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ScienceDirect

Neuromuscular Disorders 27 (2017) 856–860

www.elsevier.com/locate/nmd

Case report

Rare diagnosis of telethoninopathy (LGMD2G) in a Turkish patient

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Received 12 January 2017; received in revised form 1 May 2017; accepted 30 May 2017

Abstract

Telethoninopathy is one of the rarest forms of Limb-girdle muscular dystrophy (LGMD). So far, only a small number of LGMD type 2 G (LGMD2G) patients have been described, mostly patients from Brazil. Here we present a 35-year-old female patient of Turkish ethnicity with LGMD2G due to a novel homozygous frame-shift mutation c.90_91del (p.Ser31Hisfs*11) in the telethonin gene, probably leading to truncated protein or nonsense mediated decay. Myalgia and walking on tiptoes were the first symptoms starting in early childhood, around age 22 proximal, later distal leg muscles became affected. Muscle biopsy showed a degenerative myopathy with lobulated fibers, creatine kinase levels were elevated to 1200 U/l. No cardiomyopathy has been detected but ventricular extrasystoles were treated with verapamil. Even though telethoninopathy represents a rare condition, testing for LGMD2G should be included into the diagnostic work-up of mild myopathies with early toe walking and distal and proximal involvement.

Keywords: Telethonin deficiency; LGMD2G; TCAP; Limb girdle muscular dystrophy

1. Introduction

Limb-girdle muscular dystrophy type 2 G is caused by different mutations in the telethonin gene (also named titin-cap or TCAP) [1,2]. This relatively mild form of autosomal recessive limb-girdle muscular dystrophy was first reported in 2000 in three Brazilian families, the disease was mapped to chromosome 17q11–12 and is caused by different mutations in the sarcomeric protein telethonin with consecutive telethonin deficiency in the muscles of the affected patients [1]. Telethonin is a sarcomeric protein of 19 kD present in heart and skeletal muscle and in gastrointestinal smooth muscles and is located in the Z-disc [3,4]. Titin kinase activation in differentiating myocytes and the resulting phosphorylation of telethonin are involved in the reorganization of the cytoskeleton during myofibrillogenesis [5]. The clinical phenotype of LGMD2G with mutations in the gene encoding telethonin shows a rather homogenous phenotype with proximal and distal weakness predominantly in the lower extremities [2]. Allelic conditions that are associated with autosomal dominant TCAP-Mutations are hypertrophic and dilated cardiomyopathy [6–8]. Among the limited number of LGMD2G patients who have been described worldwide most patients were of Brazilian origin [1,9–12], while only few cases have been reported of Indian [13,14], French [15], Portuguese [16], Moldavian [17], Spanish [2] and Chinese [18–20] origin. Here we present a 35-year-old female patient of Turkish ethnicity with LGMD2G due to a novel homozygous frame shift mutation c.90_91del (p.Ser31Hisfs*11) in the TCAP gene (NM_003673.3) that probably leads to truncated protein or nonsense mediated decay.

2. Case report

We report the case of a 35-year-old female patient of Turkish origin (Fig. 1E "A") born from a consanguineous marriage – the parents are second degree cousins. The patient has three younger siblings – two brothers and a sister – who are healthy. However, one son of a paternal aunt (Fig. 1E "B") had been clinically diagnosed with Duchenne muscular dystrophy in Turkey. Unfortunately, they were not available for further follow-up. The patient has three children, a son and two daughters; the marriage is also consanguineous (her mother-in-law is the cousin of the patient's grandmother). Retrospectively, the patient showed

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https://doi.org/10.1016/j.nmd.2017.05.017
0960-8966/

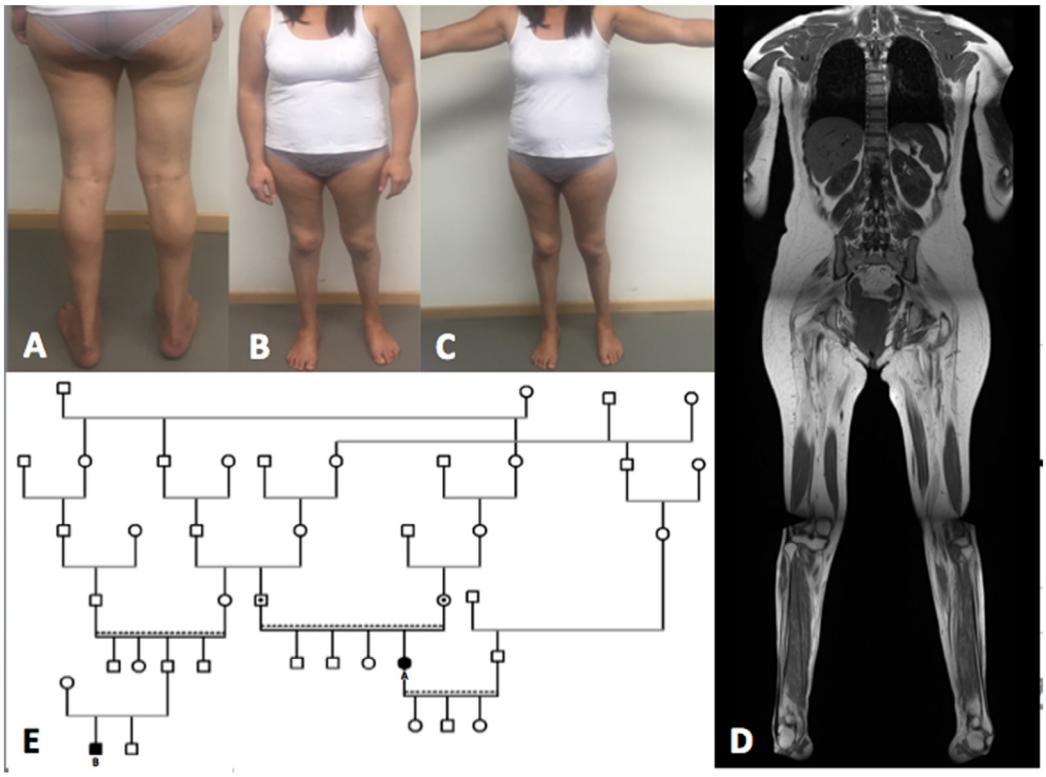

Fig. 1. Clinical phenotype of the patient: A: Atrophy of dorsal thighs and calves, mild right-sided Achilles tendon contracture. B: Marked atrophy of tibialis anterior muscles and ventral thighs. C: Normal upper limb muscles with defined muscle structure; the arms can be easily lifted above the head. D: Severe atrophy and fatty infiltration predominantly in the glutei, hip and thigh muscles. E: Pedigree of the family. Affected members are shown in black. Consanguineous marriages are marked with double lining. A: Patient with p.Ser31Hisfs*11 mutation, B: Patient with suspected Duchenne muscular dystrophy.

first symptoms at the age of two, presenting as tiptoe-walking. During childhood, she was regularly suffering from myalgia following muscular activity. At the age of 14, she underwent Achilles tendon surgery due to the Achilles tendon contractures; however, back then no muscular weakness was reported. Proximal leg weakness was first noted around age 22, mainly presenting while climbing stairs. Since age 28, rising from the floor was no longer possible. Muscle weakness was slowly progressive, to date affecting proximal and distal muscles only of the lower extremities. So far, there are no signs of respiratory insufficiency. The patient first presented at our department at age 34, displaying marked symmetric atrophy of the dorsal thighs and calves and distinct hyperlordosis. Muscle strength testing showed weakness of the proximal and distal leg muscles (Medical Research Council Scale (MRC): M. iliopsoas 4/5, M. quadriceps 2/5 MRC, ischiocrural muscles: 2–3/5, leg abduction 4/5, M. tibialis anterior 1–2/5, M. gastrocnemius 3/5). Walking on tiptoes and on heels was impaired. No facial involvement and no weakness of the upper extremities were noted, there was no calf or tongue hypertrophy, no scapular winging, and cognitive function was not impaired (Fig. 1A–C). Serum creatine kinase (CK) levels were only moderately increased (150–1200 U/l). The electromyogram showed a severe myopathic pattern in tibialis anterior muscles. Whole body magnetic resonance imaging (MRI) showed a symmetric atrophy and fatty infiltration with predominant changes of the glutei, hip and thigh muscles with sparing of the sartorius muscles along with atrophy of tibialis anterior muscles (Fig. 1D). Spirometry and echocardiogram showed normal results; however, ECG revealed ventricular extrasystoles, and a therapy with verapamil was initiated. A muscle biopsy from the deltoid muscle showed a changed muscular architecture with increased numbers of central nuclei and a myopathic muscle with fiber atrophy (Fig. 2 A,B); no nemaline bodies were detected. Immunohistochemical analysis for adhalin, merosin, caveolin-3, alpha-B-Crystallin/Desmin, dysferlin, alpha-dystroglycan and Collagen-6 revealed no abnormities. On oxidative stain reactions many small lobulated fibers were found, correlating with type 1 fibers (Fig. 2 C,D). Immunoblotting using a polyclonal antibody for telethonin (NBP1-85544, Novus Biologicals) showed a complete absence of the telethonin protein (Fig. 3).

Next generation sequencing identified a homozygous mutation c.90_91del (p.Ser31Hisfs*11) in the TCAP gene (NM_003673.3). The deletion affects two nucleotides in the first of the two TCAP gene exons and creates a frame shift starting at the codonSer31. The new reading frame ends in a STOP codon 10 positions downstream. This novel frame-shift mutation probably leads to truncated protein or nonsense mediated RNA decay which is in line with absent telethonin protein in immunoblotting.

This variant has not been previously reported in population-specific databases or in literature. For segregation analysis, the parents were tested for the mutation; both carried the mutation in heterozygous state.