



## Case report

# Congenital muscular dystrophy with dropped head phenotype and cognitive impairment due to a novel mutation in the *LMNA* gene

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## Abstract

Mutations in A-type nuclear lamins are known to cause a variety of diseases, which can affect almost all organs of the human body including striated muscle. For lamin-related congenital muscular dystrophy two different phenotypes are known to date. Here, we describe a 3-year-old, white Caucasian girl with a novel *de novo* mutation in the *LMNA* gene with marked hypotonia of neck and trunk muscles with dropped head posture, loss of cervical lordosis and marked joint laxity. In addition to this novel mutation, the patient also had cerebral white matter lesions on MRI and cognitive impairment on developmental testing. This is only the second A-type lamin-related congenital muscular dystrophy patient in which white matter lesions are described. Thus, white matter involvement might be a feature in A-type lamin-related congenital muscular dystrophy, warranting screening of these patients for both white matter lesions and cognitive impairment.

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## 1. Introduction

A-type lamin-related congenital muscular dystrophy (L-CMD) is caused by mutations in the *LMNA* gene on chromosome 1q22. Lamins are nuclear envelope proteins. A variety of human diseases, affecting not only striated muscle but almost all other organs, have been linked to impaired type-A lamin function due to mutations in the *LMNA* gene. Two different phenotypes of muscle

impairment in L-CMD have been described, but brain involvement, in contrast to other forms of CMD [1], has not yet been considered to be a common feature in L-CMD. Here, we describe a novel heterozygous mutation in exon 1 (c.93G>C) of the *LMNA* gene leading to CMD with dropped head sign, white matter lesions, and cognitive impairment in a 3-year-old girl.

## 2. Case report

The patient is a 3-year-old white Caucasian girl. She is the second daughter of a family with no previous history

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of any muscular disorders. No consanguinity is known. She has a 6 year old healthy sister.

At the age of 14 months she was referred to our outpatient department due to failure to thrive and difficulties swallowing. Past medical history revealed that she had already been found to be small for gestational age in prenatal screening. A chorionic villus sampling was therefore done in the first trimester which showed normal results. Because her perinatal weight was below P3, an elective Caesarean section at 38 weeks of gestation was performed. After weaning she never started to chew nor tried to eat solid food. She repeatedly choked on dry food but never had an aspiration or a pulmonary infection. From the age of 8 months motor development delay was noticed by her paediatrician. Due to failure to thrive with poor weight gain and delayed growth she was referred to our outpatient department at the age of 14 months. Elevated CK levels were discovered and a muscular dystrophy was suspected.

Neurological examination at first presentation showed marked hypotonia of neck and trunk muscles with dropped head posture, loss of cervical lordosis (as a first sign of rigid spine syndrome), and lumbar hyperlordosis. While lying on her tummy, she could not lift her head or upper body from the ground. She was able to sit unsupported and moved in shuffle-position but was unable to crawl. She pulled herself up to a stand while holding onto furniture and walked with support. Fine motor skills were not impaired. No ataxia was found. She had no contractures but marked joint laxity, especially in her ankle and foot joints. Deep tendon reflexes were symmetrical in the upper limbs, but absent in the lower limbs. Free ambulation was reached with delay at 24 months of age, when she was able to walk 10 m without support. Due to marked joint laxity of her foot and ankle joints, which impaired her walking ability (see Fig. 1A and B), orthotics to support ankle joint stability were tried but were scarcely beneficial. Free

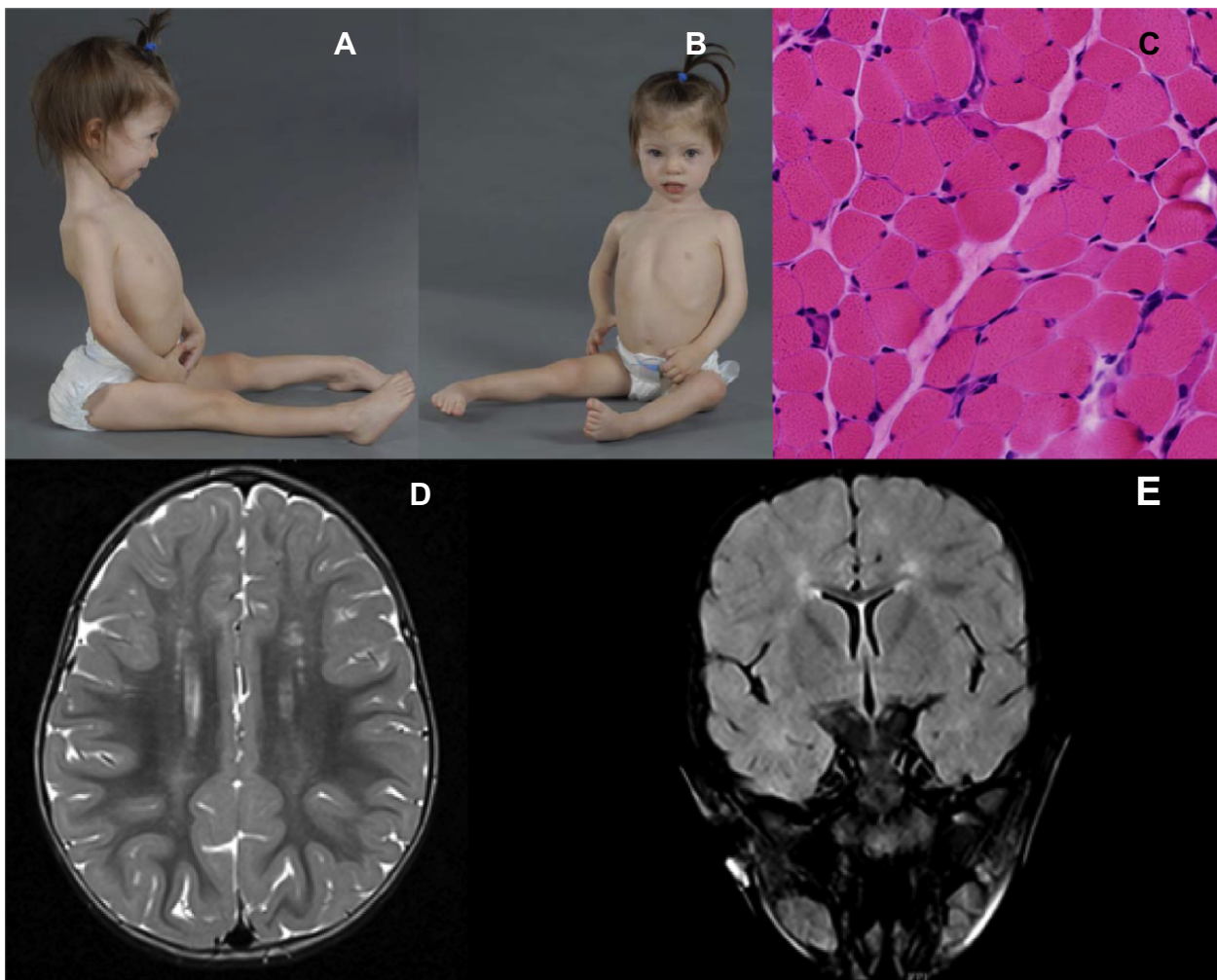


Fig. 1. (A/B) Patient at age 2 years and 8 months. Note the dropped head phenotype, the missing cervical lordosis and the marked laxity seen in the ankle joints. (C) Hematoxylin–eosin stained muscle tissue from the patient showed mild myopathic changes consisting of increased variability of fibre diameters, few necrotic and regenerating fibres, and macrophages. (D/E) Coronal (D) and axial (E) T2 weighted MR-images of the brain showing point like parasagittal disturbances of myelination (arrows).

ambulation was lost at the age of 2 years and 8 months after a minor fall.

At first presentation serum CK level was 2759 U/l (normal <200 U/l), suggestive of a (congenital) muscular dystrophy. Pulmonary and heart exams including echocardiography and electrocardiogram, were normal. Histology of tissue from the right vastus lateralis muscle at the age of 15 months revealed nonspecific myopathic changes (see Fig. 1C). Staining for merosin, spectrin and glycosylated alpha-dystroglycan was normal on immunohistochemical assessment. T2-weighted and T2-weighted fluid attenuating inversion recovery (FLAIR) MRI sequences of the brain showed few small dot-like hyperintensities of the parasagittal deep white matter bilaterally possibly reflecting gliosis or disturbed myelination (Fig. 1D and E). To evaluate cognitive development the Mental Scale of the Bayley Scales of Infant Development Second Edition (BSID II) was performed repeatedly [2]. Results indicated a delay in task related actions such as building towers due to impaired motor function but also a mild delay in other cognitive domains such as language and higher-order thinking skills. When tested last at the age of 2.9 years, she had a scaled score below average of 75.

Due to dropped head CMD phenotype, a *LMNA* gene mutation was considered and the *LMNA* coding region sequenced. This revealed a novel – *de novo* – heterozygous missense mutation c.93G>C, which leads to an exchange of amino acids at codon 31 (p.Glu31Asp). *In silico* analyses predicted the mutation to be disease causing (MutationTaster score:0.9998) [3], probably damaging (PolyPhen-2 score: 0.994) [4] and damaging (SIFT score:0.0) [5]. This mutation has not yet been described according to the Leiden Open (source) Variation Database (LOVD) and the UMD-*LMNA* mutations database. However, another codon 31 missense mutation (GAG>AAG (Lys)) was recently described by Menezes et al. [6] in a patient with a very similar phenotype.

### 3. Discussion

L-CMD is a relatively new entity, first described in 2005 by D'Amico et al. [7]. Transmission can be autosomal recessive or dominant. As in our patient, *de novo* mutations appear to be frequent. So far, two L-CMD subtypes have been distinguished: (a) an early-onset severe phenotype with poor spontaneous movements and limited motor achievements; (b) an initially milder phenotype with the ability to stand and walk, but inability to obtain free head control with dropped head sign [8].

White matter changes and to a lesser degree structural changes are frequently found in the brain in various forms of CMD, in Emery-Dreifuss muscular dystrophy, as well as in patients with B-type lamin mutations [1], but has not been described in A-type lamin mutations so far.

Here, we describe a novel *LMNA* mutation presenting as a L-CMD with dropped head phenotype and cognitive impairment. Brain MRI at 1.4 years showed few dot-like white matter lesions bilaterally that we interpreted as gliosis. As a differential diagnosis, disturbed myelination could be a possible cause. A higher risk for developmental delay is known for children born small for gestational age (SGA) [9]. However, several confounding factors have to be taken into account and in most of the cases no white matter lesions in MRI are found. Also, in our patient the white matter changes are slightly asymmetric and occur in an area where we expect myelination to be completed at this age. In contrast to the lesions found in our patient, Virchow Robin Spaces are also found in this part of the brain, but are well delineated and isointense to cerebrospinal fluid [10]. Therefore, the cognitive delay and brain MRI changes seen in this patient are less likely to be a consequence of SGA or motor dysfunction (less learning experiences) but rather a cerebral manifestation of the *LMNA* mutation. Interestingly, a recent case report described very similar white matter lesions in a 22 months old Japanese girl with L-CMD [11] which, in conjunction with our patient suggests that white matter cerebral involvement can occur in patients with *LMNA* mutations. Menezes et al. [6] recently reported on a patient carrying a *LMNA* mutation in the same codon as our patient, and displaying a very similar clinical phenotype with dropped head sign, hypotonia, axial weakness, and elevated CK (1066 U/L). In contrast to our patient, early ankle joint contractures were present. Unfortunately, no brain MRI imaging or developmental testing results were provided.

Undoubtedly, further patients need to be studied to answer the question of whether white matter lesions are a common feature of L-CMD. We therefore suggest that L-CMD patients should be screened for brain involvement and cognitive impairment.

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