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Case report

Late onset distal myopathy: A new telethoninopathy

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1. Introduction

Autosomal recessive limb-girdle muscular dystrophy type 2G (LGMD2G) is caused by mutations in *TCAP* gene, located on chromosome 17q12 [1]. It encodes the sarcomeric protein telethonin, also called titin cap, a Z-disc protein of 19 kDa and 167 aminoacids which is present in skeletal muscle, heart and gastrointestinal smooth muscle [2,3]. It interacts with titin and other sarcomeric proteins, playing an important role in sarcomeric assembly, sarcomere-membrane interactions and stretch sensing [4].

The clinical phenotype of LGMD2G described thus far is a rather homogenous picture, showing young onset limb-girdle weakness, affecting first and predominantly the lower extremities, with prominent anterior tibial muscles weakness and early foot drop in some cases [5]. The symptoms are usually present in the second decade of life, but a congenital form of telethonin deficiency has also been described [6,7]. Allelic conditions that are associated with *TCAP* mutations are dilated and hypertrophic cardiomyopathy [8]. Isolated intestinal pseudo-obstruction related to altered telethonin function has been reported as well [3].

Most patients reported to have telethonin deficiency are of Brazilian origin; nevertheless, a few patients of Asian and European ancestry have recently been described [1,5–7,9–22].

We report a novel mutation in *TCAP* manifesting as late onset anterior distal weakness, mimicking Udd distal myopathy.

2. Case report

A 75-year-old woman was referred to our department complaining of a 25-year history of slowly progressive walking difficulty. She experienced her first symptoms at the age of 50. She first complained about difficulty to raise her feet while walking, resulting in frequent falls and stumblings. Later on, the symptoms progressed to involve proximal muscles, manifesting with problems climbing stairs and getting up from chairs. She never noticed any symptoms involving the upper extremities.

The patient was born from a consanguineous marriage. Her parents were first degree cousins originating from Toledo, in central Spain. She also had four siblings and two daughters who were in their forties; all of them were asymptomatic and there was no family history of muscle or heart disease. Her past medical history was unremarkable.

Current motor examination showed symmetrical weakness of the proximal and distal leg muscles, with marked bilateral involvement of tibialis anterior muscle. The segmental strength was 3/5 in Medical Research Council (MRC) scale in the iliopsoas, 4−/5 in the gluteus maximus and medius, 4+/5 in the quadriceps, 4−/5 in the hamstring, 3/5 in the plantar flexion muscles and 0/5 for ankle dorsiflexion. The extensor digitorum brevis showed no atrophy and her toe dorsiflexion function was almost normal (4+/5). The gait was waddling and showed bilateral steppage.

The upper extremities and axial muscles were spared. There was neither focal atrophy, hypertrophy nor joint contractures. The rest of her neurological and systemic examination was unremarkable.

Serum creatin kinase (CK) levels were nearly normal (< 300 U/l) on repeated testing. The electromyogram (EMG)

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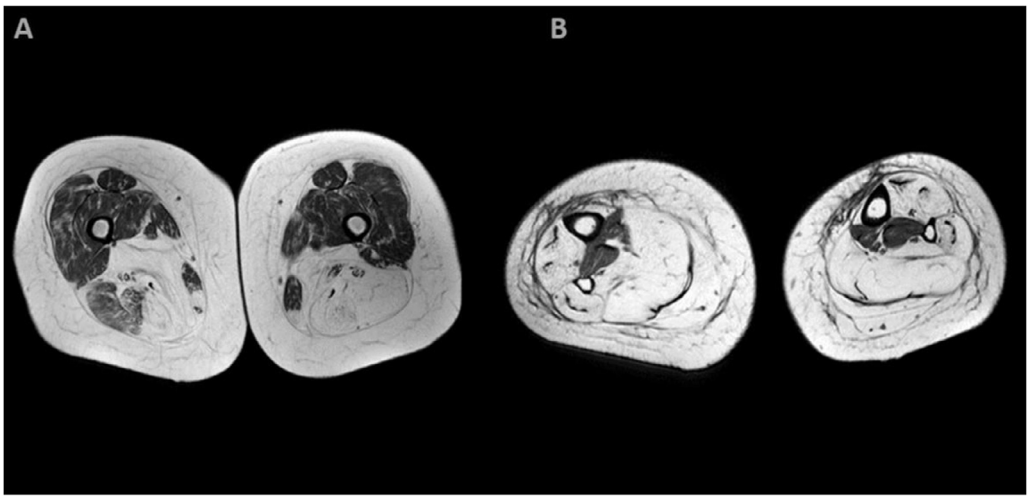

Fig. 1. (A) *Lower-limbs T1-weighted MRI of the thighs.* Bilateral fatty infiltration of adductor and hamstring muscles is noted. Left thigh is slightly more affected. Quadriceps, sartorius and gracilis muscles are well spared for the age. (B) *Lower-limbs T1-weighted MRI of the legs.* Note the severe atrophy and fat substitution of almost every muscle. Tibialis posterior muscle and flexor digitorum longus are spared.

showed a myopathic pattern. Lower limb magnetic resonance imaging (MRI) demonstrated fatty infiltration at thighs with predominant changes of the adductor and hamstring muscles. Quadriceps, sartorius and gracilis muscles were well spared for the age. Almost every muscle in the legs showed a severe fat substitution, with the exception of tibialis posterior muscle, flexor digitorum longus and flexor hallucis longus (Fig. 1). Spirometry, echocardiogram and electrocardiogram exhibited normal results.

A muscle biopsy obtained from the left biceps brachii showed moderate variation of the fiber size. It was noteworthy the presence of frequent rimmed vacuoles. Subtle signs of mitochondrial proliferation on succinate dehydrogenase (SDH) reaction with subsarcolemmal increase of oxidative activity were detected. No necrotic, regenerative nor lobulated muscle fibers were present. ATPase activity revealed mild predominance of type I fibers. There was no increase in endomysial, connective nor adipose tissue. Immunohistochemical analysis for dystrophin, α-, β-, γ- and δ-sarcoglycans, dysferlin, caveolin-3, desmin and myotilin revealed no abnormalities (Fig. 2).

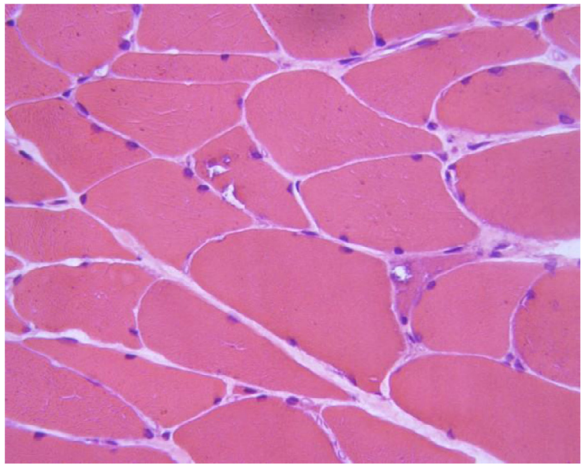

Fig. 2. *Left biceps brachii biopsy, H&E staining (x400).* It is noteworthy the presence of frequent rimmed vacuoles and moderate variation of the fiber size. There was no increase in endomysial, connective or adipose tissue. No necrotic, regenerative nor lobulated muscle fibers are present.

The definitive molecular diagnosis was achieved using next generation sequencing (NGS) of a targeted panel of genes related to myopathies. The study identified the homozygous variant c.256C > T in exon 2 of the *TCAP* gene (NM_003673.3), which has not been previously reported. This mutation is predicted to replace glutamine at codon 86 with a stop signal (p.Gln86*), resulting in a truncated telethonin protein. Subsequent Western Blot (WB) analysis using a monoclonal antitelethonin antibody (G-11: sc-25,327, Santa Cruz) revealed a complete absence of signal in the patient's skeletal muscle (Fig. 3).

3. Discussion

We report a novel *TCAP* mutation manifesting with some unique phenotypical features, never previously described in patients with telethoninopathy. Previously reported patients usually display young-onset muscle weakness in the four limbs, most of them with marked involvement of distal anterior leg muscles.

In this patient, the late onset of symptoms, which appeared throughout the sixth decade of life; and the distribution of weakness, with tibial muscle weakness as the first and predominant sign over years, resembled Udd distal myopathy [23]. Selective involvement of tibialis anterior muscle is one of the LGMD2G hallmarks and early foot drop has been described in some cases; nevertheless, early pelvic-girdle involvement is almost universal.

To our knowledge, this is the first reported case of telethonin deficiency where symptoms started in late adulthood. Previously, there were no reports of symptoms starting beyond the beginning of the third decade of life [11].

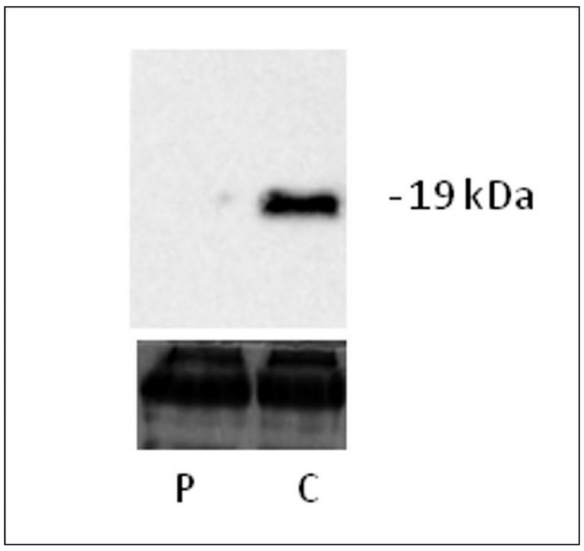

Fig. 3. *WB analysis* of patient's muscle proteins reveals complete absence of telethonin (19 kDa band) compared to the control.

Although a congenital form has been described [6,7], the median age at onset is about 15 years-old [9].

As described above, these clinical features are strikingly in contrast with all cases reported thus far [6,9,10] and expand the clinical spectrum of telethonin deficiency from congenital limb-girdle weakness to late onset myopathy with isolated initial tibial anterior weakness.

The presence of rimmed vacuoles in muscle biopsy, as seen in our patient, has been described in some cases [1,11–13]. Typical findings are lobulated fibers and mild dystrophic changes [5,9,11,17,22], but they were not present here. The MRI pattern seen in this case, with atrophy and fatty infiltration predominantly in hamstrings and adductor magnus of the thigh, and in all lower leg muscles (except tibialis posterior and toe flexors), is in line with other LGMD2G reported before, also considering the age of the patient and the duration of the disease [5,9,11,20].

We report a new *TCAP* mutation, c.256C > T, not previously reported in the Single Nucleotide Polymorphism database, the 1000 Genomes database or the ExAC database. This is the second patient of Spanish origin found to have mutation in *TCAP*. The pathogenicity of the mutation was assessed applying the ACMG consensus criteria [24,25], classifying it as pathogenic. WB studies confirmed the pathogenicity of the variant, showing a complete telethonin deficiency, suggesting a deficient sarcomere assembly.

The other mutation found in the first Spanish patient with telethonin defficiency, also reported by our group, c.255C > A (p.Tyr85*), is located just one base pair away and actually exhibited an early onset limb-girdle phenotype with contractures [9]. All of the reported *TCAP* mutations identified in individuals with a predominant skeletal muscle phenotype are nonsense mutations with a recessive pattern of inheritance, leading to a truncated protein or total absence of the protein [6,9,10]. The most commonly reported mutation is c.157C > T (p.Gln53*) and it has been found only in Brazilian and Portuguese patients [7,11,12,13]. Allelic conditions as hypertrophic and dilated cardiomyopathy are associated with autosomal dominant *TCAP* mutations [8].

In conclusion, this case shows that telethonin deficiency should be included among differential diagnosis of late onset distal myopathies and constitutes another example of the great contribution of NGS, expanding the clinical spectrum of a large number of myopathies over last years.

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