

X-linked myotubular myopathy and recurrent spontaneous pneumothorax

A new phenotype?

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X-linked myotubular myopathy (XLMTM) is a rare hereditary disorder of the skeletal muscle. Symptoms include impaired respiration and muscular hypotonia, usually present at birth and leading to death during infancy or early childhood.¹ Pneumothorax, defined as trapping of air in the pleural cavity, can be caused by surgery or can occur spontaneously.² Pneumothorax has been reported only in a small number of cases with hereditary myopathies, but usually not spontaneously and never in XLMTM.

Case report

Our index patient presented at age 42 because of problems in raising his arms and climbing stairs. His one-year-older brother reported no symptoms. During childhood and adolescence, all motor milestones were reached normally. Both brothers were good at sports, but could not climb up a rope. Chronic bronchitis was diagnosed in both at around age 6, yet no treatment was required. Both started to smoke cigarettes at ages 15 and 16. Between age 18 and 26, the index patient had recurrent spontaneous pneumothorax (SP), which affected the right lung 9 times and the left lung once. The older brother had a first SP of the left lung at the age of 25. At the age of 29, 3 instances of SP of the left lung occurred within short intervals and a micro-surgical intervention was performed. Several days later, he developed SP of the right lung and received microsurgical intervention of that side. All 5 instances of SP were associated with physical activity. At age 44, the index patient developed respiratory insufficiency and required noninvasive ventilation during the nights and for some hours during the day. An inhalation therapy with tiotropium, formoterol, and budesonide was required, and he stopped smoking. At age 47, another SP of the right lung occurred during non-invasive ventilation (NIV) and a partial lung resection was performed. There was no family history for chronic bronchitis, SP, or neuromuscular disorders.

Chest x-ray revealed no evidence of lung emphysema (figure, A), and alpha-1-antitrypsin deficiency as the cause for SP was genetically excluded (*SERPINA1* gene). A moderately combined respiratory disorder was found by body plethysmography.

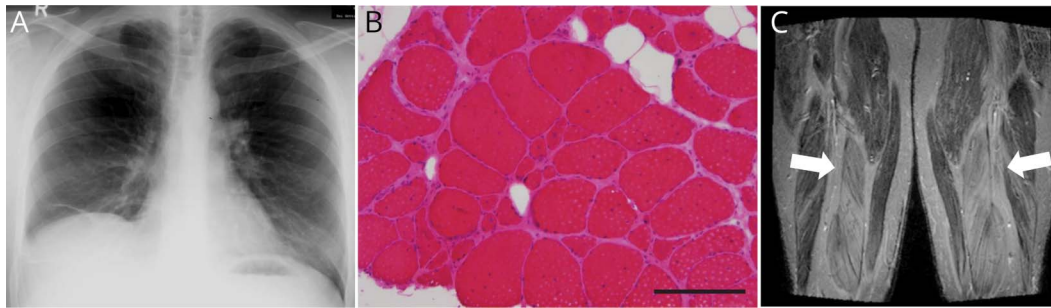
Clinical examination of the index patient revealed a paresis of arm abduction (muscle research council [MRC] grade 2) and hip flexion (MRC 4). The older brother could not walk on his heels and had no other paresis. Myogenic changes on EMG and slightly elevated creatine kinase (CK) were noted in both patients. The muscle biopsy and MRI of the index patient revealed signs of myopathic damage and displayed fatty degeneration of the muscle (figure, B–C). The

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(A) Routine chest x-ray of the older brother at the age of 43 displays dystelectasis of the middle lobe of the right side without evidence of lung emphysema. (B) Muscle biopsy of the index patient. Myopathic muscle tissue with internalized nuclei, fiber size variability, and increase of endomysial connective tissue (105 of 220 muscle fibers display an internalized nucleus [47.7%]). In the older brother, 861 of 1,429 muscle fibers depict an internalized nucleus [60.2%]. HE staining, scale bar = 200 µm. (C) Muscle MRI of the index patient. The arrows depict fatty degeneration of the quadriceps muscle. T1w sequence.

diagnosis of XLMTM was based on the detection of the frameshift variant c.98dupA (p.(Ala34Glyfs*13)) in exon 3 of the *MTM1* gene in both patients by next-generation sequencing. The patients have no other siblings and their mother died before genetic testing could be performed. Over the following 10 years, both brothers developed proximal and distal tetraparesis, ptosis, and dysphagia, which led to major restrictions in daily life activities.

Discussion

MTM1 codes for myotubularin, which is involved in mitochondrial homeostasis and regulation of the cytoskeletal system in muscles.³ To our knowledge, the here-described variant c.98dupA (p.(Ala34Glyfs*13)) has not been described in databases (ExAC, gnomAD, Human Gene Mutation Database) or in the literature before. Truncating variants of *MTM1* are normally associated with a more severe phenotype than nontruncating variants.¹ Although the variant c.98dupA (p.(Ala34Glyfs*13)) leads to a frameshift with a premature stop codon and a truncated protein or a nonsense-mediated mRNA-decay, interestingly, it was associated with a much more moderate phenotype of adult onset.

In our 2 patients, muscular weakness became apparent after the age of 40 years and respiratory impairment occurred only in one brother after recurrent SP and partial lung resection. Dyspnea on exercise was diagnosed as a chronic bronchitis in childhood but might be interpreted as a mild respiratory failure because of the myopathy.

SP in hereditary myopathy has been reported only in a small number of patients with nemaline myopathy,⁴ limb-girdle muscular dystrophy,⁵ collagen VI-related dystrophy,⁶ and Duchenne muscular dystrophy.⁷ However, most pneumothoraces were nonrecurrent and associated with assisted ventilation. So far, no association between XLMTM and SP has been reported. Because of the recurrent and bilateral appearance of the SP in both brothers,

a genetic predisposition can be assumed. The current knowledge of myotubularin is not sufficient to explain why SP may occur.

This case report is of interest for clinicians and human geneticists in 3 different ways: (1) A novel frameshift variant in the *MTM1* gene is described. (2) The new variant is associated with a moderate, adult-onset course of XLMTM. (3) The variant might be associated with recurrent SP, which has not been reported before for XLMTM.

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Eva Maria Christina Schwaibold, MD	Institute of Human Genetics, Heidelberg University, Germany	Author	Planned and supervised the genetic testing; revised the manuscript for intellectual content
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Appendix (continued)

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