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# X-Linked Myotubular Myopathy and Chylothorax

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## ABSTRACT

Myotubular myopathy, also known as centronuclear myopathy, is a congenital muscle disease. There are three main types according to its inheritance, which differ in clinical severity, age of onset, and prognosis. The most common and most severe type is X- linked myotubular myopathy. X-linked myotubular myopathy usually manifests with hypotonia and respiratory distress at birth. Patients with severe types of the disease are often lost during the neonatal period due to respiratory failure. In muscle histopathology, central nucleation is typical in the majority of muscle fibers, and pleural effusions are frequently described in congenital myopathies. A 20-day-old male neonate born via C-section at 36 gestation weeks and 2400 g was referred to our hospital due to hypotony, edema, and

respiratory distress. In this article, we present a severe form of the disease in a neonate with chylothorax.

**Key words:** Neonate, Chylothorax, X-linked myotubular myopathy

## ÖZET

Sentronükleer miyopati olarak da bilinen miyotübüler miyopati konjenital bir kas hastalığıdır. Hastalığın kalıtımına göre klinik şiddeti, başlangıç yaşı ve prognozu farklı olan üç ana tipi vardır. En sık ve en ağır tipi X'e bağlı miyotübüler miyopatidir. X'e bağlı miyotubular miyopati genellikle doğumda hipotoni ve solunum sıkıntısı ile kendini gösterir. Ağır seyreden tipleri sıklıkla yenidoğan döneminde solunum yetersizliği nedeniyle kaybedilir. Kas histopatolojisinde kas liflerinin çoğunluğunda santral yerleşimli çekirdek bulunması tipiktir. Plevral efüzyonlar konjenital miyopatilerde sıklıkla tanımlanmaktadır. Ancak şilotoraks ile X'e bağlı miyotübüler miyopati ilişkisi bugüne kadar sadece iki olguda tanımlanmıştır. Bu yazıda hastalığın şiddetli formu ve şilotoraks kliniği ile başvuran bir yenidoğan olgusunu sunmaktayız.

**Anahtar kelimeler:** Yenidoğan, Şilotoraks, X bağlı miyotübüler miyopati

## INTRODUCTION

Congenital myopathies are a heterogeneous group of diseases in which muscle defect is the primary cause. Although signs may be detected immediately after birth, some patients may not have symptoms until early childhood (1]). Among congenital myopathies, myotubular myopathy has the most severe clinical course. Polyhydramnios and decreased fetal movements during pregnancy, severe hypotonia after birth, and limited extraocular eye movements are the most common clinical findings (2). Patients are often lost due to respiratory failure. In the non-progressive forms of the disease, patients are sustained with long-term mechanical ventilation, and there are rare cases characterized by chylothorax and diffuse edema (2,3). We present a case of X-linked myotubular myopathy that was admitted to our clinic with chylothorax findings and early onset of respiratory distress.

## CASE REPORT

A 20-day-old male neonate born via C-section at 36 gestation weeks and 2400 g was referred to our hospital due to hypotony, edema, and respiratory distress. The parents were nonconsanguineous. He was the second living baby born of the second pregnancy to a 38-year-old mother. The pregnancy was characterized by a decrease in fetal movements in the last trimester and polyhydramnios in the prenatal ultrasonography. Apgar scores were 1/5/5 in the $1^{st}$, $5^{th}$, and $10^{th}$ minute, respectively. Due to poor respiratory effort, resuscitation and intubation were performed in the operating room. The patient, with asphyxia history and hypotonia as preliminary diagnosis, was admitted to our clinic, and upon examination, lack of feeding, areflexia, severe extremity, and truncal hypotonia were detected. Physical

appearance was characterized by a head circumference of 36 cm (25-50p), > 97p, wide frontal fontanel, and a thin long and apathetic face. Eye movements were present in all directions but limited. The patient also exhibited a high palate, long philtrum, lowly located ears, wide forehead, long fingers, and widespread edema that left 3+ pitting in the whole body. The patient was unable to wean off the mechanical ventilator during the follow-up period.

Thoracic drainage was performed upon detecting pleural effusion from a chest x-ray and pericardial and right pleural effusion from echocardiography (Fig. 1). Laboratory studies were compatible with chylothorax (215 leukocytes and 42 erythrocytes, triglycerides 1968 mg / dL, LDH: 430 mg / dL). Lymphangiography was performed to determine chylothorax etiology. Significant obstruction in lymphatic drainage and no risk factors affecting lymphatic flow were identified. Regarding cranial tomography, significant ventricular dilatation, increase in subarachnoid space, and appearance compatible with cerebral cortex atrophy were present. The patient's creatine kinase level was 70 U / L (30-200 U / L). Metabolic screening results (blood-urine amino acid profile, acyl carnitine profile, organic acid and fatty acid oxidation defects) were normal. Chromosomal analysis was done due to hypotonic infant findings and dysmorphic facial features, and the result was 46XY. Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA) were excluded by genetic testing. On the other hand, the gene analysis for myopathy was reported as X-linked MTM1 genes hemizygote variant c.1261-10A> G, which is compatible with the X-chromosome-linked myotubuler myopathy type 1. Despite the fact

that enteral feeding was discontinued due to chylothorax, special formula containing medium chain fatty acid (MCT) was given through an oro-gastric tube, and daily thoracentesis was performed for chylous fluid withdrawal, chylothorax findings in the right lung persisted. Therefore, somatostatins long-acting synthetic analogue octreotide acetate (10mcg/kg/day) treatment was started. Simultaneously, feeding was continued with the medium chain fatty acid formula. Due to recovery of chylothorax findings, the treatment was completed and terminated at 30 days. After the treatment, chylothorax did not recur. The patient was gradually fed breast milk, and MCT formula was discontinued.

**DISCUSSION**

The patient was admitted to our clinic with dysmorphic facial appearance and hypotonic infant preliminary diagnoses and had a widespread edema and pleural effusion at the time of admission. During the edema etiology research, cardiac or renal etiology was ruled out. The pleural effusion in this case was found to be the result of puncture. Chylothorax, defined as lymphatic fluid accumulation in the pleural space, occurs congenitally but can be acquired as well. Although the etiology of congenital chylothorax is not fully understood, it is thought to be the result of developmental disturbance of the lymphatic system (3,4). Similar to our case, two cases of chylothorax associated with X-linked myotubular myopathy have been reported in the literature. Chylothorax was detected on the 11$^{th}$ day of the case reported by Koenraad and at 9 weeks of the other case (5,6). In our case, chylothorax was detected on the 3$^{rd}$ day, and when admitted on the 20$^{th}$ day with widespread edema, which did not respond to treatment, thoracentesis was performed and

chylothorax was diagnosed. When evaluated together with previously published cases, the chylothorax etiology of our case suggests that myotubular myopathy may be related to developmental delay in the early stages of the lymphatic system development, which causes disruption of the lymphatic system.

The genetic analysis did not reveal DMD and SMA gene mutations. The X-linked MTM1 gene hemizygote variant c.1261-10A> G was detected, and X-related myotubular myopathy type 1 was diagnosed. Due to the clinical course of the case and the diagnosis being confirmed by the gene analysis, muscle biopsy was not performed.

Of all three patients (including this case) in the literature that were diagnosed with X-linked myotubular myopathy with chylothorax, two had the same gene mutation and were from Turkish families. This should be taken into consideration in future events.

Studies are ongoing to determine whether gene therapy for the neuromuscular junction can help in the treatment of patients with X-linked myotubular myopathy. In some animal studies, improvement in hypotonia has been observed (7,8). Childers et al. showed that gene therapy on dogs improved muscle strength and increased survival (9). We presented our patient as a candidate for The Gene Transfer Clinical Study in X-Linked Myotubular Myopathy (ASPIRO), which is currently being conducted in phase I/II and explores the potential for treatment in humans (10). ASPIRO, the first study in humans, was granted a study permit for a total of 12 patients to be conducted in collaboration with eight clinics in the USA, Canada, UK, France, and Germany; thus, this study was not able to include our patient. Satisfactory data are still unavailable regarding the effects of these gene therapies

on humans. We believe that further research is needed, including human trials, to determine whether this potential therapy has a positive effect in the treatment of patients with X-linked myotubular myopathy.

In conclusion, differential diagnosis of brain, muscle, and metabolic diseases should be considered in the etiology of patients with significant congenital hypotonia and X-linked myotubular myopathy, which may also be associated with common edema, pleural effusion, and chylothorax along with the classical findings.

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