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Brief Communication

Exome sequencing is a valuable approach in critically ill patients with suspected monogenic disease: Diagnosis of X-linked centronuclear myopathy in preterm twins

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1. Introduction

X-linked centronuclear myopathy (CNMX) is a severe congenital myopathy resulting from mutations in the *myotubularin* (*MTM1*) gene.[1] Patients with CNMX usually present with profound weakness, muscular hypotonia, and respiratory failure in the neonatal period.[2] Diagnosis is based on characteristic histopathological findings in skeletal muscle specimens from males with suggestive clinical features and the identification of supporting genetic defects.[3] However, muscle biopsy requiring general anesthesia can be a high-risk procedure in premature infants or in patients with a poor general condition.

Here, we report on preterm monozygotic twins with profound weakness and unexplained respiratory failure in whom whole exome sequencing (WES) as a noninvasive procedure was performed early in the diagnostic approach. A novel, hemizygous missense mutation in *MTM1* (c.1505T>A, p.Ile502Lys) was identified suggesting CNMX. After clinical stabilization of the infants, the genetic diagnosis was further supported by typical features in the muscle biopsy performed at 6 months of age.

2. Case Report

Two male, monozygotic twins were born by cesarean section at 32 + 0 weeks of gestation to healthy, nonconsanguineous Caucasian parents. At birth, weight, length, and head circumference were normal for both infants. Family history was unremarkable for muscular disorders. The pregnancy was complicated by intermittent bleeding, polyhydramnios, and decreased fetal movements. After birth, both twins initially presented with severe generalized muscular hypotonia, shallow breathing, and peripheral cyanosis.

Following nasal continuous positive airway pressure, mechanical ventilation was initiated in the 1st hours of life due to persistent respiratory distress. After extubation on

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Day 2 (Twin 1) and Day 4 (Twin 2), both infants were stable on noninvasive ventilator support and minimal handling in the following weeks. Due to feeding difficulties, the boys initially required nasogastric feeding, and a gastrostomy tube was later inserted.

In the diagnostic work-up, including imaging and laboratory and electrophysiological investigations, a broad spectrum of differential diagnoses was addressed, but the underlying disease presenting with persistent profound weakness and ventilator dependency could not be identified. Therefore, at the age of 8 weeks, whole exome sequencing with DNA samples from Twin 2 was performed, as described previously.[4] A search for rare (minor allele frequency (MAF) $<$ 0.1% in 6800 in-house control exomes) nonsynonymous biallelic or hemizygous variants prioritized a rare missense variant (c.1505T>A, p.Ile502Lys) in the X-chromosomal *MTM1* gene. The hemizygous *MTM1* mutation was confirmed by Sanger sequencing in both twins, but was absent from maternal blood DNA, indicating that the mutation occurred *de novo* at an early embryonic stage or based on a germline mosaicism. The pathogenicity of the c.1505T>A variant was confirmed by a muscle biopsy in Twin 2, which revealed the typical histological features of myotubular myopathy. Muscular biopsy was performed in parallel with a tracheotomy that was necessary in both children at 6 months of age due to prolonged ventilator dependency.

3. Discussion

Using WES, we identified a novel *de novo* missense mutation in *MTM1* (c.1505T>A, p.Ile502Lys) in the monozygotic preterm twins and established the diagnosis of CNMX. WES was performed early in the diagnostic process. At that stage, the infants presented with clinical features of myopathy, thus making a muscle biopsy the next reasonable step. However, invasive long-term ventilation was suspected as a consequence of an invasive procedure requiring general anesthesia. In addition, it was arguable that a sufficient amount of muscle tissue could be collected due to the preterm age and low weight of these infants. Thus, a different genetic diagnostic approach was warranted. As successive single-gene analysis is time-consuming, expensive, and inappropriate with respect to the genetic heterogeneity of congenital myopathies, WES was performed, which revealed the underlying genetic disease of these twins. Because of the early diagnosis, family counseling, and management decisions about long-term life-supporting interventions (e.g., tracheotomy) were possible in our patients.

Recently, results of WES and targeted sequencing of 45 patients from 38 families with early-onset neuromuscular disorders were reported by Dhamija and Chambers.[5] Mutations in known and novel neuromuscular genes (e.g., in *MTM1*) were identified, and a definitive genetic diagnosis was achieved in 18 of 38 families. In addition, Chae et al[6] investigated the feasibility of WES in 43 patients presenting with early-onset neuromuscular disorders. In 48.8% of the patients, the causative gene mutations could be identified; one of these patients showed a novel hemizygote missense mutation in *MTM1*. In line with these previous reports, our case report emphasizes WES as a noninvasive and appropriate diagnostic tool in critically ill newborn patients suspected of suffering from monogenic diseases.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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