X-linked Myotubular Myopathy with a Novel MTM1 Mutation in a Taiwanese Child

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We report a male, preterm newborn infant with X-linked myotubular myopathy, the most severe type of the disease. He presented at birth with generalized hypotonia, difficulty in swallowing, and respiratory distress with frequent episodes of atelectasis. The infant had a long thin face, generalized hypotonia, and arachnodactyly. Diagnosis was based on fetal history, muscle histopathology, electron microscopy and a genetic study. A base pair change was detected in exon 11 of the MTM1 gene: c.1160C>A, which caused an amino acid change, p.S387Y. The father's gene was normal but the mother had the same mutation as her son and was thus a carrier. [J Formos Med Assoc 2008;107(12):965–970]

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X-linked myotubular myopathy (XLMTM) is a congenital condition, which was initially thought to be caused by arrest of muscle fiber maturation during myotubular development at 8–15 weeks of gestation.1 However, further investigation has revealed that these structures are not genuine myotubes, but rather mature fibers that are pathologically altered. It is characterized histologically by a row of central nuclei located within a core of myocyte cytoplasm,2,3 with a cylinder made up of contractile myofibrils around this core. MTM can be inherited as an autosomal recessive, autosomal dominant, or X-linked disorder.2 XLMTM usually affects male infants and has a severe phenotype that leads to early death. Female carriers of the disorder have been reported to have slowly progressive muscle weakness that begins in childhood.4 The genetic locus responsible for XLMTM has been mapped to Xq28, where the MTM1 gene encodes myotubulin protein, a phosphoinositol 3-phosphatase. Deficiency of this enzyme in MTM affects the phosphatidylinositol 3-kinase and phosphatidylinositol 3-phosphate pathway.5 We report a case of XLMTM with a base pair mutation change in exon 11 of the MTM1 gene (1160C>A) inherited from the mother.

Case Report

A male infant was born prematurely to a 28-year-old, gravida 1, para 1, healthy mother with polyhydramnios at 36 weeks' gestation. The infant was delivered spontaneously without perinatal insult, but he was immediately noted to have generalized hypotonia and cyanosis, and was not crying or breathing spontaneously. He was resuscitated and placed on mechanical ventilation. The Apgar scores were 4 and 6 at 1 and 5 minutes, respectively.
On admission to the neonatal intensive care unit, his temperature was 37.5°C, pulse was 148 beats/min, respiration was 36 breaths/min (ventilator-dependent), and blood pressure was 60/24 mmHg. His birth weight was 2414 g (50th to 75th percentile), head circumference was 34.5 cm (75th to 90th percentile), and length was 51 cm (>90th percentile). His face was elongated with thin, narrow cheeks, and his mouth sagged open due to weak masseters (Figure 1A). He was generally hypotonic and had arachnodactyly of both hands and feet (Figures 1B and 1C). There was bilateral ptosis, a high-arched palate, and inverted V-shaped upper lips. There was a cephalohematoma, and the baby had less temporal muscle mass than normal. Lung examination was normal. Auscultation of the heart revealed a grade II/VI systolic murmur at the left lower sternal border. The abdomen was soft and flat, the scrotum small, and the testes undescended. A complete blood count, blood sugar, serum electrolytes, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, creatine kinase, lactate, pyruvate, carnitine, and tandem mass spectrometry were all within normal limits. Chest X-ray revealed thin ribs and clavicles (Figure 2). Brain ultrasonography showed bilateral subependymal cysts. Ultrasonography of the abdomen, heart, and muscles showed no specific abnormalities. The child’s karyotype was 46XY.

The parents denied any family history of neuromuscular disease, although on the maternal side, there was a history of cleft lip and birth asphyxia. The neonate had frequent episodes of bilateral atelectasis, and aspiration pneumonia was present on admission to the intensive care unit.

Figure 1. (A) The face is elongated with thin, narrow cheeks and decreased temporal muscle mass. (B, C) Both the upper and lower extremities have arachnodactyly.
He was extubated at 16 days of age but had to be re-intubated 6 days later because of respiratory distress secondary to atelectasis. Weaning was again attempted when he was 2 months, 11 days old. However, he had frequent episodes of bradycardia and cyanosis and had to be intubated 12 days later. Tracheostomy and gastrostomy were performed when he was 3 months old.

Light microscopy of tissue from a muscle biopsy performed on the second day after birth was consistent with MTM (Figure 3A), a diagnosis confirmed by electron microscopy (Figure 4). We used nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) (Figure 3B) and modified Gomori's trichrome stains to differentiate his disorder from other neuromuscular diseases. All 14 coding exons of the MTM1 gene from the patient’s genomic DNA were amplified and sequenced by polymerase chain reaction in both forward and reverse directions. This revealed a single substitution at nucleotide 1160 of exon 11 (c.1160 C>A), which resulted in a serine-to-tyrosine substitution.

Figure 2. Chest X-ray shows thin ribs and clavicles.

Figure 3. (A) Muscle biopsy specimen with moderate variation in fiber size, ranging from 5 μm to 15 μm. Almost all the fibers are small and round. No necrotic or regenerating fibers are seen. The amount of interstitial connective tissue is mildly increased. The nuclei are large and centrally placed (as the arrow indicates), and comprised about 35% of cell volume (hematoxylin & eosin, 250×). (B) Differentiation from central core disease. Most fibers have a peripheral halo, which indicates aggregation of oxidative enzyme activity in the center of the muscle fibers (as the arrow indicates). (NADH-TR, 250×).

Figure 4. Electron micrograph of longitudinal section shows muscle fibers with centrally placed nuclei (7000×).
change at amino acid position 387 (p.S387Y mutation) in the gene product, the apparent cause of the patient’s MTM (Figure 5). Deletion analysis of the 5’t-untranslated exon (exon 1) of the MTM1 gene was also performed, but no deletion was detected. DNA sequencing of the parents was performed, and the mother was found to carry the same mutation (Figure 6).

Discussion

We report the case of a male Taiwanese neonate with MTM. Genetic analysis revealed this to be the X-linked form caused by a mutation in exon 11 of the MTM1 gene. Congenital myopathy should be considered in any infant with respiratory failure and ventilator dependency at birth. Severe perinatal MTM has to be considered in male fetuses and newborns with polyhydramnios and respiratory failure, or in infants who have died of unexplained postnatal asphyxia.6

MTM can be inherited as an autosomal recessive, autosomal dominant, or X-linked disorder. Wallgren-Pettersson et al7 reported that the autosomal dominant form mostly has a later onset and milder course than the X-linked form, and the autosomal recessive form is intermediate in both respects. The prognosis in the X-linked form is not always poor, and survival into adulthood cannot be regarded as proof of autosomal inheritance.

In a review by Bruyland et al,8 death secondary to respiratory failure occurred in 26 of 38 baby boys in seven families with XLMTM. A detailed family history,9 muscle biopsy, specific histochemical staining, electron microscopy, and DNA analysis may all contribute to the definitive diagnosis in a hypotonic newborn with respiratory distress at birth.10

Heckmatt et al3 reported eight unrelated children with MTM; facial diplegia was present in all eight and external ophthalmoplegia in six. These findings are similar to those in congenital myotonic dystrophy, but the mothers of infants with that condition will invariably have mild facial weakness and clinical myotonia. In our case, the mother had a normal facial appearance. Keppen et al11 found that polyhydramnios, as was present in our case, is a common feature of congenital myopathy because the swallowing muscles in the fetus are weak.

Braga et al12 reported seven cases of MTM in three families. They concluded that needle biopsy of the muscle, which demonstrates an increased number of centrally located nuclei with perinuclear halos, is an important tool for early diagnosis. The muscle histopathology in our case, with
central nuclei located within muscle fibers, was consistent with the diagnosis of MTM.

Approximately 133 mutations in the MTM1 gene, located on Xq28, have been described as the cause of XLMTM (OMIM 310400). Reported mutations include missense, nonsense, and splice site single base changes, as well as small and large genomic rearrangements. The majority of patients carry a truncating or missense mutation in MTM1. While most truncating mutations cause the severe and early lethal phenotype, missense mutations are generally associated with milder disease and prolonged survival (up to 54 years). The exception to this is missense mutations that involve the phosphatase domain or the SET (suvar 3–9, enhancer-of-zeste, trithorax)-interacting domain. According to sequence analysis, serine is the second amino acid from the phosphatase active site, so it may lead to a severe phenotype. A list of MTM1 gene mutations is maintained at the Human Gene Mutation Database (entry for XLMTM: http://www.uwcm.ac.uk/uwcm/mg/search/119439.html). We found a new missense mutation in our patient that we do not believe has previously been reported. As noted above, the base pair change in exon 11, c.1160C > A, results in an amino acid change at position 387, p.S387Y, in the gene product. This is a non-conservative amino acid change that affects an evolutionarily conserved amino acid residue in a functionally conserved domain of the MTM1 protein.

DNA analysis showed the mother to be the carrier, while the father was normal. As with other X-linked disorders, if this couple were to have another male baby, there is a 50% chance that he would also have XLMTM. This illustrates the importance of genetic analysis in such cases as an aid to genetic counseling. According to Herman et al, the presence of typical facial features and long-term ventilatory dependence imply a severe phenotype, therefore, the prognosis for this child is poor. It is impossible on the basis of one case to determine if this particular mutation invariably results in a severe phenotype. However, molecular studies such as this increase our understanding of the pathophysiology of such disorders. Perhaps someday, cumulative knowledge of the genetic basis of congenital myopathy will contribute to more than simply prognostic information.

References


