Case Report / *Olgu Sunumu*

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A Novel Frameshift Mutation in Two Siblings with Merosin-deficient Congenital Muscular Dystrophy

Merozin Negatif Müsküler Distrofi Tanılı İki Kardeşte Yeni Tanımlanmış Bir Çerçeve Kayma Mutasyonu

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Abstract

We present two siblings with elevated serum creatine kinase concentrations, developmental delay, muscle weakness, and contractures of the lower limbs. Cranial magnetic resonance imaging revealed diffuse white matter hyperintensity in both siblings. In the older sister, muscle biopsy was performed; immunohistochemical studies showed a dystrophic pattern and merosin deficiency. With the diagnosis of merosin-deficient congenital muscular dystrophy (MDC1A), *LAMA2* gene mutation analysis revealed an NM_000426.3:c.163_163delA; (p.N55Mfs*16) homozygous frameshift mutation in the siblings. This mutation leads to a premature stop codon and has not been reported previously in the literature.

Keywords: Merosin, muscular dystrophy, white matter hyperintensity

Öz

Artmış serum kreatin kinaz seviyesi, gelişim geriliği, kas güçsüzlüğü ve alt ekstremitede kontraktürlerin olduğu iki kız kardeş sunulmuştur. Büyük kardeşte yapılan elektromiyogram miyopatik bulgular ile uyumluydu. Her iki kardeşteki kranial manyetik rezonans görüntülemede yaygın beyaz cevher sinyal artışı izlendi. Büyük kardeşe kas biyopsisi yapıldı ve immüno histokimyasal çalışmalar distrofik patern ve merozin negatifliği ile uyumluydu. Merozin negatif müsküler distrofi (MDC1A) ön tanısıyla yapılan *LAMA2* gen mutasyon analizinde NM_000426.3:c.163_163delA; (p.N55Mfs*16) homozigot çerçeve kayma mutasyonu görüldü. Bu mutasyon prematür stop kodona yol açmaktadır ve daha önce literatürde saptanmamıştır.

Anahtar Sözcükler: Merozin, müsküler distrofi, beyaz cevher sinyal artışı

Introduction

Merosin-deficient congenital muscular dystrophy (MDC1A, #607855) is a disorder characterized by muscle weakness and hypotonia at birth due to mutations in the laminin α-*2 gene (LAMA2)* mapped to the 6q22-23 chromosomal location. *LAMA2 gene* encodes merosin. LAMA2-related muscular dystrophies are a clinically homogeneous group typically presenting with hypotonia and brain white-matter hyperintensity (1,2). In this study, we present a case of MDC1A in two siblings with a novel homozygous frameshift mutation c.163_163delA; (p.N55Mfs*16) in the *LAMA2 gene*. This mutation leads to a premature stop codon, which has not been reported in the literature.

Case Reports

Case 1

A 3-year-old girl was the first child of second-degree consanguineous parents (first cousins). The parents were healthy and there was a family history of two cousins with unknown neuromuscular disease. The girl was born at 39 weeks of gestation and the pregnancy was uneventful, but she was hospitalized for ten days in the neonatal unit because of hypotonia and feeding difficulties.

On physical examination, the muscle strength of her lower limb muscles was grade 3/5 of the Medical Research Council (MRC) scale and the upper limb muscle strength was grade 4/5 with contractures of the lower limbs.

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Developmental milestones were delayed; by 5 months of age, the patient was able to hold her head up, and the patient was able to sit unsupported at the age of 17 months, but she could not stand. Her deep tendon reflexes in the upper and lower extremities were absent. The cranial nerves and coordination were normal. On sensory examination, tactile, pinprick, and vibration were normal. An elevated serum creatine kinase (CK) concentration of 1690 IU/L was revealed. An electromyogram showed low amplitude polyphasic motor unit potential compatible with a myopathic process. MDC1A was suspected and magnetic resonance imaging (MRI) showed diffuse white matter hyperintensity supporting the diagnosis (Figure 1). At the age of one year, a muscle biopsy showed myofibers in different sizes and shapes with neonatal myosin, proliferated interstitial tissue with Masson's trichrome, and increased immature fiber and irregular myofibrils with nicotinamide adenine dinucleotide tetrazolium reductase and diffuse sarcolemmal merosin deficiency (Figure 2). The patient had MDC1A both with clinical and imaging presentation. We performed *LAMA2* gene sequencing and revealed a novel homozygous frameshift mutation c.163_163delA; (p.N55Mfs*16), which confirmed the diagnosis of MDC1A by molecular test.

Case 2

A 20-month-old girl was the second child of the same family. The pregnancy was uneventful but after birth, axial hypotonia was recognized and she was referred to the pediatric neurology department of our clinic. On physical examination, she had lower limb proximal muscle weakness of grade 3/5 MRC with contractures of the lower limbs. Her deep tendon reflexes in the upper and lower extremities were absent. An examination of the cranial nerves was normal. The serum CK concentration was 2140 mU/mL. MRI revealed diffuse white matter hyperintensity. *LAMA2* gene sequencing of the patient revealed a novel homozygous frameshift mutation c.163_163delA; (p.N55Mfs*16), the same as in her sister.

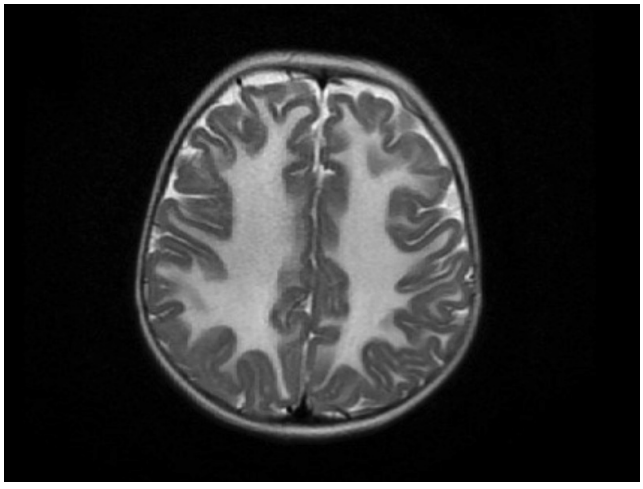

Figure 1. Case 1 MR T2 Flair axial image reveals diffuse T2 hyperintensity

MR: Magnetic resonance

Discussion

MDC1A is one of the most frequently seen congenital autosomal recessive muscular dystrophy. Muscle weakness is slowly progressive and is accompanied by arthrogryposis. In the infantile period, patients with MDC1A usually have respiratory and feeding difficulties that ultimately result in hospitalization, especially in the neonatal period. The older sibling had a history of hospitalization in the neonatal period because of feeding difficulties, but the younger sibling had no such history.

Most patients with MDC1A have the ability to sit unsupported, but cannot stand or walk. They usually have normal intellectual and speech development. Our patients had the ability of sitting unsupported and Denver Developmental Screening Test assessments were in accordance with their age.

The pattern of brain white matter abnormalities on neuroimaging is characteristic and presents in patients with MDC1A aged over 6 months (3). MRI revealed diffuse white matter hyperintensity in both siblings. In MDC1A, high serum CK concentrations are present. With the characteristic MRI pattern and high serum CK values, molecular testing for the *LAMA2* gene should be performed.

Although over 350 causative mutations have been identified for MDC1A, no treatment is yet available. There are many therapeutic approaches in development;

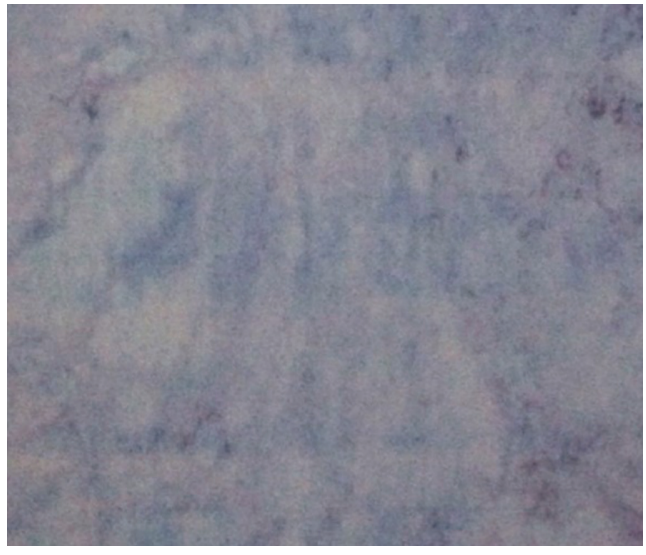

Figure 2. Muscle biopsy case 1 with diffuse sarcolemmal merosin deficiency

a recent study confirmed the recovery of the laminin-α2 chain following skipping of the mutated exon in mice (4). These findings support the future development of phosphorodiamidate morpholino oligomer-mediated therapies for MDC1A (4). Also, the orphan drug Tarix TXA127, which is a pharmaceutical formulation of the naturally occurring peptide angiotensin-1-7, has been effective in MDC1A animal models and has been granted status as a potential treatment for MDCA1 (5).

MDCA1 is inherited in an autosomal recessive manner, further pregnancies carry a one in four risk of bearing an infant with MDCA1, thus molecular diagnosis is highly recommended for parents with an affected child. Fadiloglu et al. (6) performed chorionic villus sampling for prenatal diagnosis of MDCA1 with immunohistochemical studies. They concluded that immunohistochemical studies had high specificity for the diagnosis of merosin-negative muscular dystrophy and may be evaluated as reliable.

Molecular genetic testing was planned but could not be performed for the older sibling and at that time, the parents had the second affected child. Sequencing of the two siblings revealed a novel homozygous frameshift mutation c.163_163delA; (p.N55Mfs*16) within the *LAMA2* gene. *In silico* analysis with MutationTaster, PolyPhen2, SIFT predicted this variant as a disease-causing mutation. Their parents refused to be included in the study for showing familial segregation. This mutation leads to a premature stop codon and has not been reported previously in the literature. Consistent with the phenotype of the patient, this mutation might be responsible for the early-onset disease and severe congenital hypotonia.

The aim of this study was to characterize the clinical and genetic features of the siblings with MDC1A. This study emphasizes that MDC1A should be kept in mind in individuals with congenital hypotonia, muscle weakness, elevated serum CK concentrations, and white matter abnormalities. Molecular diagnosis is essential for genetic counselling and prenatal diagnosis when required, especially in our country because consanguineous marriage is frequently seen.

Authorship Contributions

Concept: M.P., S.Ç. Design: S.A., H.B.G.Ç. Data Collection or Processing: S.A., H.B.G.Ç. Analysis or Interpretation: M.P., S.Ç. Literature Search: S.A., H.B.G.Ç. Writing: S.A., H.B.G.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

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References

1. Geranmayeh F, Clement E, Feng LH, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. Neuromuscul Disord 2010;20:241-50.
2. Pegoraro E, Marks H, Garcia CA, et al. Laminin alpha2 muscular dystrophy: genotype/phenotype studies of 22 patients. Neurology 1998;51:101-10.
3. Sijens PE, Fock JM, Meiners LC, Potze JH, Irwan R, Oudkerk M. MR spectroscopy and diffusion tensor imaging of the brain in congenital muscular dystrophy with merosin deficiency: metabolite level decreases, fractional anisotropy decreases, and apparent diffusion coefficient increases in the white matter. Brain Dev 2007;29:317-21.
4. Hara Y, Mizobe Y, Miyatake S, et al. Exon Skipping Using Antisense Oligonucleotides for Laminin-Alpha2-Deficient Muscular Dystrophy. Methods Mol Biol 2018;1828:553-64.
5. Acuna MJ, Pessina P, Olguin H, et al. Restoration of muscle strength in dystrophic muscle by angiotensin-1-7 through inhibition of TGF-b signalling. Hum Mol Genet 2014;23:1237-49.
6. Fadiloglu E, Ozten G, Unal C, Talim B, Topaloglu H, Beksac MS. Prenatal Diagnosis of Merosin-Deficient Muscular Dystrophy. Fetal Pediatr Pathol 2018;37:418-23.