CASE REPORT

Congenital Muscular Dystrophy Type 1A: The Role of Multidisciplinary Rehabilitation

Distrofia Muscular Congénita Tipo 1A: O Papel da Reabilitação Multidisciplinar

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Abstract

Merosinopathy is a subtype of muscular dystrophy with recessive autosomal transmission, resulting from an α2-chain-laminin/merosin deficiency. It affects around 1-9/1 000 000 individuals. Classically, it is subdivided in two phenotypic categories: one that is more common and severe, known as congenital muscular dystrophy type 1A, and a lesser common form of mild presentation.

Congenital muscular dystrophy type 1A presents early with severe neonatal hypotonia and inability to stand and walk. Dysphagia, respiratory failure and scoliosis may also occur. There is no curative therapy, thereby the control and prevention of complications are the available approach.

The authors present a case report of a congenital muscular dystrophy type 1A patient with a compound heterozygosity mutation presenting a global psychomotor development delay under multidisciplinary rehabilitation treatment.

Resumo

A merosinopatia é um subtipo de distrofia muscular com transmissão autossómica recessiva, que resulta de um defeito da cadeia α2 da laminina (ou merosina). Afeta cerca de 1-9/1 000 000 indivíduos. Classicamente, é subdividida em duas categorias fenotípicas: uma mais comum e grave, conhecida como distrofia muscular congénita tipo 1A, e uma forma menos comum de apresentação ligeira.

A distrofia muscular congénita tipo 1A apresenta-se precocemente com hipotonia neonatal grave, e incapacidade de ortostatismo e marcha. Pode também ocorrer disfagia, insuficiência respiratória e escoliose. Não existe um tratamento curativo, baseando-se a abordagem desta doença no controlo e prevenção das complicações.

Os autores relatam o caso de um doente com distrofia muscular congénita tipo 1A com mutação em heterozigotia composta, que apresenta um atraso global no desenvolvimento psicomotor, sob tratamento de reabilitação multidisciplinar.

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Introduction

Muscular dystrophies are considered a subgroup of primary myopathies with proven genetic cause. They can be classified according to the age of presentation in those with presentation at birth or first months of life - congenital muscular dystrophy (CMD) - and those with later onset.[1]

Merosinopathy is a subtype of muscle dystrophy, with autosomal recessive transmission, which results from deficiency of α2-chain-laminin (or merosin). It is coded by the *LAMA2* gene located in the 6q22 chromosome[2,3] and it is a tissue-specific component of the extracellular matrix with a key role in myotubes stability and apoptosis.[4] Globally, it affects about 1-9/1 000 000 individuals[5], and in the European continent it is one of the most frequent neuromuscular disorders in children, accounting for about 50% of CMD.[2,3]

This disease is classically divided into two main phenotypic categories: a more common severe early-onset form, presenting with features of CMD, also known as congenital muscular dystrophy type 1A (MDC1A), and a much less common, milder, later-onset form often presenting with a limb-girdle muscular dystrophy (LGMD) phenotype with prominent joint contractures.[4]

Generally, patients with a severe disease have complete loss of merosin and present early with severe neonatal hypotonia and inability to stand or walk, while patients with milder clinical presentations manifest later and most acquire gait.[5,6] Merosinopathy with complete loss of merosin may also present dysphagia, respiratory failure and scoliosis, and may develop seizures and demyelinating polyneuropathy.[7] Most patients do not exhibit cognitive deficits, however, in some children a moderate psychomotor development delay is observed.[2,8]

The identification of two pathogenic variants in the *LAMA2* gene is the diagnostic gold standard. However, diagnosis can be supported by high serum levels of creatinine kinase, alterations in visual evoked and somatosensory potentials, white matter changes on brain magnetic resonance imaging and dystrophic characteristics on muscle biopsy.[2,4,8,9] Prenatal diagnosis can be made by immunocytochemical and molecular genetics studies of trophoblast.[2]

Since there is no curative therapy for this muscle dystrophy, the therapeutic approach focuses on clinical manifestations through a multidisciplinary rehabilitation treatment.[5]

Case Report

A male patient was referred to the physical medicine and rehabilitation (PM&R) consultation by his pediatrician at 6-month-old.

He is the first son of healthy Caucasian parents, with an uneventful pregnancy and delivery. He was delivered at 38 weeks of gestation, with an Apgar score of 9, 10 and 10 at 1, 5 and 10 minutes, respectively. Birth weight and height were 2830 g and 49 cm, respectively.

As postpartum complications, he developed neonatal jaundice at day 2, requiring phototherapy. Feeding difficulties were also noted at day 3, with weak suction reflexes and discoordination of suction/swallowing movements. At 3-week-old he developed an acute bronchiolitis due to respiratory syncytial virus (RSV), with respiratory failure, and need for invasive mechanical ventilation (IMV) initially and continuous positive airway pressure (CPAP) posteriorly, having been hospitalized in the intensive care unit (ICU).

At 6-month-old, patient was referred to pediatric neurology consultation for general hypotonia noticed on general pediatrics consultation. Here, it was identified axial and peripheral hypotonia with important weakness of the shoulder girdle, absence of cephalic control not tolerating prone position, and inability to roll over.

At 12-month-old, in PM&R consultation, the patient was able to fix and follow the gaze, babble, abduct the shoulders to 40º and remain seated without support, despite the axial and peripheral hypotonia. In supine and prone positions, he could not raise his head and showed scarce spontaneous movements of the lower limbs. He was also not capable of assuming standing position or walking and showed an ineffective cough.

Currently, at 18-month-old, he is unable to raise his head in the prone or supine positions, assume standing position, or roll over. He can remain seated **(Fig. 1)** without support, exploring the environment only in the midline without axial control outside this axis. He is able to abduct the left shoulder up to 90º, but not the right one **(Fig. 2)**. In the assessment of orofacial musculature,

Figure 1. Patient in sitting position without support.

Figure 2. Impaired right shoulder abduction and axial hypotonia.

he presents low muscle tone with weak jaw movements and low diversity of tongue movements during chewing, exhibiting poor cleaning of intra and extra-oral residues. Concerning dysphagia evaluation, he presents sialorrhea and requires multiple swallows for liquid deglutition. Current diet recommendations are soft diet and thin liquids. Cognitive evaluation reveals attention deficit, rudimentary symbolic game, primitive attitude (screams and cry) to frustration, and weak social interaction. Concerning language, he presents a single word repetitive speech with reduced vocabulary.

Diagnostic work-up included biopsy of the deltoid muscle performed at 12-month-old that revealed a dystrophic profile with atrophic and occasional necrotic fibers, focal fibrosis and adipose replacement areas. Merosin immunohistochemical study demonstrated complete loss of normal sarcolemma immunoreactivity. Genetic study identified compound heterozygosity for two non-contiguous deletions in the *LAMA2* gene (deletion of exons 3 and 4, and deletion of exon 56), confirming the clinical suspicion of merosinopathy. Both deletions are presumably of the out-of-frame type, being compatible with a clinical presentation of MDC1A.

This patient is under a multidisciplinary rehabilitation program with physical, speech and occupational therapy. He performs joint mobilization, balance training in sitting and standing positions **(Fig. 3)**, standing frame, postural transfers, and respiratory kinesiotherapy. Treatment also includes cognitive stimulation, manual dexterity training and training of activities of daily living. In speech therapy, he performs orofacial motor training and language and speech development training. Due to ineffective cough, he performs cough assist 2 to 3 times a day.

Figure 3. Balance training in standing position.

Discussion

This case report presents a MDC1A with a compound heterozygosity mutation of the *LAMA2* gene resulting in complete loss of merosin.

The presentation phenotype is usually characterized by severe generalized hypotonia at birth, associated with feeding difficulties and poor weight evolution.[5,10] However, clinical manifestations may only become evident later during psychomotor development, with patients presenting poor cephalic control and inability to roll or sit.[1,5,8,10,11] In this clinical case, weak suction reflexes and a discoordination of suction/swallowing movements were noticed in the early days of life, with axial and peripheral hypotonia only noticed around 6-month-old.

Early in the first month, patient was admitted in the ICU for acute bronchiolitis with respiratory failure and need for IMV and CPAP. Due to weakness of intercostal and accessory muscles, respiratory complications with recurrent respiratory infections and respiratory failure are common in these patients. This is explained by weak cough reflex and restrictive respiratory pattern, that result in decreased secretion clearance, and decreased total lung capacity and forced vital capacity, respectively.[5,9] In fact, respiratory tract infections are the most common cause of death, with 30% dying in the first decade of life.[5]

In general, there is a development delay, with late acquisition of skills for the age group. Literature is consensual in the description of delayed motor development; however, cognitive delay is not a universal characteristic.[1-3,5,8-10] In our case, we have been assisting to a global

psychomotor development delay with deficits in multiple domains (motor: global and fine; and cognitive: attention, problem solving, social cognition and language).

Therapies are being investigated and advances are being made in the field of gene therapy.[5,12,13] However, currently there is no curative therapy for this disease, so like in other muscular dystrophies, the control and prevention of complications are the available approach. This patient is attending physiotherapy, speech therapy and occupational therapy sessions twice a week. Stretching exercises promote mobility and prevent contractures, and chest physiotherapy prevents respiratory infections. Speech and occupational therapies are also important to enhance motor and cognitive development.[4] Due to deglutition dysfunction, diet modifications may be needed, and respiratory function should be monitored as some individuals benefit from cough assist, non-invasive ventilation, or even mechanical ventilation via tracheostomy. Surgical interventions for orthopedic complications may also be considered.

This case report enhances the important role of a comprehensive multidisciplinary rehabilitation program in the approach of patients with MDC1A. Despite the absence of disease modifying therapies, rehabilitation may improve the functionality and quality of life of these patients and delay the complications of the disease. ■

Contributorship Statement / Declaração de Contribuição

RMS and CB contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted. GP, CV and IC contributed to the acquisition of data, analysis and interpretation of data, and final approval of the version to be submitted.

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