Merosin-negative congenital muscular dystrophy: Report of five cases

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Abstract

Context:
Congenital muscular dystrophy type 1A (MDC1A) is caused by mutations in the laminin α-2 gene encoding laminin-a2.

Aims:
The purpose of this study is to determine clinical and genetic results in five Turkish patients with MDC1A.

Setting and Designs:
Five children with MDC1A were retrospectively analyzed.

Results:
Three (60%) were boys, and 2 (40%) were girls. Parental consanguinity was found in all the families. In all the patients, hypotonia, weakness, delayed motor milestones, markedly elevated creatine phosphokinase (CPK) concentration, and brain white matter abnormalities on magnetic resonance imaging were detected. Mutation analysis was performed in all the patients, and 3 different mutations were detected. However, a mutation in patient 1 and 2 has not been previously described in the literature.

Conclusions:
When a patient presents with severe congenital hypotonia, muscle weakness, high serum CPK levels, and white matter abnormalities, should be suspected as MDC1A.

Keywords: Clinical findings, congenital muscular dystrophy type 1A, genetic mutations

Introduction

Congenital muscular dystrophies (CMDs) are genetically and clinically heterogeneous hereditary myopathies. Many different groups of CMDs are present. Merosin-deficient CMD type 1A (MDC1A) is the most common form of CMD. MDC1A is caused by mutation of the laminin α-2 gene (LAMA2),
localized to chromosome 6q22-23. To date, numerous mutations have now been identified in the LAMA2 gene.[1,2,3]

Patients with MDC1A present with severe neonatal hypoxia often requiring ventilatory assistance, markedly delayed motor development, and generalized muscle atrophy with the weakness of limb and trunk muscles leading to contractures and joint deformities. In contrast with other CMD patients, those with merosin deficiency have high creatine phosphokinase (CPK) levels and white matter abnormalities on brain imaging techniques.[4]

Here we report the clinical manifestations, result of muscle biopsy and genetic studies in five Turkish patients with MDC1A.

Materials and Methods

Patients

The patient 1 and 2 were siblings. Furthermore, they were triplets. Another brother was healthy. Their parents were consanguineous. They were born at preterm (32 gestational weeks). The patient 1 was a 6-year-old boy and first attended our hospital at the age of 4 years due to hypotonia, weakness, poor weight gain, and contracture of knees. From birth, he exhibited marked hypotonia with generalized muscle weakness. By 3 years of age, the patient was able to hold his head up but was unable to sit alone. At the age of 5 years, the patient was able to sit unsupported, but not stand. Intellectual and speech development was normal.

On examination, he was hypotonic, deep tendon reflexes were diminished. He had joint contractures of upper and lower extremities, myopathic facies, and pectus carinatum. His head circumference was normal. The serum CPK level was 2380 U/l (normal range <175 U/l). Echocardiography was normal. Nerve conduction studies were normal, and electromyography (EMG) showed a myopathic pattern. Magnetic resonance imaging (MRI) of the brain was performed and showed high signal in the periventricular and subcortical white matter [Figure 1a and b]. Muscle biopsy showed dystrophic changes with absent staining for merosin.

The patient 2 was the daughter of patient 1. Her problem was same with him. She had global hypotonia and was able to sit and was not able to stand. The distal tone of the four extremities was decreased, and deep tendon reflexes were diminished. She had contractures of elbow and knees, myopathic facies, and pectus carinatum. Intellectual and speech development was normal. Her serum CPK level was 1710 U/l. Echocardiogram was normal. Cerebral MRI was performed in another hospital and revealed high signal in the periventricular and subcortical white matter. EMG showed a myopathic pattern. Muscle biopsy was not performed. We analyzed the LAMA2 gene sequencing and revealed a homozygous mutation c. 639delG in the patient 1 and 2.

The patient 3 was a 7-month-old girl who presented to our hospital with complaints of developmental motor delays. Intellectual and speech development was normal. There was a history of consanguinity in parents. She had general hypotonia, proximal weakness, and normal head circumference. Joint contractures were absent. Her serum CPK level was 4073 U/l, and her echocardiogram was normal. MRI of the brain revealed hyperintense lesions in the periventricular white matter on T2A sequencing. EMG revealed the myopathic pattern. Muscle biopsy showed dystrophic changes with absent staining for merosin. We studied the LAMA2 gene sequencing and revealed a homozygous mutation p.R1350 (c. 4048 C > T).

The patient 4 and 5 were again siblings. The patient 4 was a 3 and a half year-old boy who presented with hypotonia, weakness, poor weight gain, and respiratory problem, and could not sit or stand. The parents
were also consanguineous. He had a dead sibling with same complaints. He had general hypotonia, myopathic facies, pectus excavatum, and he was not able to sit and stand. Deep tendon reflexes and Babinski's sign were negative. He had joint contractures on elbow and knees. Furthermore, he had a hemangioma on the left temple, chest, and wrist. His echocardiogram showed normal findings [Figure 2]. His serum CPK level was 2120 U/l and MRI of the brain showed similar findings with other patients. Muscle biopsy showed dystrophic changes with absent staining for merosin.

The patient 5 was a 6-month-old boy who had hypotonia. Joint contractures were absent. His biochemical investigations were normal except for elevated serum CPK levels (2950 U/l). Echocardiography was normal, and MRI of the brain showed hyperintense lesions in the periventricular white matter. EMG and muscle biopsy were not performed. We performed the LAMA2 gene sequencing and revealed a homozygous mutation p.R2578 (c. 7732 C > T) in two of them. Clinical and laboratory findings of patients are summarized on Table 1.

Discussion

MDC1A is an autosomal recessive neuromuscular disorder caused by mutations in the LAMA2 gene encoding the laminin-a2 chain a component of the skeletal muscle extracellular matrix protein laminin-211.[1] Laminin-211, the most abundant laminin in muscle, is also expressed in Schwann cells, the synaptic basal lamina of peripheral nerves, heart, epidermis and fetal trophoblastic tissue.[5] Typical clinical features of MDC1A or merosin-deficient CMD include severe floppiness at birth, elevated serum CPK, delayed motor milestones, white matter changes as seen on brain MRI. In literature, several studies have reported respiratory insufficiency, feeding difficulties, cardiomyopathy, sensory and motor demyelinating neuropathy, seizure, and external ophthalmoplegia.[3,6,7,8]

Our patients manifested with generalized hypotonia. Severe proximal weakness was also present from birth or developed within the first 6 months. In all the cases, motor milestones were delayed. Two patients could sit, but not stand and walk. In literature, a few reports were found about the mobility of these patients. Di Blasi et al.[8] reported 9 patients with MDC1A from 1 Sudanese and 3 Saudi families. Five of the 9 patients achieved independent walking. Other patients never walked, could sit or stand with or without support. Another study presented similar results: Five of 13 patients with residual merosin and two of 33 patients with absent merosin could walk independently.[9]

Merosin-negative CMD1 is known to cause bilateral white matter changes.[4] Leite et al.[10] in a study of 25 Brazilian patients with MDC1A reported that bilateral white matter involvement was frequent in the parietal, frontal, and temporal regions, brain stem, cerebellum, and internal and external capsules were also affected in the minority of cases. However, they described that there were no correlations with sites of white matter abnormalities and clinical or merosin status. In another study, Di Blasi et al.[8] reported MRI or CT, performed in 8/9 patients, and revealed white matter changes in 8 patients. Oliveira et al.[11] performed in 22/26 patients, revealed white matter changes in all cases. In addition, they detected that other cerebral changes included abnormal gyration in three patients.

In our study, all the patient showed the typical phenotype of MDC1A, including features such as hypotonia, elevated serum creatine kinase, delayed motor development, and T2 hyperintensity on brain MRI. In the patient 3, 4, and 5, we detected two LAMA2 gene mutations which have been described previously. Coral-Vazquez et al.[12] reported an 8-month-old Mexican female infant, from a consanguineous family, with MDC1A and they detected homozygous mutation p.R2578 in LAMA2 gene as similarly in our patient 4 and 5. This patient was the second child of healthy consanguineous parents. From the 1st month of life, the patient was hypotonic with poor intake, irritability, reduced spontaneous movements, and poor suction. Physical examination showed generalized muscle weakness and
contractures of elbows, wrists, knees, and ankles. However, we detected a new mutation in patient 1 and 2. These patients were triplets (2 girl, 1 boy). The mutation has not been previously described in the literature.

**Conclusions**

MDC1A is one of the most frequent forms of CMD. Patients should be suspected as MDC1A if they have early-onset severe hypotonia with joint contractures, motor developmental delay with moderately increased CPK levels, and abnormal cerebral imaging findings. Muscle biopsy and molecular genetic testing should be performed for diagnosis and especially for the genetic counseling.

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Nil.

**Conflicts of interest**

There are no conflicts of interest

**References**


10. Leite CC, Lucato LT, Martin MG, Ferreira LG, Resende MB, Carvalho MS, et al. Merosin-deficient


**Figures and Tables**

**Figure 1**

(a) Flair sequencing magnetic resonance imaging images of patient 1. showing abnormal periventricular and subcortical white matter signal. (b) Flair sequencing magnetic resonance imaging images of patient 1. Showing abnormal periventricular and subcortical white matter signal

**Figure 2**
Hemangioma on the left temple, chest, and wrist in the patient 4

**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<tr>
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<td>7 month/F</td>
<td>3.5 year/M</td>
<td>6 month/M (brother of patient 4)</td>
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CPK: Creatine phosphokinase, MRI: Magnetic resonance imaging, EMG: Electromyography, No: Not performed

Clinical and laboratory datas of the patients

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