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CASE REPORT

Limb-girdle muscular dystrophy in a Portuguese patient caused by a mutation in the telethonin gene

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Limb-girdle muscular dystrophy 2G is caused by mutations in the telethonin *(TCAP)* gene in chromosome 17q11-12. This rare form of hereditary muscle disease was originally described in Brazilian patients and was recently identified in Chinese and Moldavian patients. We present the first Portuguese patient with a limb-girdle muscular dystrophy caused by a mutation in the *TCAP* gene. A Caucasian male, 50 years old, presented in his early twenties, slowly progressive weakness in the upper and lower limbs. Neurologic examination revealed severe atrophy and weakness in the muscles of the arms, thighs and legs' anterior compartment. Muscle MRI of the thighs and legs revealed severe atrophy of all the muscles of the thighs and legs' anterolateral compartment, in a symmetrical way. Molecular studies identified the homozygous c.157C > T (p.Gln53X) mutation in exon 2 of the *TACP* gene, already described in Brazilian patients.

Key words: Telethonin gene, LGMD 2G, TCAP mutation, Portugal

Introduction

Limb-girdle muscular dystrophies (LGMD) are a group of clinical and genetic heterogeneous muscular disorders. The inheritance can be autosomal dominant identified by the number 1 (ex. LGMD 1) or more frequently, recessive, identified by the number 2 (ex. LGMD 2). Fourteen subtypes of autosomal recessive LGMD have been described so far, each designated by a suffix allocated in chronological order of gene identification (A,B,C, etc.) (1, 2). The gene location and the majority of the protein products have been identified in these subtypes. The frequency of the different recessive subtypes varies in different countries (3). The rare subtype LGMD 2G was first described in Brazilian patients in 1997 and it was mapped to chromosome 17q11-12 (4). The deficient protein identified, telethonin (5), is a sarcomeric protein of 19-kDa expressed exclusively in adult skeletal and cardiac muscle (6). Located in the Z-disc, it works as a substrate of serine kinase domain of titin. Titin phosphorilates C-terminal domain of telethonin in early differentiating myocite. The telethonin (*TCAP*) gene encompasses two exons and codes for 167 amino acids. The protein deficiency is responsible not only for the LGMD type 2G but also for a small subset of hypertrophic and dilated cardiomyopathies (7). We present a patient with LGMD caused by the mutation c.157C > T (p.Gln53X) in the *TCAP* gene.

Case report

The patient is a 50 years old Caucasian man, with preserved cognitive functions, born of a non consanguineous couple. There is no family history of muscle disease and he has a 10 years old healthy daughter. In his early twenties, he started to complain of weakness in the lower limbs, with progressive difficulty in running and walking and frequent tripping. Later he began noticing weakness in the upper limbs with difficulty in raising the arms above the head. The muscle weakness was very slowly progressive and it became severe in the lower limbs, but with retained ability to walk unaided until now. There was no history of myoglobinuria, myalgias or painful cramps. On examination, the patient had severe muscle weakness of the thighs (anterior and posterior compartments) and of the anterior compartment of the legs. The Achilles tendons were shortened and the patient stood up on his tiptoes. The arms were also severely atrophied, internally rotated with contracture of the elbows with an angle of approximately 40º. There was mild scapular winging and

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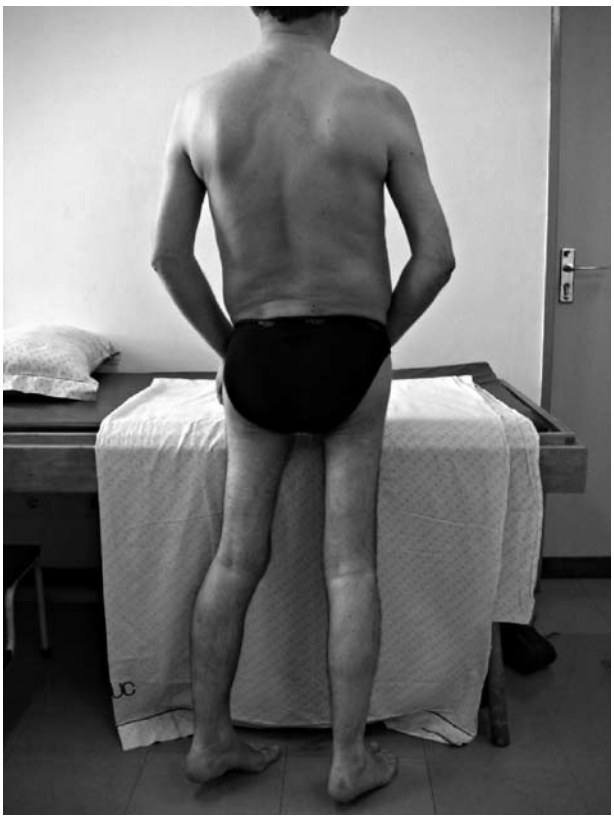

Figure 1. Standing on tiptoes, calf hypertrophy, thigh atrophy, elbows contractures and scapular winging.

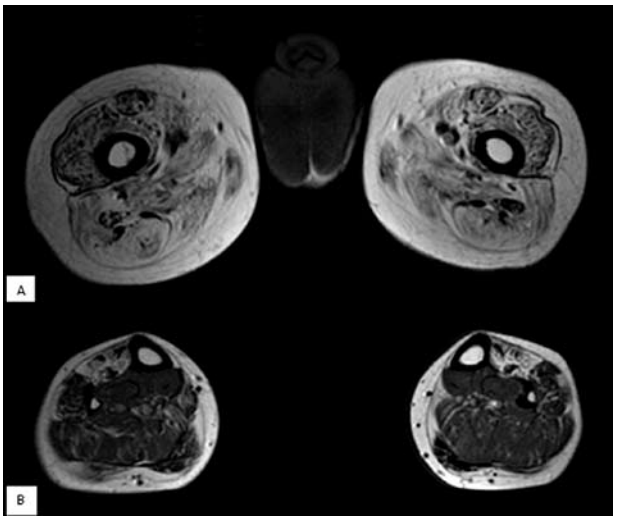

Figure 2. Muscle MRI on the thigh (A) and leg (B) levels (T1 weighted images). All the muscles in the posterior and anterior compartment of the thighs and the muscles in the anterior compartment of the legs (tibialis anterior, extensor hallucis longus, extensor digitorum longus) show significant atrophy and fat degeneration.

significant hyperlordosis (Fig. 1), aggravated on walking. The calf muscles were hypertrophied. He was not able to stand up from a chair without support and he walked slowly but unaided with a steppage gait. In the lower limbs there was prominent weakness of the quadriceps,

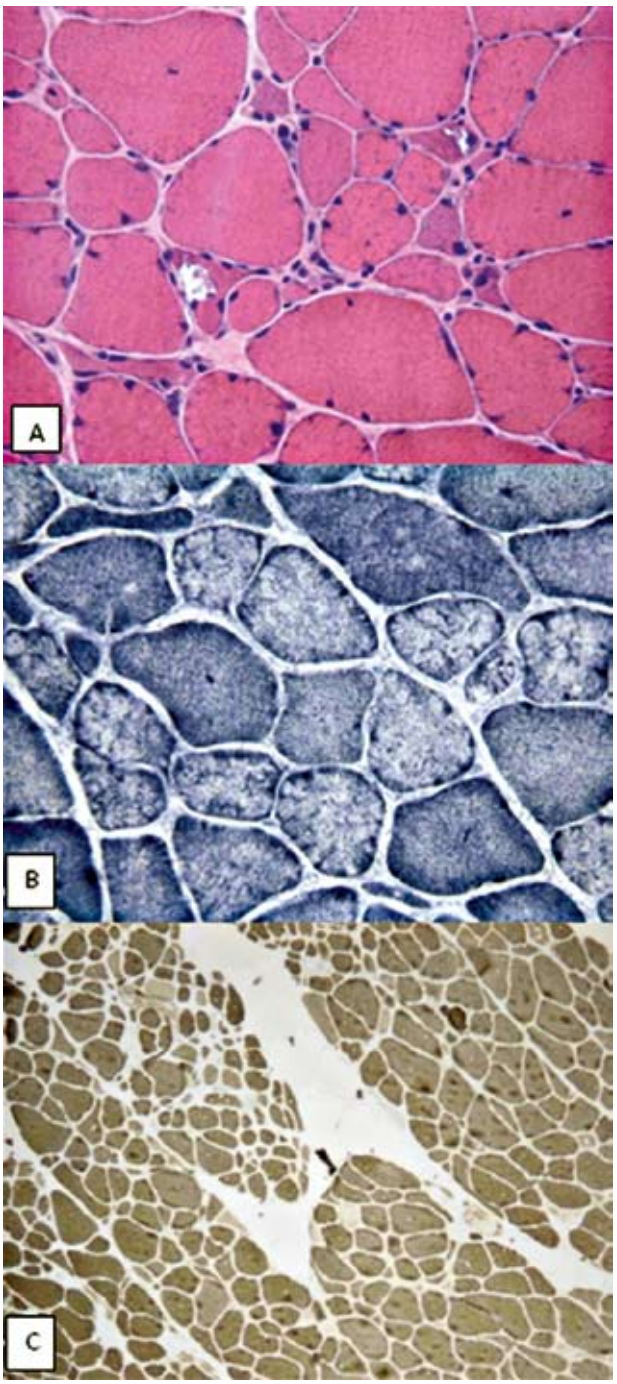

Figure 3. A: H-E (X400) Fibre type variability (atrophy and hypertrophy), central nuclei and rimmed vacuoles. B: SDHase (X400) Lobulated fibres. C: ATPase 4.35 (X100) Type 1 fiber predominance.

knee flexors and anterior tibialis muscles (0/5). The hip adductors (3/5), foot inverters (4/5), thigh extensors and flexors muscles (3/5) were moderately weak. In the arms, there was significant weakness of the biceps and external rotators of the arms (0/5). The triceps (2/5), finger flexors (4/5) and arm abduction muscles (3/5) were moderate to severely weak. Deep tendon reflexes were absent. The facial, bulbar and neck muscles were normal and sensation was normal.

Laboratory investigations

The CK values were three times above the upper limit (476 U/L; normal < 180 U/L). EMG was consistent with a myopathic lesion. Cardiac and respiratory functions were normal. Muscle MRI of the thighs and legs performed at the age of 50 showed a marked and symmetrical atrophy of all muscles of the thighs (Fig. 2A). In the legs the atrophy was pronounced at the anterior tibialis, extensor hallucis longus and extensor digitorum longus muscles. The gastrocnemius muscles were slightly atrophic (Fig. 2B).

Histological examination of the deltoid muscle: the muscle was diffusely abnormal, with increased variability of the fiber diameter. The atrophic fibers were round and were dispersed in the fascicles or in groups in the same area. Muscle fiber necrosis and basophilic fibers were rare. There were frequent central nuclei and rimmed vacuoles, one or more per fiber (Fig. 3A) and lobulated fibers (Fig. 3B). Type 1 fibers predominate (Fig. 3C). Connective tissue and adipose infiltration was increased in the endomysium and perymisium. Immunohistochemistry revealed normal labeling for dystrophin, sarcoglycans, dysferlin and emerin.

Molecular studies

The molecular study was performed by PCR with sequencing of the entire codifying region, including the adjacent intronic regions of the *TCAP* gene (reference of the sequencing: NM_003673, being the A of the initial ATG the position 1). The homozygous c.157C > T (p.Gln53X) mutation in exon 2 of the *TCAP* gene was detected. The 157 C→T transition creates a premature stop codon.

Discussion

Limb-girdle muscular dystrophy 2G is a rare muscle disease. Despite the small number of patients described outside Brazil [3 Chinese (8) and 1 Moldavian (9)], the clinical features described in these patients, including the present one, constitute an homogeneous phenotype: significant thighs and legs' anterior compartment muscle atrophy and weakness, mild to moderate limb girdle muscle weakness, mild scapular winging, calf hypertrophy and depressed deep tendon reflexes. The tightness of the Achilles tendons, already described by Olivé et al. (9), was severe enough to disable the patient from placing the plantar face of the feet on the ground. He presented elbow contractures, probably secondary to long lasting weakness of the elbow extensors muscles. Cognitive function has been reported normal in all patients as well. The patient here reported is the oldest one with a LGMD 2G diagnosis, with disease duration of almost 30 years. The results of the laboratory investigations seem uniform among all patients described: the CK is abnormally elevated, the EMG shows a myopathic pattern and the cardiac and pulmonary functions are normal. The histological features are of the dystrophic type. Rimmed vacuoles were identified in the Brazilian patients (3) but not lobulated fibers, which is the opposite of what was found in the Moldavian patient (9). The muscle specimen from our patient presented both histological features. The muscle MRI was in accordance with the clinical examination in the lower limbs. The molecular studies identified the same mutation present on the Brazilian patients, but their Italian ancestry does not allow us to establish a relationship with our patient (which could be possibly due to the large history of Portuguese emigration to Brazil). Regarding LGMD 2G (2), Moreira et al. have remarked that there are several muscle diseases which share some of the clinical, laboratory or histological features of LGMD 2G and with which these patients can be mistaken for, especially LGMD 2A, LGMD 2B, the sarcoglycanopathies and distal myopathy with rimmed vacuoles (DMRV). The first disease does not present thigh atrophy or rimmed vacuoles; the second one has distal muscle weakness primarily of the posterior compartment of the legs and calf hypertrophy is not observed as a permanent clinical feature. In the sarcoglycanopathies, footdrop and rimmed vacuoles are not part of the clinical and laboratory spectrum of the disease and in DMRV the preserved motor autonomy 30 years after the first symptoms places this disease as a very unlikely diagnostic alternative. Olivé et al. (9) also considered the LGMD 2I subtype in the differential diagnosis. The absence of cardiac and/or respiratory involvement and the significant atrophy of the quadriceps and anterior tibialis in LGMD 2G argues against LGMD2I.

This is the first time this subtype of limb-girdle muscular dystrophy is diagnosed in patients from Iberian origin. The phenotype, the results of the laboratory investigations, the muscle histopathology and muscle MRI are in agreement with what has been reported by others.

Acknowledgements

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