Merosin-deficient congenital muscular dystrophy in an Omani boy

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CASE REPORT

A first-born male child of cousin related parents was referred to Sultan Qaboos University Hospital, Muscat, Oman at the age of 10 months for evaluation of delayed gross motor milestones. Antenatally, his mother reported reduced fetal movements and had polyhydramnios. He was born at full term by spontaneous vaginal delivery with Apgar scores of 7 and 9 at one and 5 minutes. His cry was instantaneous, but weak and low pitched. He had difficulty breast-feeding due to poor sucking and was nourished by bottle feeds of expressed milk for the first month of life after which he was able to suck adequately. His mother noticed that he was floppy and his limb movements were minimal soon after birth. He also had congenital bilateral talipes equina varus, which was corrected by 3 months of age. His gross motor milestones were noted to be significantly delayed. He was able to support his head with no lag at 8 months of age, turn supine to prone at 10 months, prone to supine at 11 months, and sit without support at 13 months. However, he had been attaining his fine motor skills and social milestones normally. He had pincer grasp, was able to hold a pencil, and had a vocabulary of 15-20 words. He had no respiratory problems. He had no family history of developmental delay, neurological, muscular, or metabolic disorders. His examination at 10 months of age revealed an alert looking infant with normal muscle bulk, no fasciculations and muscle power of 2/5 to 3/5 of the main groups of muscles. There was hyporeflexia. His cranial nerves and the different sensory modalities were intact. Examinations of the respiratory, cardiovascular, and gastrointestinal systems were unremarkable and he had no joint deformities or muscle biopsies show dystrophic changes. The muscle histopathology proved merosin-deficient type of CMD in our patient. The rarity of this condition prompted us to report this patient.

ABSTRACT

Merosin-deficient congenital muscular dystrophy is an autosomal recessive disease that can manifest differently in different ethnic groups. This often presents as a floppy infant, and normal mental development. The creatine kinase is usually elevated with white matter abnormalities on brain imaging. In this report, we describe an infant with Merosin-deficient congenital muscular dystrophy who presented with delayed motor milestones and hypotonia. The clinical features, biopsy findings, and neuroimaging abnormalities in our patient are described.

Neurosciences 2008; Vol. 13 (3): 305-307

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Received 16th July 2007. Accepted 17th December 2007.

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Congenital muscular dystrophies (CMDs) are a heterogeneous group of skeletal muscle disorders that typically manifest at birth or within the first few months of life. They are characterized by muscle hypotonia, generalized muscular weakness, and contractures. The serum creatine kinase level is usually elevated, and muscle biopsies show dystrophic changes. The muscle histopathology proved merosin-deficient type of CMD in our patient. The rarity of this condition prompted us to report this patient.
contractures. Investigations showed a normal routine blood work including a complete blood count, urea and electrolytes, liver function test, and bone profile. The creatine kinase (CK) level was elevated 1979 IU/L (normal 25-195 IU/L). The electromyogram (EMG) revealed myopathic changes and the nerve conduction test was normal. Muscle biopsy of his right quadriceps showed mild variation in the size of fibers, no evidence of regeneration or degeneration, and normal vessels. Immunohistochemistry for muscle membrane proteins dystrophin showed a normal staining pattern (Figure 1). However, laminin α2 staining (Novocastra Laboratories, Newcastle Upon Tyne, United Kingdom, clone number mer 3/22 b2) was negative (Figure 2). Magnetic resonance imaging of the brain with contrast enhancement revealed diffuse, wide spread, white matter changes in both cerebral hemispheres, including the sub cortical white matter, but sparing the basal ganglia and thalamus. Lesions appeared hypo intense on T1 and hyper intense on T2. The echocardiogram and chest x-ray were both normal. The parents were counseled, given nutritional advice and regular physiotherapy.

Discussion. The CMDs are autosomal recessive disorders with different clinical phenotypes. Congenital muscular dystrophy is commonly categorized by the presence or absence of clinically evident cerebral involvement. The classic “pure” form with no CNS involvement is usually found in the western world, while the other form with central nervous involvement, like Fukuyama-type CMD, is found mostly in the Japanese population and muscle-eye and brain syndromes (Walker-Warburg CMD, and Santavouri CMD) found in European regions. The pure form of CMD can be further subdivided into merosin positive or merosin-negative (laminin α2) CMD. The patients with laminin α2 CMD are more severely affected compared with patients of merosin-positive CMD. Our patient had laminin α2 CMD.

We describe a case of laminin α2 CMD in an Omani patient. There are few reports of CMD from the Middle East mainly Kuwait, Israel, and Jordan. The CMD formed 1.6% of cases of all muscle diseases from Jordan. Patients with merosin-negative CMD often present as a floppy infant as our patient. They may show severe neonatal hypotonia, with sucking, swallowing, and respiratory difficulties. Such infants will have generalized motor weakness and decreased spontaneous movements associated with markedly delayed motor development. Multiple contractures with joint deformities and kyphoscoliosis are common clinical features, which may develop later during the disease. Cardiac function is usually normal, however, some patients may develop dilated cardiomyopathy. Serum CK is markedly elevated in the early phases of the disease and tends to come down with time, where it could be normal particularly at the age of 5 years or older. However, normal serum CK level in an infant with suspected CMD makes it very unlikely to be laminin α2 deficient.

Characteristically, the patients with pure type of CMD have normal mental functions even though in brain imaging white matter changes are constantly being found. Philpot et al postulated that the white matter changes were specific to laminin α2 CMD type patients, than with pure CMD. Merosin is expressed in the fetal brain and this may account for the dysmyelination as seen in the MRI studies. The EMG is generally considered myogenic as it was found in our patient, but slow motor conduction velocities were found in a series of cases. In
Muscle biopsy is the gold standard in diagnosing and differentiating congenital muscle diseases. Histologically, laminin α2 congenital CMD shows no specific ultrastructural features, generally they are characterized by large variation in the size of muscle fibers, a few necrotic and regenerating fibers, and marked increase in endomysial collagen tissue, with absent laminin-2α (merosin) on histochemistry implicated in this disease. Laminins are a family of large extracellular trimeric glycoproteins. Laminin-2 is composed of 3 chains: one heavy (α2) and 2 light chains (β1, and γ1). Laminin-2 has been shown to be necessary for myogenesis as well as for the survival and stability of myotubes in vitro.

Genetically, the human LAMA2 gene was implicated in this disease. There are many mutations described since the first one was identified in 1995. To date no specific treatment is available, but physiotherapy can improve the quality of life by reducing contractures.

References


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