CASE REPORT

Identification of a mutation in the MTM1 gene, associated with X-linked myotubular myopathy, in a Greek family

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Abstract
X-linked myotubular myopathy (XLMTM) is a rare congenital myopathy, usually characterized by severe hypotonia and respiratory insufficiency at birth, in affected, male infants. The disease is causally associated with mutations in the MTM1 gene, coding for phosphatase myotubularin. We report a severe case of XLMTM with a novel mutation, at a donor splicing site (c.1467+1G) previously associated with severe phenotype. The mutation was also identified in the patient's mother, providing an opportunity for sound genetic counseling. Hippokratia 2011; 15 (3): 278-279

Key words: X-linked myotubular myopathy, MTM1 gene, mutation, Greek

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X-linked myotubular myopathy (XLMTM) is a rare congenital myopathy, usually characterized by severe hypotonia and difficulty in establishing spontaneous respiration at birth, in affected males. The incidence of XLMTM is estimated at 2/100,000 male neonates. It was first described by Van Wijngaarden et al. in 1969, and most patients die within the first year of life due to respiratory failure[1]. The disease affects only males and is causally linked to mutations in the MTM1 gene, located on Xq28 and coding for myotubularin, a phosphatase involved in signal transduction networks (phosphatidylinositol 3-kinase/-phosphatase pathways) which are active in the process of differentiation and maturation of muscle fibers[2].

While the extensive mutational heterogeneity in addition to intrafamilial variability of phenotype has limited the use of mutation analysis for prognostic purposes, the identification of MTM1 mutations in individuals affected by myotubular myopathy is of great diagnostic value since it allows the confirmation of the diagnosis as well as the determination of carrier status of the context of genetic counseling. In this report we describe a case of MTM with a confirmed MTM1 gene mutation, in a family with a history of unexplained miscarriages and male neonatal deaths.

Case report

A male neonate, of two phenotypically healthy non-consanguineous Greek parents, was born by cesarean section at 30 weeks of gestation (Apgar score 1'5, 5'7; birth weight 910g). He was the second of a dichorionic, diamniotic twin pregnancy, following in vitro fertilization (IVF). During pregnancy, fetal movements were difficult to distinguish by the mother. Polyhydramnios was also reported. The baby was born floppy, with no spontaneous respiratory activity and needed resuscitation with intubation. He was admitted to the Neonatal Unit and during his hospitalization the required level of ventilatory support remained high. He was diagnosed with severe respiratory insufficiency and was treated with two doses of surfactant (Curosurf, 200 mg/Kg), with a poor response. His respiratory system gradually deteriorated, to the extent that the infant became fully dependent on mechanical ventilation. Lack of spontaneous movement, muscle weakness, generalized severe hypotonia and absence of tendon reflexes were noted. The baby required feeding by a nasogastric tube. No malformations were detected. Cerebral ultrasound was normal. Chromosome analysis revealed normal karyotype. There was no evidence of a metabolic disorder and CPK was found to be normal. Serology for congenital diseases (TORCHES) was negative. The infant died at 5 months of age, after a prolonged period of mechanical ventilation, due to cardiorespiratory failure. The first twin was unaffected. The mother had a history of miscarriages but there was no history of stillbirths in her side of the family (Figure 1).

The patient's signs – mainly hypotonia and respiratory insufficiency - were suggestive of severe myotubular myopathy. Mutation analysis was suggested, in order to assist diagnosis. Genomic DNA was isolated - after parental consent was obtained - from peripheral leukocytes of the patient and subjected to direct sequencing of all 15 exons of the MTM1 gene. A single mutation,

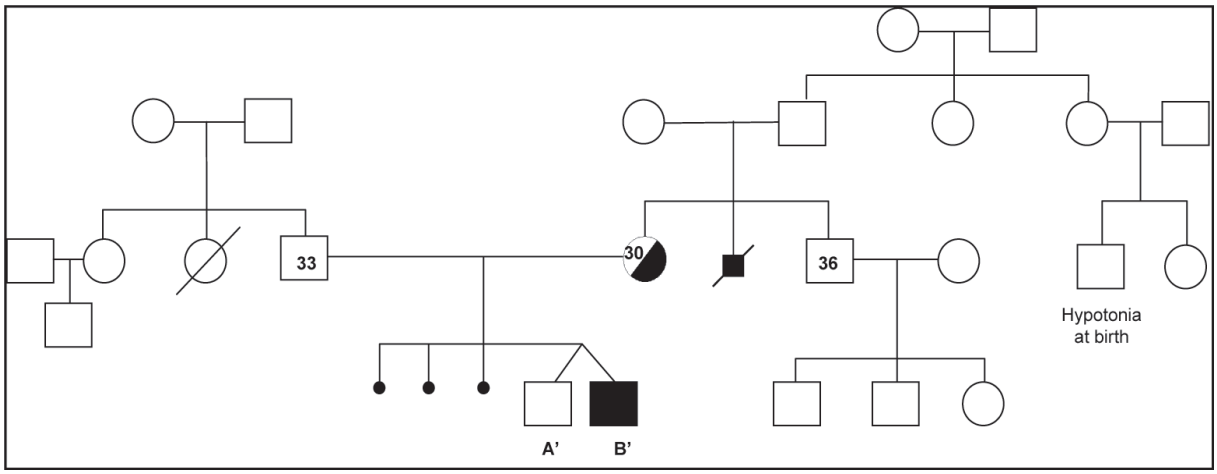

Figure 1: Pedigree of the family: the couple had already a history of miscarriages and a brother of the mother/carrier had died at neonatal age of unknown cause

c.1467+1G>T, resulting in the abolishment of a donor splicing site, was detected in exon 13. The same mutation was subsequently identified in the DNA of the boy's mother. Neither this nor any other MTM1 mutation was detected in the DNA of the boy's dizygotic twin brother.

Discussion

Detection of the mutation in the patient's DNA established the clinical diagnosis of X-linked myotubular myopathy, as opposed to other myopathies or myotonic dystrophy, proving that mutation analysis is a valuable tool for differential diagnosis in such cases.

A large number of missense, nonsense and splice site (donor and acceptor) mutations have been described in the MTM1 gene as causative of XLMTM[3]. Mutations are distributed throughout the gene although there is some clustering in exons 3, 4, 8, 9, 11, 12 and 13 (an updated list of MTM1 mutations can be found at the Human Gene Mutation Database, http://www.uwcm.ac.uk/uwcm/mg/search/119429.html).

There is only one previously reported case of a mutation at the 1467+1G site of MTM1, a G to A transition, in a North American patient[4]. In our case the mutation was a transversion (G>T), however both mutations were associated with a severe phenotype, supporting the pathogenicity of these mutations and suggesting that the loss of the 1467+1G donor splice site might prevent normal mRNA splicing, resulting in a modified protein with impaired function. As not all splice site mutations result in a severe phenotype[4,5], it would be very interesting to establish their exact functional significance with a systematic in vitro analysis.

In conclusion, we report a novel mutation at a site only reported once until today, namely c. 1467+1G of the MTM1 gene, associated with severe phenotype of XLMTM. As congenital myopathy is normally considered in any infant with respiratory failure and ventilator dependency at birth, the identification of potentially pathogenic mutations in the DNA of the mother provides a sound base for genetic counseling, especially when the mother is asymptomatic as in the present case. Moreover, prenatal diagnosis should also be offered even if the mother is not apparently a carrier of the mutation found in the index patient, as germinal mosaicism may be present, which carries a significant risk of recurrence[3].

No conflict of interest

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