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Short communication

A novel *HSPB1* mutation in an Italian patient with CMT2/dHMN phenotype

M. Luigetti [a], G.M. Fabrizi [b], F. Madia [a], M. Ferrarini [b], A. Conte [a], A. Del Grande [a], G. Tasca [a], P.A. Tonali [a,c], M. Sabatelli [a,*]

[a] Institute of Neurology, Catholic University of Sacred Heart, Rome, Italy
[b] Department of Neurological Sciences and Vision, University of Verona, Verona, Italy
[c] Don Carlo Gnocchi Onlus Foundation, Italy

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ABSTRACT

Mutations in the gene encoding 27-kDa small heat-shock protein B1 (*HSPB1*) have been reported in association with Charcot-Marie-Tooth disease type 2F or dHMN type II. We describe an Italian patient with wasting and weakness of distal muscles, involving primarily and mostly the lower limbs and later the upper limbs, in which a novel mutation of *HSPB1*, T180I, was detected. Electrophysiological evaluation disclosed a pure motor axonal neuropathy. Sural nerve biopsy showed a mild reduction of myelinated fibre density. All these findings suggested a CMT2/dHMN phenotype.

1. Introduction

Charcot–Marie–Tooth disease (CMT) is a group of clinically and genetically heterogeneous motor and sensory neuropathies classically divided into demyelinating (CMT1) and axonal forms (CMT2) [1,2]. Distal hereditary motor neuropathy (dHMN) is a motor neuronopathy which resembles CMT (it is also known as spinal CMT) but lacks a significant clinical or neurophysiologic sensory involvement [1,2]. Mutations in the gene encoding the 27-kDa small heat-shock protein B1 (*HSPB1*, also called heat shock 27-kD protein 1, *HSP27*) cause the allelic Charcot-Marie-Tooth disease type 2F (CMT2F; OMIM 606595) and dHMN type II (OMIM 608634). Since the first description in 2004 many mutations of HSP27 causing CMT2F or dHMN type II (dHMN-II) have been reported [3,4]. Herein we describe an Italian patient with a CMT2/dHMN phenotype in which a novel mutation of *HSPB1* was detected.

2. Case Description

The patient was a 19-year-old girl who was referred to our Neurology department when she was 11. She reported walking difficulties since the age of 7 and she required ankle foot orthosis for deambulation since the age of 9. Neurological examination revealed pes cavus, marked atrophy and weakness in the distal muscles of the lower limbs graded 1 on the MRC scale and strength impairment of intrinsic hand muscles graded 4. Sensory examination was unremarkable. Tendon reflexes were all absent. Extensive laboratory studies were normal including complete blood count, electrolyte levels, erythrocyte sedimentation rate, C-reactive protein, immunofixation electrophoresis, FT3, FT4, TSH, hepatic enzymes, creatinine, urine analysis and screening for infections, malignancies, malabsorption and systemic autoimmune disorders. Creatine kinase level, assessed after rest, were slightly elevated at 220 IU/l (normal range 30-160). Sensory nerve conduction studies showed normal conduction velocities as well as normal amplitude of sensory nerve action potentials (SNAPs) in all tested nerves. Motor nerve conduction studies, at the age of 11 years, showed reduced amplitudes of the compound muscle action potentials (CMAPs) registering from upper and lower limbs with conduction velocities in the lower range of normal values (Table 1). Needle electromyography revealed a neurogenic pattern with high frequency of large motor-unit potentials in the tibialis anterior and first digiti interosseous bilaterally.

Sural nerve and rectus femoris muscle biopsies were performed after obtaining informed consent. Muscle biopsy of rectus femoris showed signs of both acute and chronic denervation, consisting of a marked increase in fiber size variability with many atrophic angulated fibers, either scattered or collected in small groups (Fig. 1a), and presence of atrophic fibers with pyknotic nuclear clumps. ATPase and NADH-tetrazolium reductase stainings revealed the presence of diffuse type grouping phenomena (Fig. 1b). Nerve biopsy revealed a mild loss of

* Corresponding author. Institute of Neurology, Largo F. Vito 1, 00168 ROMA, Italy. Tel.: +39 06 30154435; fax: +39 06 35501909.
E-mail address: msabatelli@rm.unicatt.it (M. Sabatelli).

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Table 1
Nerve conduction study.

Nerve	Tract	MCV (m/s)	dL (ms)	CMAP (mV)
Ulnar	Ax-Ab. E	48		2.0
	Ab. E-Bel. E	42		2.0
	E - W	45		2.0
	W - ADM		2.9	2.0
Deep Peroneal	A - EDB		-	absent
	PF - FH	40		1.0
	FH -TA		2.9	1.0
		SCV (m/s)		SAP (μV)
Sural	A - SURA	50		19
Median	IF - W	58		27
Ulnar	VF - W	53		7.0
Radial	IF - W	59		9.0

Legend: **MCV**, motor conduction velocity; **dL**, distal latency; **CMAP**, compound muscle action potential; **SCV**, sensory conduction velocity; **SAP**, sensory action potential; **Ax**, axilla; **E**, elbow; **W**, wrist; **Ab. E- Bel. E**, above elbow-below elbow; **ADM**, abductor digiti minimi; **PF,** popliteal fossa; **A**, ankle; **FH**, fibula head; **TA**, tibialis anterior; **EDB**, extensor digitorum brevis; **IF,** first finger; **VF**, fifth finger.

myelinated fibers with a density of 6546/mm^2 (n.v.>9000). There were some regenerating clusters and occasional fibers with thin myelin sheaths. There were no onion bulbs and the fascicular area was not increased (Fig. 1c). Ultrastructural examination revealed normal myelin compaction in the remaining fibers. The density of unmyelinated fibers was 30275/mm^2 (n.v.>28000); occasional collagen pockets were detected (Fig. 1d).

Periodical clinical examinations revealed a progressive worsening of motor symptoms and signs over a eight-year period of follow-up. At her last visit, at age 19, muscle strength was graded 0 in distal muscles of lower limbs and 2 in distal muscles of the hands. Muscle atrophies became obvious (Fig. 1c-d). Follow-up sensory nerve conduction study of sural nerve, performed at the age of 17, revealed SNAP amplitude of 12 μV.

Sequence analysis of *MPZ, MFN2, GDAP1, HSP22, BSCL2* and *GARS* genes was normal. Sequencing of all the coding exons and flanking introns of the *HSPB1* gene disclosed the novel missense mutation c.539C>T, T180I, located in exon 3 (Fig. 2a-b). The patient had no siblings. Both parents were normal at clinical and electrophysiological examinations; genetic analysis, after obtaining informed consent, excluded the presence of the mutation. The mutation was not found in 100 ethnically matched control subjects.

3. Discussion

In our patient clinical examination revealed wasting and weakness of distal muscles, involving primarily and mostly the lower limbs, and later the upper limbs; electrophysiological studies were consistent with a pure motor axonal neuropathy; sural nerve biopsy showed mildly reduced density of myelinated fibers (6546/mm^2). All these findings suggested a CMT2/dHMN phenotype.

CMT2 is clinically characterized by a typical peroneal muscular atrophy syndrome, and electrophysiological studies show normal or slightly reduced motor and sensory nerve conduction velocities and decreased amplitudes of CMAPs and SNAPs [1]. Eight causative genes have been detected, accounting for about 25% of all CMT2 cases [2].

dHMN usually presents as a classical peroneal muscular atrophy syndrome without sensory symptoms; different genes have been identified in this condition [5,6]. Mutations in *HSPB8*, *HSPB1*, *GARS* and *BCSL2* may cause various clinical phenotypes including CMT2 or dHMN [4,7–9].

In our case regular clinical visits over a period of almost ten years documented the progression of motor weakness, without any sign of sensory disturbances. According to Harding's classification our patient was affected by HMN I and showed a quite fast progression of motor impairment [10]. *HSPB1* mutations generally cause adult onset motor neuropathy classified as HMN IIb or CMT2F [11–15] however few cases with early-onset phenotype (HMN I) have been reported too [15,16]. Our data confirm the presence of an overlap between dHMN I and dHMN II phenotypes caused by *HSPB1* mutations [17,18].

However, in our case, follow-up nerve conduction study of sural nerve, eight years after the first evaluation, revealed an amplitude reduction of SNAP with a low-borderline value. Furthermore nerve biopsy was consistent with a mild axonal pathology. All these findings suggested that there is a continuum between CMT2 and dHMN.

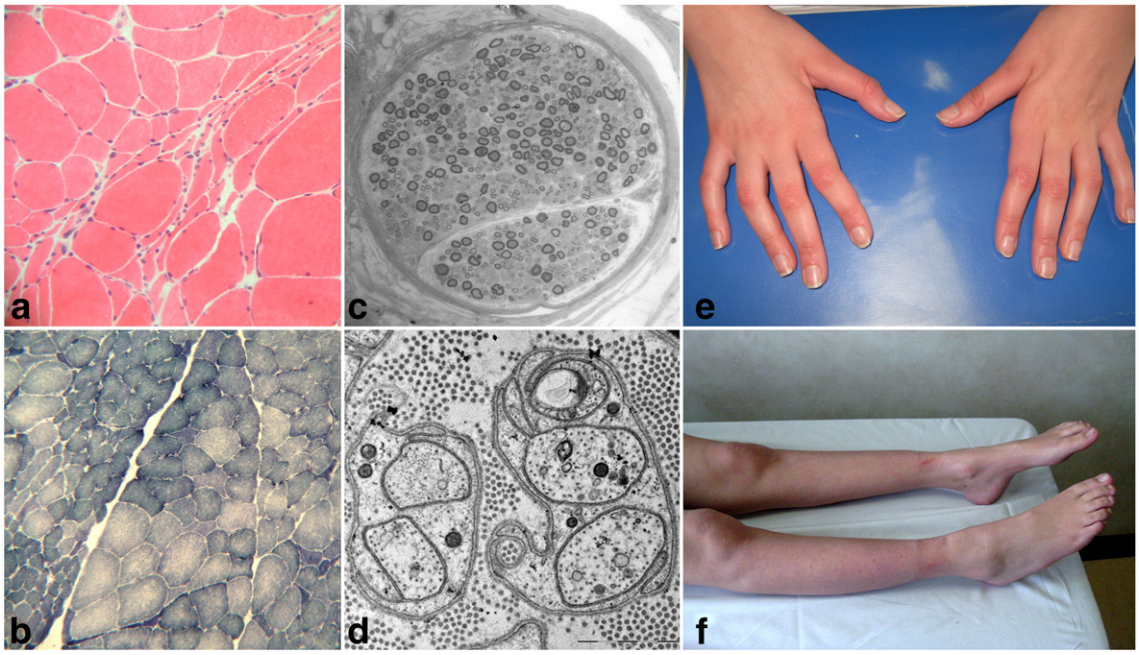

Fig. 1. parts a-f: a-b. Muscle biopsy showing grouped angulated fibers (HE staining in a) and fiber type grouping (NADH-tetrazolium reductase staining in b). c-d. Nerve biopsy. Semithin sections stained with Toluidine blu showing one fascicule with mild loss of myelinated fibers (c). Electron microscopy examination showing normal unmyelinated fibers; a single collagen pocket is visible (d). e-f. Marked atrophy of distal muscles more pronounced in lower limbs.