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Case report

Tubular aggregate myopathy with features of Stormorken disease due to a new STIM1 mutation

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Abstract

STIM1 is a reticular Ca^{2+} sensor composed of a luminal and a cytosolic domain. Missense mutations in the luminal domain have been associated with tubular aggregate myopathy (TAM), while cytosolic mutations can cause Stormorken syndrome, a multisystemic disease associating TAM with asplenia, thrombocytopenia, miosis, ichthyosis, short stature and dyslexia. Here we present the case of a 41-year-old female complaining of exercise intolerance. Clinical examination showed short stature, scoliosis, proximal muscle weakness with lower limb predominance, and ophthalmoplegia. Laboratory tests revealed hypocalcemia, mild anemia and elevated creatine kinase (CK) levels. Whole-body muscle magnetic resonance imaging (MRI) revealed asplenia. Muscle biopsy was consistent with TAM. *STIM1* gene analysis disclosed the novel c.252T>A, p.D84E missense mutation which was shown to induce constitutive STIM1 clustering in a functional study. This study reports a novel *STIM1* mutation located in the Ca^{2+}-binding EF domain causing TAM with features of Stormorken syndrome.

Keywords: STIM1; Stormorken syndrome; Tubular aggregate myopathy; Asplenia

1. Introduction

STIM1 is the main Ca^{2+} sensor in the endoplasmic reticulum and acts as a key factor in store-operated Ca^{2+} entry (SOCE). Upon Ca^{2+} store depletion of the sarcoplasmic reticulum, STIM1 oligomerizes and activates the plasma membrane Ca^{2+}-released-activated Ca^{2+} channel (CRAC) ORAI1 [1].

Recessive *STIM1* mutations are responsible for severe young-onset immunodeficiency with muscle hypotonia, ectodermal dysplasia, splenomegaly, lymphadenopathy, auto-immune manifestations including auto-immune thrombocytopenia and hemolytic anemia, and iris hypoplasia [2]. Missense dominant mutations in the highly conserved intraluminal Ca^{2+}-binding EF domain have been identified in isolated tubular aggregate myopathies (TAMs) [3], whereas mutations in the coiled-coil 1 domain can cause Stormorken syndrome [4–6], a disease characterized by the association of TAM, hematological disorders (thrombocytopenia or thrombocytosis, anemia, asplenia), and hypocalcemia, with additional features such as miosis, short stature, ichthyosis, migraine and dyslexia [7].

We described here a patient with a novel heterozygous *STIM1* EF-hand mutation presenting TAM and features of Stormorken syndrome.

2. Case report

A 41-year-old female of Portuguese origin was admitted to our Neuromuscular Center with a 3-year history of exercise

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intolerance and diffuse cramps affecting the four limbs and the trunk. She had a medical history of migraine and recent tooth enamel hypocalcification. She also described previous muscular difficulties, such as slow running and frequent falls during childhood and a progressive muscle weakness that had restricted her walking distance since adolescence.

Clinical examination showed short stature (148 cm) without dysmorphic signs, and Achilles tendon contractures. She had a symmetrical muscle weakness with predominant involvement of the proximal lower limbs (MRC score 3 + /5), and a milder involvement of the upper limbs and axial muscles. She also had ophthalmoplegia with lateral gaze paresis and upward gaze palsy, without diplopia, ptosis or pupillary abnormalities. She was fully ambulant, although she experienced exercise intolerance.

Laboratory tests revealed mild hypocalcemia (1.98 mmol/L) with normal phosphatemia, mild anemia (hemoglobin level was 11 g/dL) with increased platelet count and Howell–Jolly bodies on blood smear. Coombs test was negative. Antinuclear antibodies were elevated (>1/1280) with positive anti-Sp100 and anti-PML antibodies.

Creatine kinase (CK) levels were elevated (5 × N). Electroneuromyography showed mild myogenic changes in the trapezius muscle and some complex repetitive discharges.

Whole-body muscle magnetic resonance imaging (WB MRI) on T1 showed predominant alterations of subscapularis, anterior serratus and latissimus dorsi at the scapular girdle level (Fig. 1A, C, and D). Masticatory muscles (temporal, masseter and lateral pterygoid) were spared (Fig. 1B). At the upper limb level, triceps and biceps brachii were slightly affected (Fig. 1E). At the trunk level, lumbar extensors were the most affected muscles (Fig. 1F). This trunk MRI examination and analysis revealed asplenia (Fig. 1A). Examination of the pelvic girdle showed a predominant involvement of medius and minimus glutei (Fig. 1G). At the thigh level, vastus lateralis as well as semi-tendinous and semi-membranous were the most affected muscles (Fig. 1H and I), and the symmetric involvement was more pronounced at the distal parts of muscles. At the leg level, flexor hallucis longus was very involved (Fig. 1K). Preservation of tibialis anterior and posterior was noticed (Fig. 1J). No bright signal was detectable on STIR sequence.

We performed a deltoid muscle biopsy, which showed the presence of multiple small inclusions with H&E staining (Fig. 2A), associated with fiber size variation, augmented internalized nuclei, and type 1 fiber predominance with type 2 fiber atrophy. The inclusions, found uniquely in type 1 fibers, consisted in tubular aggregates (TA) and presented a fuchsinophilic peripheral rim with the Gomori trichrome technique (Fig. 2B). They were intensely stained with the NADH-TR reaction (Fig. 2C) and remained unstained with SDH immunoenzymatic reaction (not shown). Electron microscopy analysis confirmed the presence of TAs composed of single-walled (250 nm diameter) membrane tubules (Fig. 2D).

The clinical presentation together with the whole-body MRI and the TA observed in the muscle biopsy was compatible with TAM/Stormorken syndrome. *STIM1* gene analysis disclosed the novel c.252T>A, p.D84E missense mutation, which affects a highly conserved EF domain amino acid (Fig. 3A). The mutation resides within the mutation hot spot of TAM, and affects the same amino acid as in a previously described TAM family with D84G mutation, presenting with childhood/adolescence onset of proximal muscle weakness of the lower limbs, contractures, upward gaze paresis, and 4–8× elevated CK levels [3]. A functional study was performed with C2C12 myoblasts transfected with wild-type or D84E mCherry-STIM1 constructs. Wild type STIM1 was evenly distributed in the endoplasmic reticulum (ER), while STIM1 D84E was found to cluster constitutively (Fig. 3). This mutation was absent in the mother. The DNA of the father could not be obtained; however, this 70-year-old male reported no muscle or systemic complaint.

3. Discussion

Described in 1985 by Stormorken et al. [7] in a Norwegian family with a dominant inheritance pattern, Stormorken syndrome is the only known syndrome associating congenital asplenia and myopathy. It is characterized by the association of TAM, hematological disorders (thrombocytopenia or thrombocytosis, anemia, asplenia), and hypocalcemia, with additional features such as miosis, short stature, ichthyosis, migraine and dyslexia. *STIM 1* mutations have recently been identified as a cause of Stormorken syndrome [4–6] with the same gain-of-function p.R304W mutation in the coiled-coil 1 domain in all unrelated families.

Dominant mutations in the highly conserved intraluminal Ca^{2+}-binding EF domain have been mainly identified in TAMs [3] without symptoms of Stormorken syndrome. There is only one description of a patient with a mutation is this domain with TAM and systemic symptoms with a condition called York platelet syndrome [8], which shares similar features with Stormorken syndrome. In this latter patient, the spleen was still present, although of small size.

These phenotypes share a common muscular involvement pattern. It consists in a slowly progressive muscle weakness with proximal lower limb predominance associated with ophthalmoparesis without ptosis or diplopia, joint contractures, exercise intolerance and elevated CK levels [9], although an asymptomatic family has been described [10].

Muscle imaging in patients with *STIM1*-associated TAM has been described in a series of five patients [11], with upper and lower girdle imaging but no whole-body MRI. In the lower limb, calf and peroneal muscle fatty replacement and diffuse thigh involvement with sparing of tibialis anterior and gracilis were noted. Flexor hallucis longus was constantly involved in its distal section and sartorius was often affected. In the upper limb, the subscapularis muscle was invariably affected and the trapezius was spared. This pattern was similar to that in our patient, especially in the leg with sparing of tibialis anterior and involvement of flexor hallucis longus. In our patient, WB MRI revealed asplenia and was a clue for the diagnosis of Stormorken syndrome.

The plasma membrane Ca^{2+}-released-activated Ca^{2+} channel (CRAC) ORAI1 is activated by STIM1 oligomerization and *ORAI1* mutations are responsible for similar phenotypes [9]. Loss-of-function or null mutations are associated with severe,