AN ADULT WITH A RARE FORM OF CONGENITAL FIBER TYPE DISPROPORTION

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INTRODUCTION

To date more than 20 genes have been identified as causes of congenital myopathies (CM); mutations in various genes may lead to the same distinct pathological phenotype.\(^1,2\) Therefore, the identification of the underlying genetic defect of a specific CM may require targeting more than one gene. Congenital fiber type disproportion (CFTD) is a CM characterized by type 1 fiber hypertrophy in the absence of other histopathologic abnormalities.\(^3\) Mutations in α-tropomyosin (TPM3), ryanodine receptor 1 (RYR1) and skeletal muscle α-actin (ACTA1) are the most common causes of CFTD.\(^3\) Rarely, mutations in myosin heavy chain 7 (MYH7), selenoprotein N 1 (SEPN1) or β-tropomyosin (TPM2) cause CFTD.\(^1\) Herein, we report an adult patient with TPM2-myopathy manifesting with the rare pathological phenotype of CFTD.

CASE REPORT

A 56-year-old woman presented for evaluation of dyspnea and muscle weakness. She was born at term with no complications, did not walk until age 18 months, had difficulty keeping up with her peers, and had a hoarse voice. Around age 17 years, she noted generalized weakness and fatigability, which remained stable over the years. In her early forties, she was diagnosed with mitral valve regurgitation requiring valve replacement. Around age 55, she developed left ptosis and dyspnea on exertion in the absence of cardiac abnormalities. She had a high arched palate, elongated face, mild rigid spine (Fig. 1A-B), mild scoliosis, wrist and metacarpophalangeal joint contractures limiting extension, and mild elbow hyper-extensibility. Scapular winging was absent. Her neurological examination showed mild-to-moderate proximal> distal limb weakness with weakness of facial and axial muscles. Tendon reflexes were hypoactive or
absent. Family history revealed a brother who died a few hours after birth from respiratory distress, and easy fatigability in the father beginning in his 30s (father died at age 88).

Serum creatine kinase was 63 U/L (normal 38-176). EMG showed rapid recruitment of short duration, low amplitude motor unit potentials without fibrillation potentials or myotonic discharges. There was no decrement upon 2Hz repetitive stimulation of ulnar, spinal accessory and facial nerves. Biopsy of the biceps brachii muscle, performed at age 17, showed histological features of CFTD (Figure 1). Pulmonary function tests revealed a restrictive pattern. Fluoroscopy showed normal and symmetric excursion of the hemidiaphragms without paradoxical movements on sniffing. Overnight oximetry revealed episodic desaturation. Electrocardiogram and echocardiogram were normal. Molecular analysis by next generation sequencing (Invitae, San Francisco CA) identified a known pathogenic mutation in exon 3 of the TPM2 gene (c.349G>A, p.Glu117Lys) and no variants in other genes causative of CFTD. Immunohistochemical studies of the muscle biopsy for α-actinin, obtained after the detection of the TPM2 mutation, were normal and revealed no subsarcolemmal caps.

DISCUSSION

Our patient was found to have an extremely rare form of autosomal dominant CM due to a TPM2 mutation causing CFTD. TPM2-CM accounts for a very small proportion of CM with an estimated frequency of less than 5%. The spectrum of histopathological and clinical phenotypes in TPM2-CM includes cap myopathy, nemaline myopathy, CFTD, nonspecific type 1 fiber predominance, distal arthrogryposis, and Escobar syndrome (multiple pterygium syndrome and flexion contractures at birth). Cap myopathy is the most common TPM2 pathological phenotype, characterized by subsarcolemmal, crescent-shaped, well-demarcated accumulations
of disorganized thin filaments and Z-disc constituents. Therefore, caps immunoreact for \( \alpha \)-actinin, actin, troponin T, tropomyosin and desmin but are devoid of thick filaments. \( TPM2 \)-CFTD is extremely rare. \( TPM2 \)-CM can stem from \( TPM2 \) missense, splice-site mutations, deletions and duplications with no genotype-phenotype correlation.

Our patient’s \( TPM2 \) mutation (c.349G>A, p.Glu117Lys) was previously described in 3 patients with CFTD: a patient with hypotonia at birth, failure to thrive and distal arthrogryposis; a child with severe hypotonia at birth and feeding difficulty; and his mother, who was never able to run. Similar to these individuals, our patient showed no other structural abnormalities in muscle, and specifically no nemaline rods, caps or minicores. Electron microscopy (EM) studies, which may reveal changes that can be missed on light microscopy in CFTD, were not performed in our patient, but immunocytochemical studies showed no \( \alpha \)-actinin accumulations suggestive of caps or nemaline rods. In addition, the previously reported son and mother, who harbored the same \( TPM2 \) mutation present in our patient, had no caps, rods or mini-cores by EM.

Our patient’s muscle biopsy was performed at age 17 (not in infancy/childhood). Therefore, it is unlikely that it was performed before the development of additional structural abnormalities.

\( TPM2 \) encodes for \( \beta \)-tropomyosin. Together with troponin and actin, \( \beta \)-tropomyosin is a component of the sarcomeric thin filaments. It drives the interaction between the myosin head and actin and controls calcium sensitivity. Therefore, \( \beta \)-tropomyosin is crucial in regulating muscle contraction. The patient’s mutation (\( TPM2 \) p.Glu117Lys) has been shown to affect the actin and myosin head conformational changes, compromising the interaction between these two proteins and causing a contractile defect. \( TPM2 \) p.Glu117Lys has also been shown to reduce the ATPase activation of actomyosin, and calcium sensitivity.
β-tropomyosin is preferentially expressed in type 1 fibers and to a lesser extent in type 2 fibers and cardiac tissue. Therefore, cardiac muscle involvement, although not present in our patient, can infrequently accompany TPM2 mutations. Conversely, respiratory compromise is frequent in TPM2-myopathy and severely affected patients may require mechanical ventilation.

In conclusion, our patient underscores the clinical phenotypic variability of TPM2 p.Glu117Lys and confirms that this mutation can result in true CFTD. In addition, the case highlights the possible late onset respiratory compromise of TPM2-CM in the setting of a relatively stable limb myopathy.
LEGEND

FIGURE 1. Patient and muscle biopsy.

Photographs depict patient’s elongated face (A) and limited ability to flex the neck (B). ATPase section pH 4.3 (C) shows smallness of type 1 muscle fibers and larger type 2 fibers. Modified Gomori trichrome stained section (D) shows no nemaline rods. NADH stained section (E) reveals no caps.
ABBREVIATIONS:

Congenital fiber type disproportion (CFTD)

Congenital myopathies (CM)

Myosin heavy chain 7 (MYH7)

Ryanodine receptor 1 (RYR1)

Selenoprotein N 1 (SEPN1)

α-actin (ACTA1)

α-tropomyosin (TPM3)

β-tropomyosin (TPM2)
REFERENCES


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Photographs depict patient’s elongated face (A) and limited ability to flex the neck (B). ATPase actin section pH 4.3 (C) shows smallness of type 1 muscle fibers and larger type 2 fibers. Modified Gomori trichrome stained section (D) shows no nemaline rods. NADH stained section (E) reveals no caps.