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AUTOSOMAL DOMINANT HMSN WITH PROXIMAL INVOLVEMENT

New Brazilian cases

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Abstract – We report four Brazilian siblings with Autosomal Dominant Hereditary Motor Sensory Neuropathy with Proximal Dominant Involvement (HMSN-P), a rare form of HMSN, that was characterized by proximal dominant muscle weakness and atrophy onset after the age of 30 years, fasciculation, arreflexia and sensory disturbances with autosomal dominant inheritance. Electrophysiological study and sural nerve biopsy were in the accordance with axonal sensory motor polyneuropathy and laboratorial analysis disclosed serum lipids and muscle enzymes abnormalities. Our report is the first done by a group outside Japan, where the disease initially seemed to be restricted and stressed the phenotypic variability from the original report.

KEY WORDS: HMSN, HMSN-P, proximal motor neuropathy, axonal neuropathy, proximal muscle atrophy.

HMSN autossômica dominante com envolvimento proximal: novos casos brasileiros

Resumo – Relatamos os casos de quatro irmãos brasileiros com Neuropatia Sensitivo Motora Hereditária com Envolvimento Proximal Dominante (HMSN-P), uma forma rara de HMSN caracterizada por fraqueza muscular de predomínio proximal e atrofia de instalação após os 30 anos, fasciculações, arreflexia, distúrbios sensitivos e padrão de herança autossômica dominante. Os estudos eletrofisiológicos e de biópsia do nervo sural confirmaram o diagnóstico de polineuropatia sensitivo-motora com padrão lesional axonal. Laboratorialmente foram constatadas anormalidades séricas no metabolismo lipídico e enzimas musculares. Nosso relato é o primeiro feito por um grupo fora do Japão, onde a doença parecia restrita até então e ressalta a variabilidade fenotípica apresentada nos casos Brasileiros.

PALAVRAS-CHAVE: HMSN, HMSN-P, neuropatia motora proximal, neuropatia axonal, atrofia muscular proximal.

Inherited disorders of peripheral nerves represent a heterogeneous group of neurological diseases, with varied symptoms, signs and temporal courses. Charcot-Marie-Tooth (CMT) neuropathy, also called Hereditary Motor and Sensory Neuropathy (HMSN), is the most frequent of them. Its classification is based on the pathological aspect (axonal or demyelinating), neurophysiologic findings and inheritance (dominant or recessive autosomal or X-linked)[1].

We report a family with a rare form of HMSN, Autosomal Dominant Hereditary Motor Sensory Neuropathy with Proximal Dominant Involvement (HMSN-P). The disease was first described in 1997 by Takashima et al.[2] who established diagnostic criteria: slowly progressive proximal dominant muscle weakness and atrophy first manifested after the age of 30 years; family history of autosomal dominant inheritance; fasciculation in the extremities and trunk; absent deep tendon reflexes; and presence of abnormalities in sensory nerve conduction. Needle electromyography frequently displays fasciculation and fibrillation potentials. Laboratorial abnormalities most commonly include high serum levels of creatine kinase, glucose and lipids. Neuropathologic studies revealed decreased number of anterior horn cells and marked loss of myelinated fibers in posterior funiculus, cauda equine, posterior roots, tibial nerve, and sural nerve, without onion-bulb formations[2]. Its locus was mapped to chromo-

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some 3q13.1 region, and the underlying gene still remains to be identified[3-5]. Maeda et al.[6] reported HMSN-P in a Brazilian family of Japanese ancestry. Our aims were to describe the clinical, electrophysiological and pathological features in another Brazilian family with HMSN-P.

METHOD

All patients had assigned the informed consent and this study was approved by our Ethical Committee. The neurological examination and laboratory tests were done with standard techniques. Electrophysiological studies were performed in all patients using Polimed model PL 1002 or Nihon Kohden model neuropack 2 and consisted of motor and sensory nerve conduction studies, late responses and needle electromyography in proximal and distal muscles of upper and lower limbs[7]. The whole sural nerve and muscle biopsies were taken under local anesthesia and tissue samples were processed for light and electron microscopic studies following standard procedures[8,9]. Morphometric analysis in nerve tissue was carried out by stereology-based measurements and compared with our reference value[10,11].

RESULTS

The four affected siblings were born in São Paulo, Brazil. Their grandparents had immigrated to Brazil from Okinawa, Japan. Their father was also born in São Paulo and had presented with weakness in upper limbs for several years and had deceased when the Case 1 was evaluated (Fig 1).

Case 1

A 59 year-old male, first noticed muscle weakness in proximal upper limbs at the age of 46. After one year similar symptoms appeared in the lower ones. At 49, his first neurological evaluation revealed muscle weakness in the upper (Medical Research Council, MRC, grade 3 proximal and 4 distal) and lower limbs (grade 4 proximal and 5 distal), decreased reflexes, mild muscle atrophy of the scapular girdle, and thermal, tactile and painful hypoesthesia in extremities, with no gait disturbances. The symptoms progressively increased, and currently he presents greater weakness in the lower limbs (grade 2 proximal and 5 distal) and severe muscle atrophy in scapular and pelvic girdles, myotonia in hands, shoulder fasciculations, dysphagia, global areflexia and anarthrestesia. He is unable to stand up or walk without assistance, being restricted to wheelchair.

Case 2

A 45 year-old male, reported a long history of muscle cramps. At 35, his first neurological examination showed only decreased reflexes and dysesthesia in feet. At 38, he started presenting paresthesia of four limbs and difficulty in climbing into his truck. He had no gait complaints except for running. Only five years after the first evaluation, a mild muscle atrophy in the scapular and pelvic girdles could be noted, with accompanying muscle weakness (grade 4 in the four limbs more intense in proximal than in the distal segments) and difficulty in rising from the

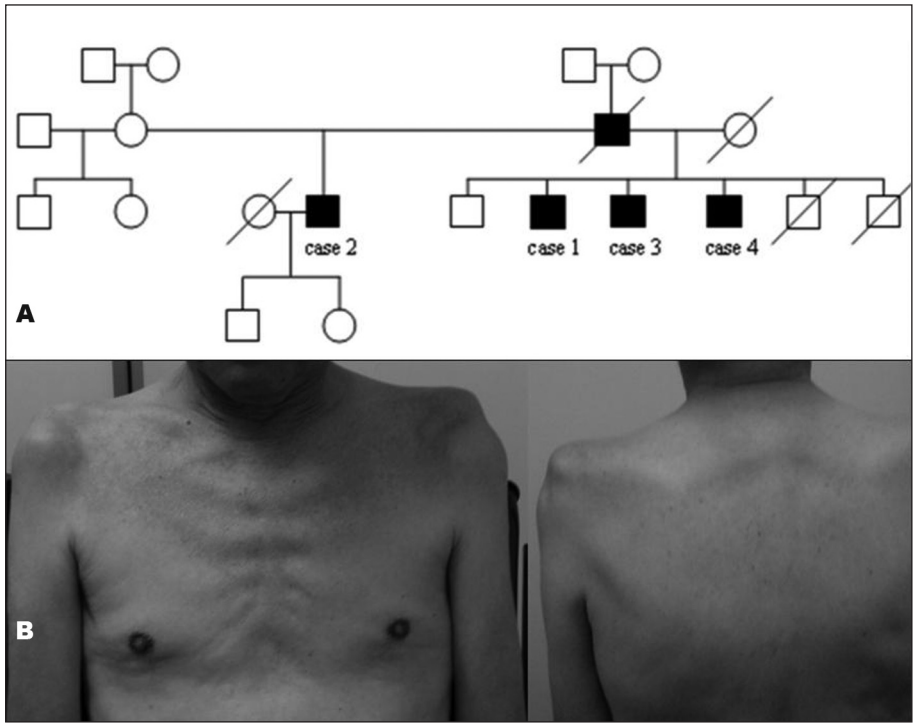

Fig 1. [A] Pedigree analysis shows male-to-male gene transmission suggesting autosomal dominant inheritance. [B] Proximal muscle atrophy in upper limbs and scapular girdle in Case 1.

Table 1. Conduction studies on motor and sensory nerves.

Nerve	Normal value	Case 1	Case 2	Case 3	Case 4
Sensory					
Median					
A (μV)	>15	8	8	6	8
CV (m/s)	>50	47.3	59.1	54.3	54.3
Ulnar					
A (μV)	>15	8	8	4	6
CV (m/s)	>50	54.7	65.6	57.5	54.7
Radial					
A (μV)	>15	5	5	4	5
CV (m/s)	>50	64.3	63.1	45.0	55.8
Sural					
A (mV)	>10	5	5	4	12
CV (m/s)	>47	59.6	42.3	52.1	55.0
Motor					
Axilar					
A (mV)	>5.0	4.0	3.0	2.3	1.8
L (ms)	<3.0	3.0	4.3	2.5	1.8
Median					
d-Amp (mV)	>5.0	10.0	13.0	10.0	7.0
DL (ms)	<3.8	3.6	2.4	3.5	2.7
CV (m/s)	>47	60.0	64.6	55.8	51.7
Ulnar					
d-Amp (mV)	>5.0	13.0	10.0	12.0	10.0
DL (ms)	<3.0	1.9	2.0	2.2	1.8
CV (m/s)	>47	65.2	77.7	68.3	58.1
Femoral					
A (mV)	>5.0	20.0	1.8	25.0	20.0
L (ms)	<3.7	2.2	3.9	2.0	2.0
Tibial					
d-Amp (mV)	>4.0	15.0	17.0	10.0	23.0
DL (ms)	<5.0	2.1	2.6	2.7	2.4
CV (m/s)	>47	59.0	59.3	52.0	55.5
Fibular					
d-Amp (mV)	>2.0	12.0	18.0	6.0	11.0
DL (ms)	<5.0	3.2	3.1	4.1	3.5
CV (m/s)	>47	52.9	51.2	48.5	53.6

Numbers represent media value; A: amplitude; CV: conduction velocity; L: latency; DL: distal latency; d-Amp: distal amplitude; mV: microVolt; mV: milliVolt; m/s: meter per second; ms: millisecond.

sitting position. Currently his neurological examination shows a "stock and glove" tactile and painful hypoesthesia, worsening of muscle weakness in the proximal lower limbs (grade 3), global areflexia and myotonia in the right hand with proximal muscle atrophy. He also reports difficulty with manual activities and mild dysphagia, but he can still walk independently.

Case 3

A 56 year-old male, first noticed proximal weakness in upper limbs when he was 47, followed by weakness in lower limbs (distal and then proximal) and myalgia. At 51, his initial neurological examination displayed an independent gait, muscle weakness (upper limbs grade 2 proximal and 3 distal, lower limbs grade 4 proximal and distal), global areflexia and a "stock and glove" tactile hypoesthesia. The symptoms worsened and nowadays he refers difficulty in the performance of manual tasks. His latest exam shows a "pseudomyopathic" gait (requiring a cane), worsening of muscle weakness and muscle atrophy of the scapular girdle, and a persistence of the sensitive abnormalities and areflexia. Hypertension and dislipidemia were also noted.

Case 4

A 55 year-old male, reported muscle cramps since the age of 16. With 37 years old, he started noticing proximal weakness in the upper right limb. Two years later, the

Table 2. Sural nerve fibers density and serum creatine kinase levels.

Patient	Myelinated fiber n/mm^2	Unmyelinated fiber n/mm^2	Creatine kinase U/L
Case 1	4.017	69.551	336*
Case 2	nd	nd	652**
Case 3	nd	nd	1.125**
Case 4	3.580	78.453	162*
Normal values	10.479	32.560	0-97 U/L* 39–308 U/L**

n/mm^2: number of nerve fibers per mm^2 of endoneural area; U/L: units per liter; nd: not done; *COBAS Integra 700; **MODULAR Analytics.

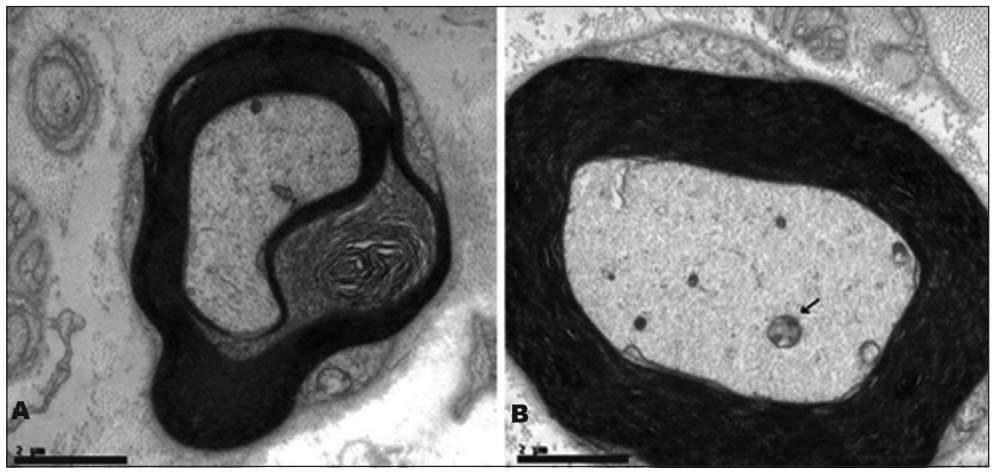

Fig 2. Cross section of myelinated axons in sural nerve. Focal thickening of degenerated myelin sheath that seems to cause entrapment of adjacent axon [A] and abnormal mitochondrial cristae [B] (arrow) (uranyl acetate, X10,000).

symptom spread to the contralateral upper limb as well as the lower ones. One year later he presented paresthesia of the extremities. At 46, his neurological examination displayed paresthesia of the hands, anarthrestesia in distal lower limbs, superficial hypoesthesia in extremities, global areflexia, muscle weakness (upper limbs: grade 3 proximal and 5 distal, lower limbs: grade 4 proximal e distal), myotonia, and muscle atrophy in upper and lower girdles with no gait disturbances, accompanied by a complaint of dysphagia. This patient was lost to follow up until last year when he returned to the hospital. He has been unable to stand up or walk without assistance since last year, being restricted to wheelchair nowadays. Currently, his neurological examination shows a "stock and glove" tactile and painful hypoesthesia, muscle weakness (upper limbs: grade 1 proximal and 3 distal, lower limbs: grade 1 proximal e 3 distal), global areflexia with proximal muscle atrophy and myotonia in the hands. He also reports mild dysphagia.

Electrodiagnostic examination was performed on all patients (1 to 7 years from the onset of symptoms) and was consistent with axonal motor and sensory polyneuropathy (Table 1). The needle electromyography revealed fibrillation and positive waves in the four patients, fasciculation in cases 1 and 4, myotonic discharges in case 2 and signs of chronic reinnervation (giants and polyphasic motor potentials) in all patients.

Laboratory analysis disclosed

Level of serum creatine kinase eleved in all cases (Table 2) in the early phase of the disease with normal values nowadays; elevated fasting serum glucose in case 4 (121 mg/dL); elevated total cholesterol in case 1 (208 mg/dL) and elevated triglycerides in cases 1 (241 mg/dL) and 4 (160 mg/dL). Renal and hepatic function, immunoglobulins, white blood count, rheumatoid factor, antinuclear antibodies, cryoglobulins, thyroid function, and immunological essays for hepatitis, syphilis and HIV had normal results in all. Cerebrospinal fluid analysis, performed in cases 1 and 3, showed no abnormalities.

Duplication of chromosome 17p11.2–p12 was the only routine genetic test available for HMSN in our institution and showed negative results in all patients.

Sural nerve biopsy (cases 1 and 4) showed rarefaction of microtubules and neurophilaments and reduction of nerve fibers when compared with our normal reference[7] (Table 2). Focal thickening of myelin sheath and abnormal

mitochondrial cristae were common (Fig 2). No onion-bulb formations were found. Unmyelinated fibers structures were normal. Muscle biopsy (case 4) revealed neurogenic atrophy.

DISCUSSION

The current cases were classified as HMSN-P because they fulfilled all diagnostic criteria published previously[2]. In comparison with Takashima's series, our patients had similar clinical onset (muscle cramps, proximal muscle weakness and dysesthesia of the extremities) at almost same median age (41.25 years). In contrast with Takashima's cases in which muscle weakness was first noticed in lower limbs, our patients showed an early and significant proximal muscle involvement of upper ones. The course of the disabilities seemed to be the same, however, in our 12-year follow-up, only one patient (case 1) had progressed to bedridden and none had developed ventilator distress until now. The nerve conduction studies of our cases also displayed axonal motor and sensory polyneuropathy. Pathological findings were in accordance with axonal degeneration predominating in large myelinated fibers, but we observed mitochondria with abnormal cristae in some almost normal thick fibers and focal thickening of the myelin sheath that seemed to entrap adjacent axons, not reported in the original description, and the increased number of unmyelinated fibers could represent axonal sprouting. It could be hypothesized that the mutation in HMSN-P might interfere with mitochondrial dynamics and/or axonal transport (cytoskeleton or microtubule motor proteins) as identified in axonal variants of CMT disease[12-14]. However, our cases led to an unsolved question – how can the same mutation cause non-length dependent motor features and characteristically length dependent sensory involvement at the same time? Finally, the analysis of our family pedigree suggested a clearly dominant inheritance. Although no female cases were observed in our family, we assumed an autosomal fatherly transmission in our cases whose daughters are still too young to present symptoms. Unfortunately, we had no knowledge of the Brazilian cases identified in Japan and described by Maeda et al.[6]. Like in our patients, these authors reported clinical onset with proximal weakness in upper limbs rather than in the lower ones and the presence of fasciculation at neurological examination as in the original description.

In conclusion, HMSN-P might be included as one of differential diagnosis of the diseases which have proximal neurogenic amyotrophy phenotype in our population who had received past immigration waves coming from Japan. We believe being dealing with descendents of one of the families reported by Takashima et al. It is important to point out that upper limb and girdle weakness and amyotrophy could be phenotypic variability that has been observed in other HMSN types or represent a different gene or mutation involved in Brazilian families.

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