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CASE REPORT

Bethlem myopathy in a Portuguese patient – case report

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Mutations of the encoding genes of collagen VI *(COL6A1, COL6A2* and *COL6A3*), are responsible for two classical phenotypes (with a wide range of severity), the Ullrich congenital muscular dystrophy (UCMD) and the Bethlem myopathy (BM). We present a male patient of 49 years old, with symptoms of muscle weakness beginning in childhood and of very slowly progression. At the age of 42, the neurological examination revealed proximal lower limb muscle weakness and contractures of fingers flexors muscles, positive Gowers manoeuvre and a waddling gait. Serum creatine kinase (CK) values were slightly elevated, electromyographic study revealed myopathic changes and muscle MRI of the lower limbs showed a specific pattern of muscle involvement, with peripheral fat infiltration in vastus lateralis and intermedius and anterocentral infiltration in rectus femoris. Respiratory and cardiac functions were unremarkable. Whole exome sequencing identified the homozygous mutation c.1970-9G>A in *COL6A2* gene.

Key words: congenital muscular dystrophy, Bethlem myopathy, collagen VI

Introduction

Type VI collagen, a nonfibrillar collagen, is a major component of microfibrils in many connective tissues including tendons, ligaments, muscle, skin, cornea, cartilage, bone tissue and periosteum. Collagen VI is a heterotrimeric protein consisting of three different alpha-chains and it is involved in various cellular interactions such as cell adhesion, migration and apoptosis, through its binding to cell-surface molecules (1).

Mutations of the collagen VI coding genes (*COL6A1, COL6A2* and *COL6A3*) are responsible for two clinical phenotypes, the Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy (BM). In UCMD, the symptoms are usually present at birth and are characterized by the presence of a pronounced and progressive muscle weakness, hyperlaxity and contractures of proximal joints, with early loss of ambulation and decrease in life expectancy (2). The BM phenotype is associated with mild proximal muscular weakness and typical distal contractures of the fingers and ankles joints. There is usually a slow progression, with preserved ambulation in adult life, and respiratory function is typically unremarkable. Cardiac and cognitive functions are not affected and the patient has a normal life expectancy (3). BM has an autosomal dominant mode of inheritance, although a few cases of autosomal recessive inheritance have been reported (4). CK levels are usually slightly elevated (below 1000 UI/L) (3). Concentric fatty infiltration in vastus lateralis and intermedius, and an anterocentral infiltration in rectus femoris, corresponding to a "central shadow" or a "U-shaped" infiltration may be found in the MRI muscle of BM patients (5).

We report the first Portuguese patient with molecular confirmed BM.

Clinical case

The patient is a 49 years old male, with a normal social and professional life. He was born of a consanguineous couple (third degree cousins) and familial history was negative for neuromuscular disorders. He began walking at 2 years of age and experienced a slight difficulty in running and competing with his peers at school. At the age of 40 he reported increasing motor difficulties. Neurological examination at the age of 42, revealed mild proximal lower limb muscle weakness (grade 4, MRC score), a waddling gait with lumbar hyperlordosis, contractures of

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fingers flexors muscles and shortening of the Achilles tendons. Gowers manoeuvre was positive. Myotatic reflexes were abolished throughout and sensory examination was normal.

Laboratory studies revealed a slightly elevated CK value (472 UI/L). Respiratory parameters and cardiac evaluation (eco and electrocardiogram) were unremarkable. Electromyography presented myopathic features with normal nerve conduction studies. Left deltoid muscle biopsy identified a nonspecific moderate dystrophic pattern with effaced architecture and adipose tissue infiltration, increased fibre diameter variability and internal nuclei and a few necrotic and ring fibers (Fig. 1). Immunostaining with monoclonal antibodies against dysferlin, dystrophin, calpain and sarcoglycans (α, β, γ, and δ) revealed normal staining pattern.

Lower limb muscle MRI – thigh level – (Fig. 2), showed a specific pattern on the anterior thigh muscles with concentric fatty infiltration in vastus lateralis and intermedius, and an anterocentral infiltration in rectus femoris, corresponding to a "central shadow" or a "U-shaped" infiltration.

Molecular studies, using the whole genome sequencing technology, identified the homozygous mutation c.1970-9G>A in *COL6A2* gene, with the parents being heterozygous for the mutation (Fig. 3).

Discussion

We present a typical case of BM, with slowly progressive proximal muscle weakness and distal contractures, beginning in childhood and with preserved ambulation in adulthood.

BM was first described in 1976 by Bethlem and Wijngaarden based on 28 patients from different families (6). It is a rare disease, with an estimated frequency of 0.77/100.000 habitants on European countries (7). However, its benign and slowly progressive course may lead to under diagnosing. BM corresponds to the milder end of a collagen pathology spectrum, with UCMD at the other end of clinical severity. Muscular weakness associated to contractures are also present in other diseases, such as *Emery Dreifuss* muscular dystrophy (EDMD) (8) and some variants of early onset limb girdle muscular dystrophy (LGMD) (9). In EDMD, the presence of cardiac electrical abnormalities and eventual dilated cardiomyopathy, help to differentiate it from BM. Muscle MRI abnormalities are also useful in making the distinction, with a predominantly posterior compartment involvement, while in BM the anterior muscles of the thigh are the most affected (2). BM may resemble some LGMD when the prominent clinical signs are related to proximal muscle weakness. Immunohistochemistry with specific antibodies is of special importance in making the differential diagnosis. Also, serum CK levels might be use-

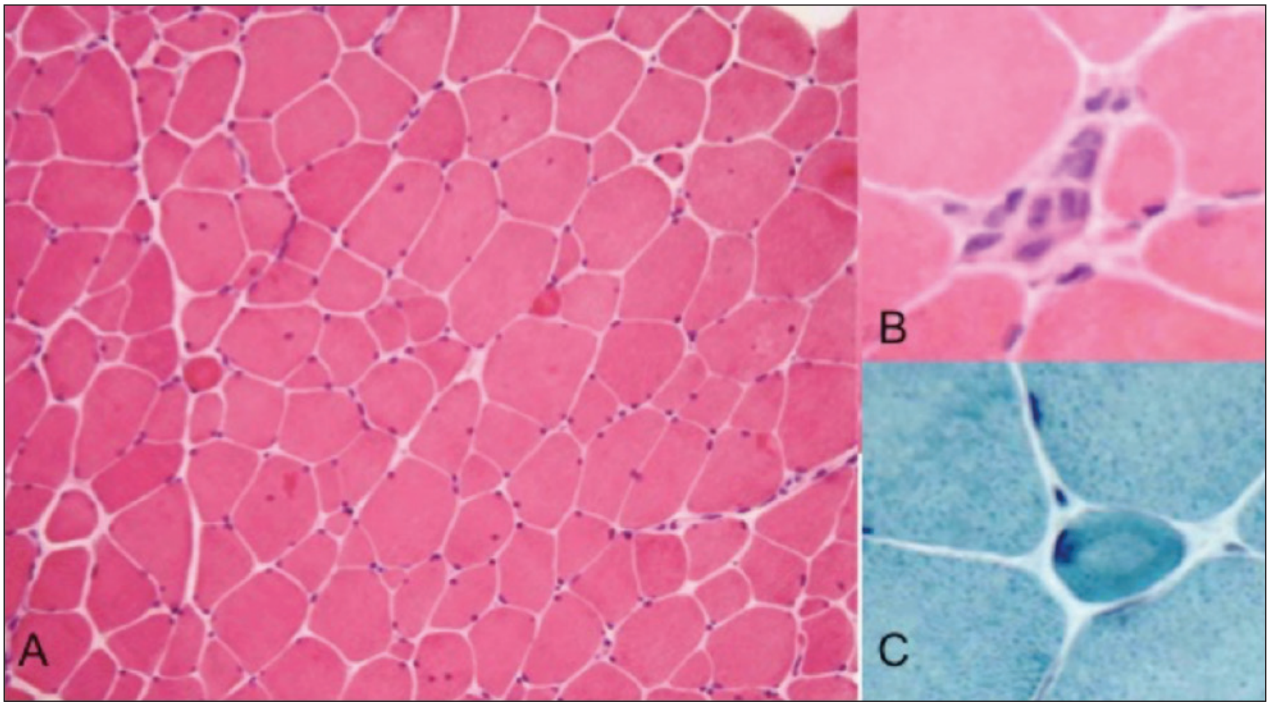

Figure 1. A) Increased variability of fiber diameter and internal nuclei (HE 200x); B) necrotic fiber (HE 400x); C) ring fiber (modified Gomori Thrichrome 400x).

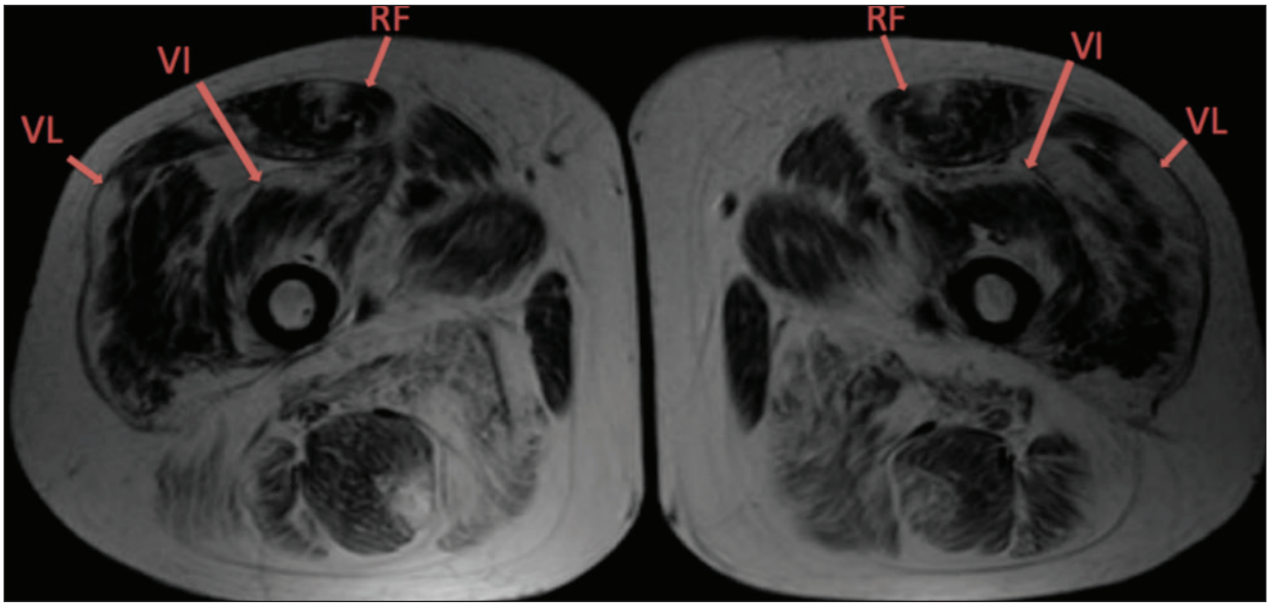

Figure 2. Lower limb muscle MRI, axial thigh level: concentric fatty infiltration in vastus lateralis (VL) and intermedius (VI) and an anterocentral infiltration in rectus femoris (RF), corresponding to a "central shadow" or a "U-shaped" infiltration.

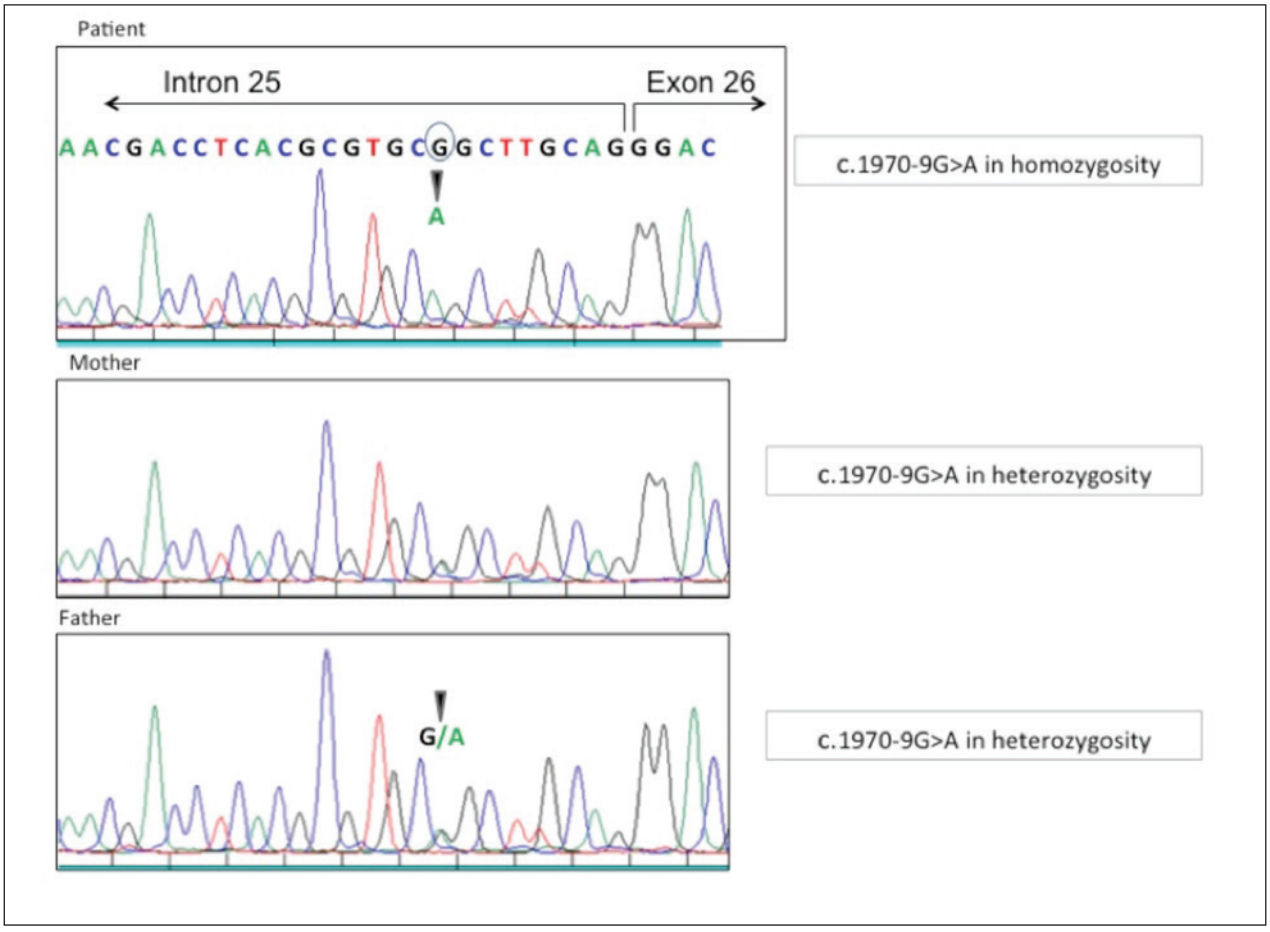

Figure 3. Mutation analysis (electropherogram) of *COL6A2* gene (Chromosome 21).

ful in making the distinction, as in BM they are mildly elevated, while most of the LGMD have CK levels are significantly elevated, like sarcoglycanopathies and dysferlinopathies (9). In the presence of joint laxity, *Ehlers-Danlos* syndrome should also be suspected, particularly in a teenager or adult patient. However, the presence of the characteristic skin hyperlaxity helps to differentiate it from BM. Keloids and hyperkeratosis, which are frequently reported in BM, were not present in our patient, but they are not essential to BM clinical diagnose (3). Muscle biopsy and immunostaining techniques with antibodies to collagen VI and also to sarcoglycans, caveolin, dysferlin, α-dystroglycan and merosin are usually normal in BM patients. Conversely, in UCMD, these techniques reveal a decreased/total absence of collagen VI immunostaining, being a striking difference between the two phenotypes (1).

Muscle MRI findings have been used to characterize some specific muscle diseases and those described in our patient have been considered specific of BM.

The molecular findings of our patient have been already identified in other patients with similar clinical characteristics and prognosis (10) and its pathogenic role is certain. Although BM is mostly inherited dominantly, recessive inheritance has also been described (4) – as occurred in our patient.

To our knowledge, this is the first Portuguese patient diagnosed with BM, a rare cause of benign and slowly progressive muscular dystrophy.

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