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Case report

A TPM3 mutation causing cap myopathy

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ABSTRACT

Cap disease is a rare congenital myopathy associated with skeletal malformations and respiratory involvement. Abnormally arranged myofibrils taking the appearance of a "cap" are the morphological hallmark of this entity. We report a case of cap disease concerning a 42-year-old man, without any family history and presenting a p.Arg168His mutation on the TPM3 gene. His first biopsy at 7 years had only shown selective type I hypotrophy. Mutations of TPM3 gene have been found in nemaline myopathy, congenital fiber type disproportion, but never before in cap disease.

1. Introduction

As affirmed by Goebel [1] much of what we know about cap myopathy is due to the efforts of Fidzianska and her co-workers [2,3], who described this disease in 1981. Patients with cap myopathy have "cap" structures peripherally located in their muscle fibers. These structures are in fact disarranged myofibrils with enlarged Z discs and no thick filaments. The severity of the disease is related to the number of fibers affected. Therefore, patients may present with a neonatal fatal form (70–75% of fibers containing caps) or have a more stable course of the disease in the infant non-fatal form (20–30%) [3]. Muscle weakness, high arched palate and myopathic facies are often observed. Respiratory involvement may be severe.

For more than twenty five years no causal mutation was found to be implicated in this disease. Cuisset et al. [4] published two familial cases that remained unsolved. However, they offered interesting speculations regarding the possible genes implicated. Following this publication Lehtokari [5] reported the first confirmed genetic explanation for cap myopathy: a TPM2 mutation.

TPM2, TPM1, and TPM3 encode, respectively, the three skeletal muscle isoforms of tropomyosin: β-tropomyosin (β-Tm), α-tropomyosin fast (α-Tm^{fast}), α-tropomyosin slow (γ-Tm or α-Tm^{slow}) [6]. Tropomyosin binds to actin and helps to regulate muscle contraction [7]. A lack of or an abnormal tropomyosin could explain muscle deficit and consequent atrophy that cap myopathy patients suffer from.

We report a sporadic case of cap myopathy caused by a TPM3 *de novo* mutation. As far as we know, this disease has never been associated with this gene.

2. Case report

A 42 year-old man of Caucasian origin presented frequent falls and a distal weakness of lower limbs, since he was 4 year-old. There was no history of consanguinity or any other familial antecedent. His parents, two brothers and two sisters were normal. He had no children.

Pregnancy and delivery were uneventful. Hypotonia was noted in the first months, motor milestones were delayed. When first examined at age of 7 years, he had flat feet in valgus with external rotation, a long narrow face, high arched palate and mild lumbar hyperlordosis. There was no amyotrophy, but a slight distal weakness of lower limbs, affecting primarily the anterior compartment. The tendon reflexes were all abolished. There was no sensory disorder. A muscle biopsy was performed in the quadriceps.

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The clinical course was overall stable until the age of 42 years old, when he again came for consultation. He complained of his inability to run and difficulty in climbing stairs; the distance that could be walked without assistance was not limited, though. Clinical examination revealed a mild Gowers sign, lower limb amyotrophy (Fig. 1A) and motor weakness that predominated distally. There was neither ptosis nor neck weakness. Voice was normal. He had winging of the scapulae, mild dorsal scoliosis with marked lumbar hyperlordosis (Fig. 1B and C). He could not rise either on his heels or on his toes. Examination of the upper limb muscles was unremarkable. Serum creatine kinase level was normal. Lung function tests showed a moderate restrictive syndrome with vital capacity reduced to 74% of the predicted value. Echocardiogram was normal. Muscle computed tomography revealed a moderate fat infiltration of the paravertebral muscles, gluteal muscles, femoral biceps, soleus muscles and feet extensors (Fig. 1D and E). Biopsy was taken from tibialis anterior muscle. One specimen was fixed in 2.5% glutaraldehyde and two specimens were frozen in isopentane and liquid nitrogen. Standard techniques were then used for electronic microscopy and histochemistry. Immunohistochemical analyses included: DYS1, DYS2, DYS3 (Novocastra), caveolin-3 (BDBiosciences), actine (Dako), α-actinin (Zymed), myotilin (Novocastra). Molecular analysis screened the TPM2 and TPM3 genes for possible mutations by PCR-sequencing of the exons coding for β-Tm and α-Tm^{slow}.

The first muscle biopsy performed at 7 years of age and taken from the left quadriceps showed only type I fiber hypotrophy, with type I fibers being 4 to 5 times smaller than type II fibers (Fig. 2A and B).

The second biopsy taken from the tibialis anterior at 42 years of age showed only type I fibers (Fig. 2C–H). On hematoxylin–eosin stain there was irregularity of fiber size with occasional centrally located nuclei. Ten to fifteen percent (10–15%) of muscle fibers contained a peripherally located, eosinophilic–basophilic densely stained substance with the appearance of "caps". These cap structures were pale green on trichrome stain and completely negative on ATPase reactions and SDH. They were dark with nicotinamide adenine dinucleotide tetrazolium reductase (NADH) and contrasted with a coarse-meshed intermyofibrillary network which was also present in fibers not containing the caps. They had well defined borders on semi-thin sections of epoxy embedded muscle stained with toluidin blue and were strongly reactive to actin, α-actinin, and myotilin. On electronic microscopy, the cap structures were clearly demarcated from neighbouring preserved myofibrils and mostly located just underneath the sarcolemma (Fig. 3A–C). They consisted of abnormally arranged myofibrils, devoid of thick filaments (Fig. 3D). Thus, they had no A-band. Z-lines were thickened with some rod-like structures. There were some glycogen particles and dilated sarcoplasmic reticulum. Neither sarcoplasmic nor nuclear inclusions were found. Molecular analysis identified a

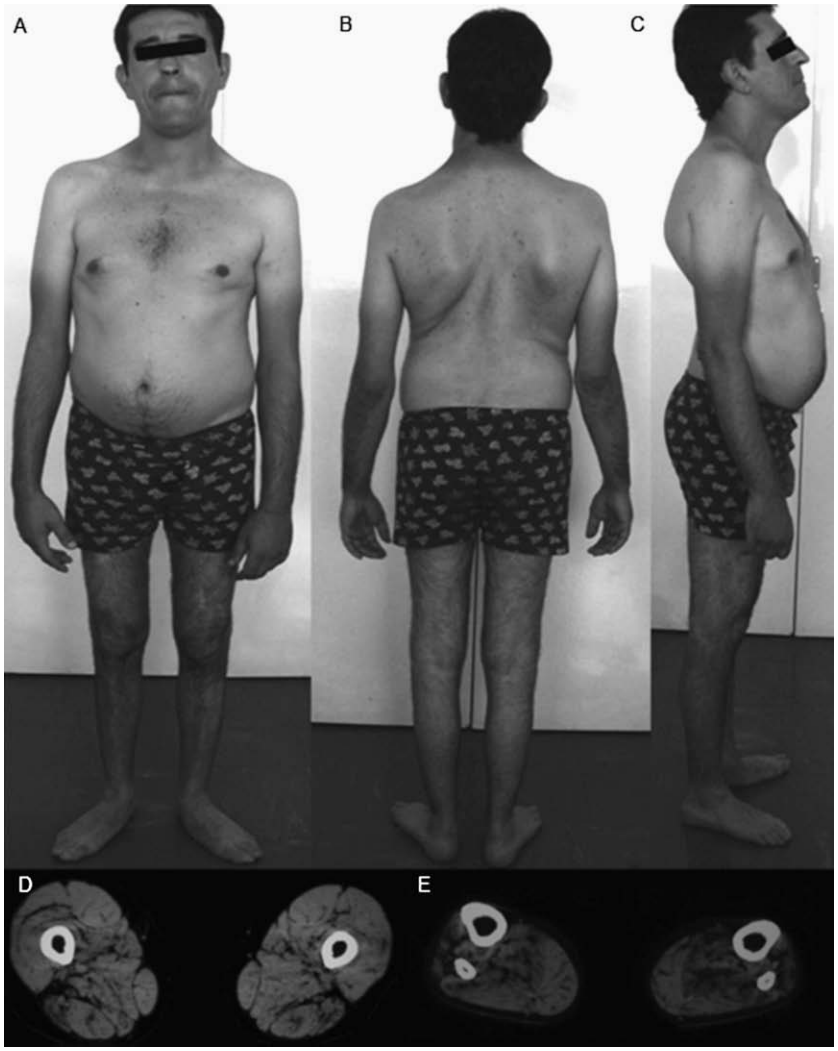

Fig. 1. Patient at 42 year-old. Distal amyotrophy of lower limbs and flat feet in valgus with external rotation (A). Winging of the scapulae and mild dorsal scoliosis (B) with marked lumbar hyperlordosis (C). Moderate fat infiltration observed in muscle computed tomography (D and E). Patient consented to publication of the photographs.