

# Dropped head related lamin A/C associated congenital muscular dystrophy case; previously defined as emery-dreifuss muscular dystrophy

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## ABSTRACT

Dropped head syndrome can be seen in many neuromuscular diseases. However, there are very few diseases in which neck extensors are weak among neuromuscular diseases. A 7 years old boy who had weakness of the neck extensor muscles, creatinine kinase elevation and dystrophy findings in biopsy followed up with the preliminary diagnosis of muscular dystrophy is presented. We detected p.N456K (c.1368C> A) heterozygote mutation by the gene sequencing in the Lamin A/C associated (LMNA) gene. This mutation was previously reported as Emery-Dreifuss muscular dystrophy.

**Key words:** congenital muscular dystrophy, LMNA, dropped head.

Congenital muscular dystrophy can be seen in clinically and genetically different forms. Most of the patients present with muscle weakness, hypotonia and delayed motor development within the first 2 years.<sup>1</sup> The diagnosis of a large number of identified genes, mutation-dependent clinic or even different clinics, even in the same mutation, can make diagnosis difficult. It is important to evaluate the mutations detected with clinical clues and their compliance with previously defined diseases. The cases that were defined as a variant form of a disease in the past as the diseases defined over time are now known with a new name and different clinical features.

LMNA-associated congenital muscular dystrophy was first described in 2005.<sup>2</sup> Transmission can be autosomal recessive, dominant or de nova. LMNA gene screening

identified heterozygous de novo LMNA mutations in 15 patients by Quijano-Roy et al.<sup>3</sup>

It has two forms; milder form and severe form. Patients with the milder form can walk but cannot control their head because of neck extensor weakness. Severe form have poor movements, may need mechanic respiration and cannot stand.

Herein, we presented a case of LMNA-associated congenital muscular dystrophy, which previously detected a p.N456K (c.1368C> A) heterozygous mutation in the LMNA gene identified for Emery Dreifuss muscular dystrophy (EDMD).

## Case Report

A 7-year-old male patient, who was born healthy from a family with a cousin marriage of second degree, applied with difficulty in walking and complaints of not being able to standing up without a support from his sitting position.

It was learned that the patient could sit at 6-7 months of age, began to take steps at 18 months, but could hold his head when he was

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36 months. At the current physical examination, neck extensors were weak, his head was falling occasionally, and weakness in other muscle groups was indistinct. Lordosis of the patient was increased, hypotonic and deep tendon reflexes were not obtained (Fig. 1). The mental capacity of the patient was normal according to his age.

Creatine kinase levels of the patient were 7-8-fold (1050-950-1208 mg/dl) higher than normal. Multiplex Ligation-dependent Probe Amplification (MLPA) genetic analysis was



**Fig. 1.** Patient with weak neck flexors and Gower sign.

found negative for spinal muscular dystrophy (SMN 1-2) and Duchenne muscular dystrophy. Myopathic changes were present in proximal muscles in electromyography. Sensory and motor nerve conduction studies was normal. Polyphasic, short-duration, low-amplitude motor unit action potentials (MUAPs) was detected. Cranial magnetic resonance imaging was normal. Echocardiography was normal. 24-hour Holter monitoring was normal. Pulmonary function test was normal. Dystrophic changes like shape-size difference, degeneration and regeneration were observed in the biopsy of the patient's triceps muscle (Fig. 2). There was an increase in interstitial tissue detected by Gromi trichrome stain. Modified tricom, NADH-TR, SDH and COX staining were normal. In Rust, dPas, Oil Red O and crystal violet staining, there were not material accumulation and amyloidosis. Fast myosin and type 2 / type 1 myofiber ratio was normal. Immunohistochemical evaluation showed that perinuclear emerlin, sarcolemmal dystrophin, spectrin, distroglikan, merosin, dysferlin, sarcoglycan, caveolin 3 and lamin A / C were stained normally. No inflammatory staining of the stains with CD45 and CD68 was detected (Fig. 2). With these findings, muscle biopsy had non-inflammatory primary myopathic and / or dystrophic disease findings. When the clinical and laboratory findings of the patient were evaluated, it was noteworthy that the patient was still suffering from inability to holding the head still, and LMNA and selenoprotein (SEPN1) gene sequencing was performed. A p.N456K (c.1368C> A) heterozygote mutation was detected in the LMNA gene. This mutation was not detected in the mother and father. It was defined as a disease-causing according to the silico analysis.

It was thought that the early onset of the disease, the lack of specific orientation of muscle biopsy, and the evaluation of patients in the literature suggest that the patient has LMNA-associated congenital muscular dystrophy (LMNA-CMD). An informed consent was received from parents for any publication.

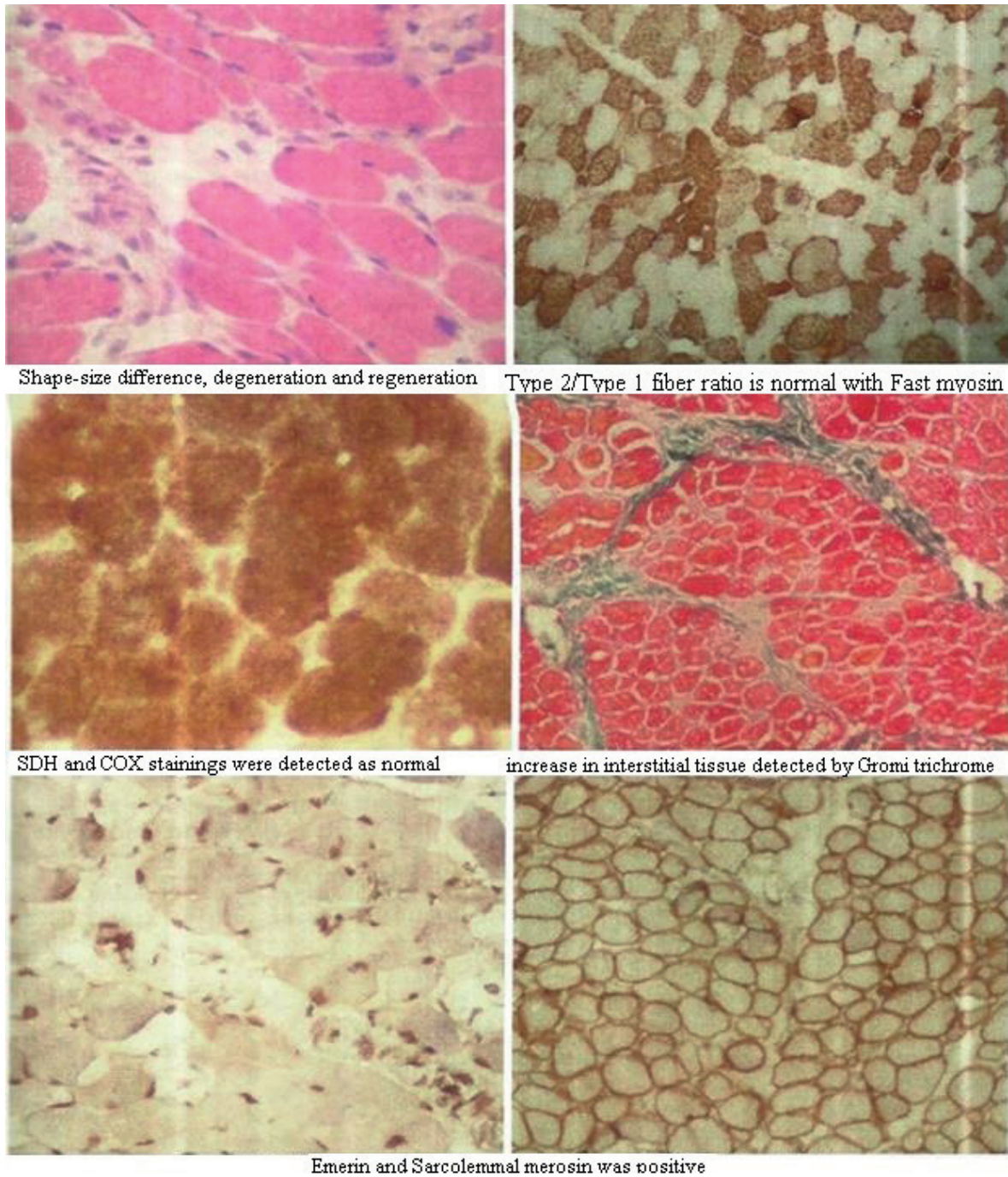


Fig. 2. Muscular biopsy findings.

### Discussion

Weakness in neck extension is called 'dropped head syndrome' and this condition can be seen in many neuromuscular diseases. LMNA and SEPN1 mutations should be investigated in

neuromuscular diseases where the weakest muscle group is neck extensors or the only finding is neck extensor weakness.<sup>2</sup>

Lamin A gene (LMNA) codes for type A laminates that constitute the nuclear envelope



proteins. Among the diseases associated with this gene are Autosomal Dominant and Autosomal Recessive Emery Dreifuss muscular dystrophy, limb girdle muscular dystrophy type 1b (LGMD1B), Cardiomyopathy with transmission defect, Charcot-Marie-Tooth type 2b and LMNA associated congenital muscular dystrophy.<sup>4</sup> LMNA mutation in patients presenting with dropped head was called LMNA-associated congenital muscular dystrophy by Quijano-Roy et al.<sup>3</sup> LMNA-associated congenital muscular dystrophy may be presented with early onset, especially if the patient has 'dropped head' due to weakness in the neck muscles, and moderate CK (creatinine kinase) elevation. There was widespread muscle weakness in our patient, but most obvious weakness was in the neck muscles and there were about 10 times higher CK values.

In these patients, biopsy findings support non-inflammatory primary myopathic and / or dystrophic disease findings but are not specific diagnostic features. In addition, type 1 fiber atrophy is more likely to occur in patient biopsies in the LMNA-CMD group.<sup>3,5</sup> In our patient, dystrophic changes were observed as expected in muscle biopsy, but there was no change in the ratio of type 2 / type 1 myofibrils to type 1 myofibril atrophy, which is usually seen or has a hint for diagnosis. One reason for this was that our patient had a slight weakness in other muscle groups other than the neck muscles. Patients with type 1 myofibril atrophy were more severe than our patients.<sup>6,7</sup> Lymphocytic inflammation was observed in biopsies of some patients with severe form. No inflammation was noted in both our and other dropped head patients.<sup>3,8</sup> Immunohistochemical stain for lamina A / C was found to be as normal. Most of the immunohistochemical staining in CMD-LMNA patients were normal and our patient also required genetic study.

Sanger sequencing of the LMNA gene coding exons and flanking introns from the genomic DNA p.N456K (c.1368C> A) heterozygote mutation was detected. Most of the LMNA de nova mutations can be normal variant. So

parental genetic analysis or in silico analysis or functional studies should be evaluated. We proved that the mutation is de nova and disease-causing with in silico analysis. This mutation was preceded by a case of Emery Dreifuss muscular dystrophy, which had a moderate CK elevation (7-fold) and non-specific findings in progressive course at 2 years of age in 2000.<sup>9</sup> This patient with the same mutation appears to be presenting with severe involvement at an early age according to EDMD. EDMD is usually seen age 10 and is characterized by wasting and weakness of shoulders, upper arms and the calf muscles. LMNA-associated CMD (LMNA-CMD) muscle weakness becomes apparent in infancy or early childhood and can worsen quickly

Some clues in the differential diagnosis of LMNA-associated muscle diseases are prominent (Table I). We believe that this mutation, previously described, is LMNA-CMD when both our patient and the patient who is published in the literature are considered.

Similar cases were detected in the European and French Laminopathies / EDMD research networks and mutation identified by LMNA-CMD in 5 of 21 patients diagnosed as EDMD2 and LGMD Type 1 and lost walking ability before infancy or before 15 years of age.<sup>3,10</sup>

The patients were divided into two groups by Quijano-Roy et al.<sup>3</sup> severe and mild. Early onset motor weakness, lack of spontaneous movement, need for ventilator and severe ventricular tachycardia were classified as severe form, and none of the patients in this group were able to walk. The mild group consists of patients who can walk and have no other serious organ involvement. However, the most prominent feature of this group is that neck extensors are relatively weak compared to other muscle groups. Our patient has been in the mild group since birth, with no ventilator requirement, being able to walk and especially having weakness in the neck muscles. Cardiomyopathy and cardiac arrhythmias are reported frequently in these patients.<sup>3,5</sup> Our

**Table I.** Diferantial diagnosis of muscular dystrophy with LMNA mutation.

	EDMD TYPE 2	LGMD-TYPE 1B	Severe L-CMD	Mild L-CMD	Our Patient	Described EDMD by Bonne in 2000.
Inheritance	OD/OR	OD	OD/OR	OD/OR	De Nova	Sporadic
Age-Onset	Late Childhood-Adolescent	Childhood-Adolescent-Adult	Birth	Birth-infancy-early childhood	infancy	Age 2
Most Affected Muscle Group	Scapuloperoneal	Hip-Shoulder	Severe hypotonia, diffuse limb and axial muscle weakness, generalizedextremite amyotrophy	Neck extensor, peroneal, proximal lower	Neck extensor, scapuloperoneal	Neck extensor- diffuse
CK Levels	N-mildly elevated	N-mildly elevated	2-10 times elevated	2-10 times elevated	7-8 times elevated	7 times elevated
Contracture	Elbow-ankle-neck	Hip-Shoulder	Ankles, fingers, wrists,rigid spine	Elbow, rigid spine		Rigid spine, elbow,ankle,wrist
Respiratory Support Requirement	No	No	Yes	No	No	No
Able to Walk	Yes	Yes/ elderly	No	Yes	Yes (age 7)	No (age 16)
Cardiac Conduction Defect/ Cardiomyopathy	Usually/ Often	Usually/ Less frequently	Yes/Yes	Yes/ Less frequently	No/No	No / na
Histopathology	Variation in fiber size, increase in internal nuclei, increase in endomysial connective tissue, and necrotic fibers. Emerin is normally expressed.	Fiber size variation with small angulated fibers	Fiber size variation, increased endomysial connective tissue, necrosis and regeneration, lymphocytic inflammation type 1 atrophic fibers	Fiber size variation, increased endomysial connective tissue, necrosis and regeneration, type 1 atrophic fibers	Dystrophic changes like shape-size difference, degeneration and regeneration	Variation in fiber size, significant increase in internal nuclei, a mild increase in endomysial connective tissue and necrotic fibers. Type 1 fibers were predominant and often relatively atrophic.

patient's ECO and 24-hour electrocardiography examinations were normal.

Respiratory distress or failure occurs in the early-onset group at the first age, whereas in the dropped head group it is usually observed before the age of 8.<sup>3</sup> Our patient had no complaints and the respiratory function test was normal according to his age.

In some of the patients, white matter anomalies were also reported in cranial examinations.<sup>6,11</sup> No abnormal findings were found in the cranial imaging of our patient. Patients should be assessed for respiratory, cardiac, and cranial involvement.

We think that our patient and the patient who was previously referred to as EDMD are also LMNA-CMD.

Patients with symptoms of non-specific muscular dystrophy, especially those with weakness in the neck muscles, whose symptoms have begun at a young age, should be evaluated for LMNA-CMD prior to invasive procedures.

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