X-linked myotubular myopathy: a clinical report and a review of the mild phenotype

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Introduction. X-linked myotubular myopathy is a rare centronuclear myopathy that affects approximately 1 in 50,000 male newborns caused by pathogenic variants in the myotubularin 1 gene (*MTM1*). The clinical severity varies, however the need for ventilatory support occurs almost invariably.

Case report. We report the case of a 4-year-old boy presenting mild muscle hypotonia at 12 months-old, expressive language disorder, global developmental delay, and a sensory processing disorder. Clinical exome sequencing identified the hemizygous variant c.722G>A p.(Arg241His) in exon 9 of the myotubularin 1 gene (NM_000252.2). The mother is a heterozygous carrier of the same variant. A diagnosis of a mild form of maternal inherited X-linked myotubular myopathy was established. The child presented significant improvement with speech, occupational, and physical therapies, with no respiratory intercurrences or ventilator dependency.

Conclusion. The presentation of a mild form of this myotubular myopathy, being less commonly reported, added challenge to the diagnosis. The combination of mild hypotonia, feeding difficulties and expressive language disorder should raise suspicion of a neuromuscular disease. There is a lack of verified motor or developmental scores specific to this myopathy to further determine prognosis and need of other therapies. While currently the severity myotubular myopathy is classified according to ventilator dependency, this may be insufficient and unapplicable to milder cases. There is an evident need for a grading system for mild and moderate cases assessing muscle weakness and fatigue, daily life limitations, motor developmental delay, early phenotypical scores, or recurrent respiratory infections.

Key words. Developmental delay. Genetic counselling. Language disorders. Muscle hypotonia. Myotubular myopathy. Myotubularin.

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Introduction

X-linked myotubular myopathy is a rare centronuclear myopathy that affects approximately 1 in 50,000 male new-borns. This myopathy was first reported by A. Spiro in 1966 in a 12 year old boy with progressive generalized motor weakness and, histologically, myotubes with central nuclei and lack of myofibrils [1]. It is caused by pathogenic variants in the myotubularin 1 gene (*MTM1*), on chromosomal region Xq28, responsible for encoding ubiquitous phosphatase myotubularin. A recent multicentre retrospective analysis revealed that loss-of-function variants due to frameshift and nonsense variants are the most common type of change [2]. The clinical severity varies and is classified by the degree of ventilatory support. Most patients present a severe phenotype (55-79%), while 6-16% are moderate and 15-29% have a mild form of the disease [3]. Patients with most severe forms require early ventilator support and frequently die within the first year of life, while long term survivors have chronic respiratory failure with ventilator dependency and are non-ambulant [4]. Mild forms have been described in patients with no need for ventilatory or feeding support and little to none motor compromise. We report the case of a 4-year-old boy with a developmental delay history and a past of lower tract infections, who was otherwise healthy.

Case report

A 12 months-old male child was admitted to the child neurology outpatient clinic due to developmental delay. He was a full-term baby, born from an uneventful pregnancy, with healthy non consanguineous parents and two older healthy brothers. The boy had an history of two viral lower tract respiratory infections since he was 6 months-old, with two hospital admissions, without need of ventilatory support, and was followed in pneumology outpatient clinic due to recurrent wheezing. On

physical examination he presented brachycephaly, mild hypotonia, normal osteotendinous reflexes and a bilateral 2-3 toes syndactyly. Head circumference was between the 85th and 97th percentiles. Stature and height were above the 97th percentile. He did not show ptosis or ophthalmoplegia. At 12 months-old, he was able to sit unassisted, but he could not get to sitting position. He seemed to understand simple orders but was not able to vocalize. Parents were also concerned with feeding; while describing that he had no problems with liquids, they reported apparent difficulty with chewing. Speech therapy, occupational therapy and physical therapy were started, with significant improvement. From born until the age of 4 years old he presented a slow but positive psychomotor evolution. He started independent walking at 18 months-old while expressive language was significantly delayed with words starting at 3 years old and sentences with 4 years-old. Social skills were always preserved; however, communication was affected. Developmental assessment revealed a global developmental delay (global developmental quotient 70) and a sensory processing disorder. He has no respiratory problems since the age of 3 years and 6 months. Cardiology assessment revealed no structural heart anomaly. Ear, nose, and throat assessments, including evoked auditory potentials, were normal. A brain magnetic resonance imaging at the age of 2 years-old revealed brachycephaly, normal brain parenchyma, adequate myelination for age, enlargement of the subarachnoid spaces in the frontal-parietal brain, with reduction of parenchymal volume, a wide posterior fossa with slight counter-clockwise rotation of the vermis and an arachnoid cyst compressing left cerebellum hemisphere. An array comparative genomic hybridization showed nonrelevant variants and a metabolic study work up was normal. Clinical exome sequencing identified the hemizygous variant c.722G>A p.(Arg241His) in exon 9 of the *MTM1* gene (NM_000252.2), associated with myotubular myopathy. This variant was classified as likely pathogenic according to the American College of Medical Genetics and Genomics variant classification guidelines and, to our knowledge, has never been reported before. Muscle biopsy revealed atrophic myofibers, some rounded myofibers with internally located nuclei and, even though not frequent, accumulation of centrally located staining with oxidative stains some with nuclear centralization, commonly related with *MTM1* gene myopathies. Genetic testing in patient's mother showed that she is a heterozygous carrier of the same variant in *MTM1* gene, which is not unexpected since only 10-20% of patients carry *de novo* mutation [5]. In addition, we found out that she presents mild neuromuscular symptoms since youth that were not valued before.

Discussion

Our patient never presented respiratory deficiency with ventilation dependency nor severe hypotonia, the most severe, hence most common, presenting symptoms of this condition. The fact that he presents a mild form of this condition, being less commonly reported, added challenge to the diagnosis. We consider relevant to highlight the high prevalence of motor developmental delay in mild cases reported in the literature, as well as the muscle weakness in older patients, since this could give clues regarding our patient's prognosis and evolution. Our case fits most of the most common clinical features, including mild hypotonia, swallowing difficulties, and lack of ventilator dependency. Interestingly, he lacks some almost ubiquitous phenotypical features, namely myotonic facies, high arched palate, ophthalmoplegia or shoulder gridle weakness. This case highlights that the presentation of mild hypotonia, feeding difficulties and expressive language disorder should also raise suspicion of a neuromuscular disease. Our patient presented expressive language disorder. Amburgey et al [4], in a review describing the natural history of this condition, reported a high incidence of learning disability (43%), likely associated with speech abnormalities including hypophonic voice, speech articulation difficulties and late first words and sentences. Intellectual disability, however, has conflicting reports in the literature. While it has been described in neuromuscular disorders such as myotonic dystrophy type 1, in patients with myotubular myopathy, cognitive impairment has been described as secondary to perinatal hypoxic ischemic encephalopathy [4]. In 1999, Herman et al described no cognitive impairment in long term survivors; it reported clinical seizures in four patients that were likely due to metabolic encephalopathies [6]. Despite myotubularin being expressed in the brain, there are no reported central nervous system malformations in animals, but research on this topic is lacking [4]. Adequate cognitive development and normal creatinine-kinase should steer the diagnosis towards a myopathic condition. Despite the phenotypical variation, this is a progressive disease that inexorably leads to regression of

motor development, including in patients with milder phenotypes [3]. The maximum development acquired appears to be determined by genotype [3]. Currently, the severity myotubular myopathy is solely and variably classified according ventilator dependency [3]. While respiratory function tests are useful to determine the need of respiratory therapies to improve this outcome [3], it is an incomplete way to characterize this condition. There is a lack of verified motor or developmental scores specific to this myopathy to further determine prognosis and need of other therapies. We believe that there is an evident need for a grading system for mild and moderate cases other than ventilator dependency, such as muscle weakness and fatigue, daily life limitations, motor developmental delay (especially independent walking and head control), early phenotypical scores (high arched palate, myotonic facies, hypotonia) or recurrent respiratory infections. The management of this condition is proposed in a standard care consensus, which describes supportive treatment, since there are, currently, no curative therapies for congenital myopathies [7]. Patients benefit from close a multidisciplinary follow-up guided by a neuromuscular specialist, who should monitor for speech, swallowing and respiratory problems. Despite not being a common presentation, heart and rhythm abnormalities must be excluded. Gene therapy is currently being investigated for X-linked myotubular myopathy. In both double blinded randomized and open label non-randomized trials, the administration of recombinant adeno-associated virus serotype 8 (rAAV8) vector expressing canine myotubularin (cMTM1) under the muscle-specific desmin promoter (rAAV8-cMTM) resulted in dose-dependent improvement in survival, strength and muscle structure in dogs without adverse effects [8]. In another study, an AAV vector was used to knockdown DMN2 expression in *Mtm1* knock-out mice, based on the hypothesis that dynamin 2 GTPase activity leads to a centronuclear myopathy-like phenotype. This resulted in improved muscle force and histology [9]. The ASPIRO trial (NCT03199469) is an ongoing a phase 1/2, multinational, open-label, clinical study in which an AAV8 vector carrying the *MTM1* gene (AT132) is being administered in individuals with X-linked myotubular myopathy aged less than 5 years old.

Although carrier females are generally asymptomatic, affected women have been described with symptoms ranging from mild to severe. Proposed mechanisms to explain this feature include skewed inactivation of the X chromosome and /or genetic variants in additional genes that can modulate the phenotype [10]. X inactivation analysis in our patient's mother showed a slightly skewed pattern (70:30). Even when the mother is asymptomatic, knowing her carrier status is important in other to offer proper genetic counselling to the family.

We report the diagnosis of a child with a neuromuscular condition presenting with non-classic features, such as global developmental delay and expressive language disorders, while having milder hypotonia and motor delay. In the presence of global developmental delay with milder motor features, a neuromuscular disorder must be considered in the differential diagnosis.

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Miopatía miotubular ligada al cromosoma X: informe clínico y revisión del fenotipo leve

Introducción. La miopatía miotubular ligada al X es una miopatía centronuclear rara que afecta aproximadamente a 1 de cada 50.000 recién nacidos varones causada por variantes patógenas en el gen de la miotubularina 1 *(MTM1).* La gravedad clínica varía; sin embargo, la necesidad de soporte ventilatorio ocurre casi invariablemente.

Caso clínico. Presentamos el caso de un niño de 4 años que presentaba hipotonía muscular leve a los 12 meses, trastorno del lenguaje expresivo, retraso global del desarrollo y trastorno del procesamiento sensorial. La secuenciación clínica del exoma identificó la variante hemicigótica c.722G>A p.(Arg241His) en el exón 9 del gen de la miotubularina 1 (NM_000252.2). La madre es portadora heterocigota de la misma variante. Se estableció el diagnóstico de una forma leve de miopatía miotubular ligada al cromosoma X de herencia materna. El niño presentó una mejoría significativa con terapias del habla, ocupacional y física, sin intercurrencias respiratorias ni dependencia de ventilador.

Conclusión. La presentación de una forma leve de esta miopatía miotubular, al notificarse más raramente, añadió desafío al diagnóstico. La combinación de hipotonía leve, dificultades de alimentación y trastorno del lenguaje expresivo debe hacer sospechar una enfermedad neuromuscular. Se carece de puntuaciones motoras o de desarrollo verificadas específicas de esta miopatía para determinar el pronóstico y la necesidad de otras terapias. Aunque actualmente la gravedad de la miopatía miotubular se clasifica según la dependencia del ventilador, esto puede ser insuficiente e inaplicable a los casos más leves. Es evidente la necesidad de un sistema de clasificación para los casos leves y moderados que evalúe la debilidad muscular y la fatiga, las limitaciones de la vida diaria, el retraso del desarrollo motor, las puntuaciones fenotípicas tempranas o las infecciones respiratorias recurrentes.

Palabras clave. Consejo genético. Hipotonía muscular. Miopatía miotubular. Miotubularina. Retraso en el desarrollo. Trastornos del lenguaje.