The first Italian family with scapuloperoneal spinal muscular atrophy due to TRPV4 mutation

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BACKGROUND

Scapuloperoneal spinal muscular atrophy (SPSMA) is a rare autosomal dominant neuromuscular disorder caused by heterozygous mutations in the transient receptor potential cation channel (TRPV4) gene, characterized by progressive scapuloperoneal atrophy and weakness. Additional features such as vocal cord paralysis, scoliosis and/or arthrogryposis are likely to occur[1]. The pattern of expression is variable in different branches of the family. Disease expression is more severe and progressive in successive generations.[2] TRPV4 is a calcium-permeable non selective cation channel. TRPV4 mutations have been identified in a spectrum of autosomal-dominant skeletal dysplasias and, recently, they have also been associated with other neuromuscular disorders: Charcot-Marie-Tooth disease type 2C (CMT2C), scapuloperoneal spinal muscular atrophy (SPSMA) and congenital distal spinal muscular atrophy (CDSMA). The pathogenic mechanism underlying the mutant TRPV4–mediated peripheral neuropathies is not yet clear[3]. We describe an Italian family with SPSMA harbouring the c. 806G>A mutation in TRPV4 gene (p. R269H), confirming the importance of an early diagnosis and the clinical heterogeneity of this disease.

CASE REPORT

L.D. L . 24 years old man ♂, (proband)

First born child of healthy non-consanguineous parents.

At birth bilateral congenital clubfoot, surgically treated at the age of one year.

He came to our Department at six years of age because of difficulty in walking, running and climbing stairs.

Last neurological examination: winged scapulae, steppage gait (> left), unable walk on heels, atrophy and weakness of anterior region of the legs; ankle jerks absent and Achilles tendon retractions (Fig 1).

Laboratory examination Serum CK: normal. Other blood tests including complete blood cell count, tests for kidney, liver, and thyroid function: normal

Neurophysiological studies

NCS and NCM: normal. cMAPS reduced mainly in lower limbs

EMG: No at rest activities. Large amplitude and duration of MUPs at proximal and distal muscles at four limbs with poor recruitment during maximal voluntary contraction.

Muscle biopsy: A vastus lateralis muscle biopsy evinced fiber size variability due to the present of scattered angulated atrophic fibers and “type grouping” (Fig. 2).

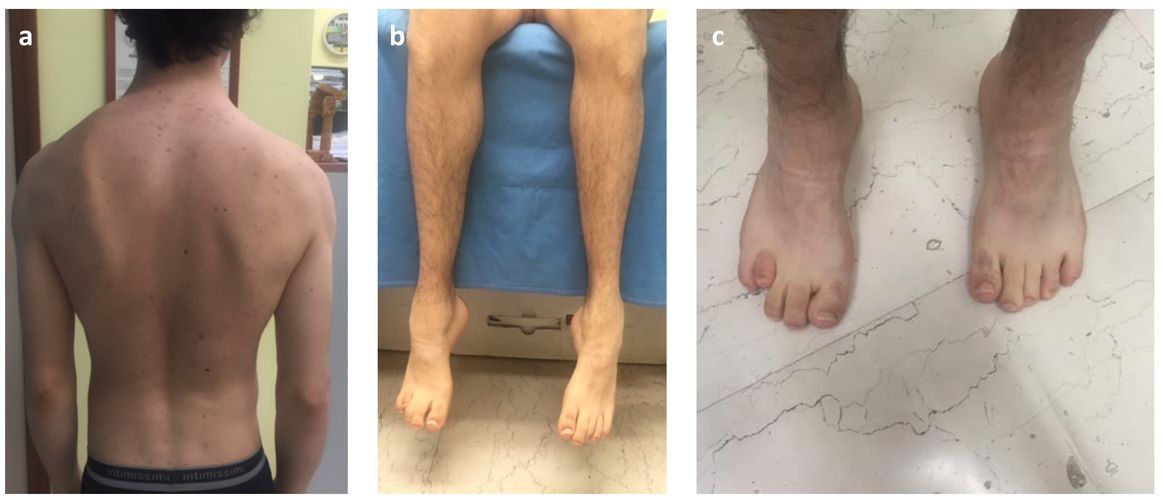

Fig. 1 (a) winged scapula. (b) atrophy of anterior regiong of legs. (c) dysplasia fourth metatarsal.

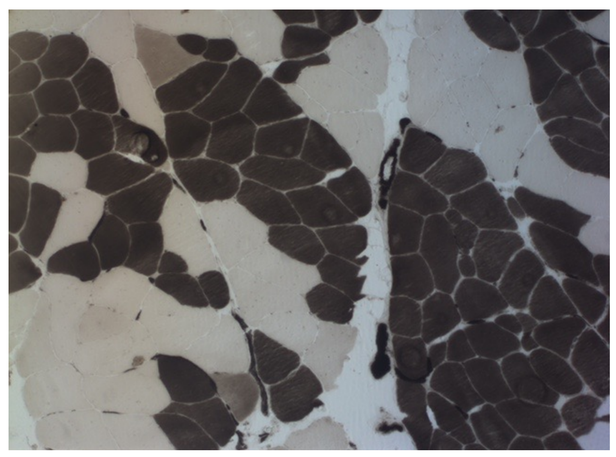

Fig.2 ATPase 4.6 stain: fiber size variability; type grouping

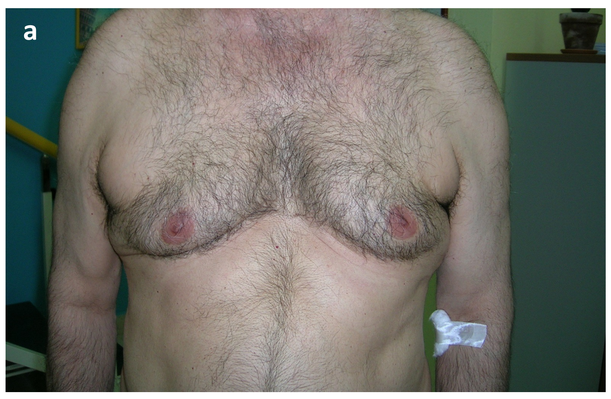

Fig.3 (a) pectoral muscle wasting. (b) winged scapula

Molecular analysis of TRPV4 gene: c.806G>A mutation in TRPV4 gene (p. R269H) in both.

This is an already reported missense substitution affecting the intracellular N-terminal ankyrin domain that affect channel maturation, leading to reduced surface expression of functional TRPV4 channels.

L.D. G . 67 years old man ♂, Father of proband.

He referred a slight difficulty in arms elevation and difficulty to walk on heels since childhood.

Last neurological examination: winged scapulae, mild steppage gait, difficulty to walk on heels, pectoral muscles wasting and weakness, distal weakness at lower limbs, more pronounced in flexor hallucis longus bilaterally, deep tendon reflexes reduced (Fig.3). **Laboratory examination** Serum CK: 358 U/L. (normal range < 200).

Other blood tests: normal

Neurophysiological analysis

NCS and NCM: normal. Small amplitude of CMAPs (ulnar and popliteal nerves)

EMG: sharp waves at rest; large amplitude and duration of MUPs.

CONCLUSIONS

In summary, we describe the first Italian family affected by scapuloperoneal spinal muscular atrophy linked to a mutation in TRPV4 gene. This disorder should be considered in scapuloperoneal syndromes presenting with an autosomal dominant inheritance and a neurogenic pattern. Our family confirms that the phenotype is more severe in the next generations.The association with skeletal deformities may help with the differential diagnosis.

An early diagnosis is necessary to consider and identify the more severe congenital form characterized by hypotonia, arthrogryposis and vocal cord paralysis

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