Arrhythmias in patients with X-linked myotubular myopathy

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Introduction. Myotubular myopathy is a congenital muscle disease caused by a mutation in the myotubularin (*MTM1*) gene. The X-linked myotubular myopathy (XLMTM) affects males with early-onset symptoms such as muscle weakness, hypotonia, and respiratory distress. To our knowledge, cardiac involvement has not been previously described in this condition, in contrast to other types of congenital myopathies such as nemaline myopathy or core myopathy.

Case reports. We report two clinical cases of XLMTM that started with severe sinus bradycardia or auriculoventricular block from the first days of life, with pathologic 24-hours Holter monitoring in both cases. A primary cardiac affection was excluded by electrophysiological studies and normal heart rate was recovered with proper respiratory support.

Discussion. These cases with sever bradyarrhythmia in a well know pathology such the XLMTM represents a nuance on the usual differential diagnostics of congenital myopathies.

Key words. Bradyarrhythmia. Cardiac monitoring. Congenital myopathies. Myotubular myopathy. Neuromuscular disorders. Pediatric diseases.

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Introduction

X-linked myotubular myopathy (XLMTM) is part of the heterogeneous group of congenital myopathies and a rare disease, with an estimated incidence around 1/50,000 male births [1,2]. Several mutations have been described in the gene encoding myotubularin (*MTM1*) responsible for the disease. Congenital myopathies should be suspected in hypotonic newborns, with absence of osteotendinous reflexes, and especially with the association of phenotypic features of fetal hypokinesia [3]. In fact, it has been reported that congenital myopathies account for 14% of all cases of neonatal hypotonia [4]. A detailed family history may also help in the clinical suspicion, and the muscular biopsy and genetic analysis are mandatory for the diagnostic confirmation and in order to offer genetic advice. A multidisciplinary supportive care is mandatory for these patients while gene therapy is being evaluated (ASPIRO trial, NCT03199469).

Heart muscle and skeletal muscle involvement are frequently associated with some primary myopathies. However, there are no reported cases of cardiac involvement in neonatal myotubular myopathy [5-7] and this parameter is used in the differential diagnostic of myopathies. We report two clinical cases of XLMTM, that started with severe sinus bradycardias and auriculoventricular block from the first days of life.

Case reports

The study was conducted in accordance with the recommendations of the Declaration of Helsinki. A written consent was obtained for both patients.

First case report

A 40 weeks of gestation male was born by vaginal delivery with low birth weight (2,610 g) with an Apgar score 1/5/7. Pregnancy had evolved normally. From birth, the patient presented severe hypotonia, areflexia and generalized weakness, as well as a characteristic phenotype with small mouth with arched palate, micrognathia, muscle contractures and bilateral cryptorchidism. A muscle biopsy was

Figure 1. Holter from the patient in the second case report. This graphic shows different bradycardia episodes during the 24-hour Holter monitoring.

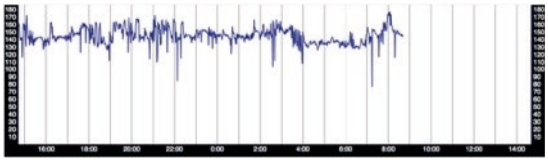
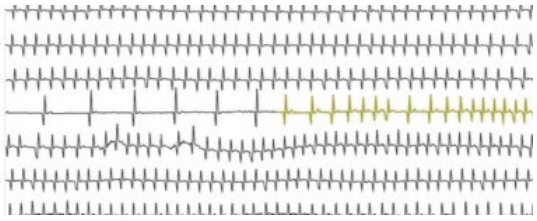


Figure 2. Holter from the patient in the second case report. Sinus bradycardia. Lowest heart rate was 37 bpm.



performed and the diagnosis of myotubular myopathy was confirmed. The genetic study showed a large deletion including the whole *MTM1* gene g.(?_149761067)_(149841616_?)del. URL: https://databases.lovd.nl/shared/variants/0000714942.

He required continuous positive airway pressure from the delivery room until when he was around 40 days old. From the first few days of life, the patient showed almost daily episodes of bradycardia down to 25 bpm of a few seconds of duration, usually associated with desaturation. High flow nasal cannula oxygen therapy could not be used due to restart of bradycardias.

The study was completed with an echocardiography, without alterations, and a Holter monitoring which registered some episodes of sinus bradycardia of up to three seconds without auriculoventricular block.

The arrhythmic events disappeared spontaneously without any specific treatment other than the optimization of ventilation (increasing pressures with non-invasive ventilation).

Finally, a tracheostomy was performed when he was three months old and a gastrostomy when he was three months old.

Second case report

A 41 weeks of gestation male newborn was delivered by caesarean birth due to the risk in fetal well-being in a long expulsion context, with low weight (2,700 g). The patient was born in apnea and extreme bradycardia (Apgar score 3/7/8) and required advanced resuscitation in the delivery room with orotracheal intubation. He had severe hypotonia, left cryptorchidism, arachnodactyly, and characteristic facial features (high arched palate, tent-shaped mouth, palpebral ptosis). Suspecting a congenital myopathy, a muscle biopsy was performed and showed signs of centronuclear myopathy. The genetic study targets the mutation NM_000252.2(MTM1):c.1420C>T (p.Arg474Ter). URL: https://databases.lovd.nl/shared/variants/0000714941.

The patient was extubated on the fifth day of life, required continuous positive airway pressure during two days and afterwards high flow nasal cannula support was started. When he was 10 days old, he started with episodes of extreme bradycardia down to 30 bpm. They were short episodes (seconds) and some of them included final tachypnea and desaturation. The electrocardiogram showed first and second degree auriculoventricular block (Mobitz I and II), occasionally complete auriculoventricular block. A 24-hours Holter monitoring was performed when he was one month old, showing more than 50 episodes of extreme sinus bradycardia and 18 episodes of sinus pause and auriculoventricular block lasting up to 4.8 seconds, which were resolved with a sinus heartbeat and finally sinus tachycardia, without any ventricular arrhythmias (Fig. 1). He was categorized with a sick sinus syndrome. The largest episode of bradycardia lasted 10 seconds and had a minimum heart rate of 37 bpm (Fig. 2). Some of the episodes of extreme bradycardia required the use of a bag valve mask. The echocardiography performed was normal. Due to the severity of the identified bradycardias, the study was completed with an electrophysiological study that did not show any alterations.

With the optimization of respiratory support (mainly high flow nasal cannula, with maximum eight liters per minute), he presented a decrease in the number of bradycardia events, confirmed by a new Holter monitoring study carried out when he was 2 months old, which identified some sinus pause (maximum 1.8 seconds), with no findings of auriculoventricular block. He required 20 days of non-invasive ventilation (bilevel positive airway pressure) and finally, he required a tracheostomy when he was three months old, as well as anti-reflux surgery and gastrostomy when he was five months old.

Discussion

To our knowledge, no cases of heart disease or arrhythmic events associated with the XLMTM have been described in the literature. However, these associations have been described in other types of congenital myopathies, for example, in nemaline myopathy, core myopathy, congenital fiber disproportion myopathy, centronuclear myopathy or myosin storage. For instance, the nemaline myopathy can be associated with hypertrophic cardiomyopathy, dilated cardiomyopathy, and heart rhythm disturbances [5,8,9]. In fact, the diagnosis of certain congenital myopathies involves specific screening for the identification of associated heart [8]. These case reports show that the identification of heart rhythm disturbances cannot be used to rule out XLMTM. Heart rhythm disorders may be related to breathing impairment, associated to altered respiratory dynamics, respiratory muscle weakness and mismanagement of secretions. A recent XLMTM retrospective cohort study described that 66.7% of deaths were attributed to the respiratory failure, and 18% of deaths to a cardiorespiratory cause. No history or documented evidence of underlying cardiomyopathy in these cases was described [10].

To conclude, we support the idea that episodes of heart rhythm disturbances, that may be fatal, can be minimized by optimizing the management of airway viability and respiratory support.

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Arritmias en pacientes con miopatía miotubular ligada al cromosoma X

Introducción. La miopatía miotubular es una enfermedad muscular congénita causada por una mutación en el gen de la miotubularina *(MTM1)*. La miopatía miotubular ligada al cromosoma X (XLMTM) afecta a los hombres con síntomas de aparición temprana como debilidad muscular, hipotonía y dificultad respiratoria. Hasta donde sabemos, la afectación cardíaca en estos pacientes no se ha descrito previamente, a diferencia de otros tipos de miopatías congénitas, como la miopatía nemalínica o la miopatía con cores.

Casos clínicos. Presentamos dos casos clínicos de XLMTM que comenzaron con bradicardia sinusal grave o bloqueo auriculoventricular desde los primeros días de vida, con Holter patológico en ambos casos. Se descartó una afectación cardíaca primaria por estudios electrofisiológicos y se recuperó la frecuencia cardíaca normal con soporte respiratorio adecuado.

Conclusión. Estos casos con bradicardia grave en una patología bien conocida, como la XLMTM, suponen un matiz en el diagnóstico diferencial habitual de las miopatías congénitas.

Palabras clave. Arritmias. Bradicardia. Enfermedades pediátricas. Miopatía miotubular. Miopatías congénitas. Trastornos neuromusculares.