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ORIGINAL COMMUNICATION

17p duplicated Charcot-Marie-Tooth 1A

Characteristics of a new population

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Abstract The most frequent type of Charcot-Marie-Tooth (CMT) neuropathy is that associated with the 17p11.2-p12 chromosome duplication, whose characteristics have been well described in European and North American populations. In this study, we analyzed a Brazilian population exhibiting the mutation, found in 57 patients from 42 families (79 %) of a cohort of 53 families with demyelinating CMT. Almost 20 % of the duplicated cases were sporadic. In 77 % of the duplicated families the mutation event occurred in the hot spot area of the CMT1A-Rep region. Forty-five percent of patients were females, 84 % were Caucasians and 13 % of African descent. Distal limb weakness was the most frequent abnormality, appearing in 84 % of patients, although uncommon manifestations such as severe proximal weakness, floppy baby syndrome, diaphragmatic weakness and severe scoliosis were also observed. One patient was wheelchair- bound, and three suffered severe hand weakness. Sensory abnormalities were detected in 84 % of the cases, but 80 % were unaware of this impairment. Twelve patients complained of positive sensory manifestations such as pain and paresthesias. Progression was reported by 40 %. Motor conduction velocities in the upper limbs were always less than 35 m/s, and less than 30.4 m/s in the peroneal nerve. The findings of this study expand the clinical spectrum of the disease.

Key words Charcot-Marie-Tooth 1A · demyelinating neuropathy · hereditary motor and sensory neuropathy · nerve conduction studies · 17p11.2-p12 duplication

Introduction

Charcot-Marie-Tooth disease type 1A (CMT 1A) is a hereditary motor and sensory neuropathy of autosomal dominant inheritance resulting from a 1.5 Mb tandem duplication of chromosome 17p11.2-p12 [34, 42]. The disease is probably the product of a dosage effect of gene PMP22 [14] located within the duplicated segment [38, 41, 50, 53], and whose expressed protein usually represents 2 to 5 % of the compact myelin of the peripheral nervous system [47]. Point mutations in the same gene also result in a demyelinating neuropathy occasionally phenotypically indistinguishable from that of the dupli-

JON 1797

cated patients, but frequently manifest as the Dejerine-Sottas phenotype [37], a more severe and precocious demyelinating neuropathy [43]. CMT is the most common inherited peripheral neuropathy [46], corresponding to 15.5% [36] and 8% [19], respectively, of the polyneuropathies of known diagnosis detected and followed up at two Brazilian University hospitals. CMT 1 identifies the demyelinating group, and CMT 1A the subgroup resulting from mutations located in the 17p11.2-p12 region, either a duplication (dupl-CMT1A) or point mutations. Besides the PMP22 gene, myelin protein zero (MPZ or P0) and the early growth response gene 2 (EGR2) also cause a dominantly inherited demyelinating neuropathy although their frequency is significantly lower than that of the duplication [6].

The characteristics of dupl-CMT1A patients have been described in a few series [5, 17, 24, 31, 49] and in several case reports. Most patients develop the classical manifestations described by Charcot, Marie and Tooth, and confirmed by others, although variant manifestations run in some families or appear as isolated characteristics in certain patients [49]. Uniform reduction in nerve conduction velocity (CV) [32] is always present in CMT1A patients by the age of 5 years [21].

Most analyses of dupl-CMT1A patients, however, have been limited to populations from North America [26, 28, 55] and Europe [5, 17, 24, 40, 49]. In this study we analyze the characteristics of a Brazilian population with this neuropathy.

Subjects and methods

The study included all patients with the 17p duplication whose DNA was tested at the Molecular Biology Section, Laboratory of Clinical and Experimental Neurology (School of Medicine of Ribeirão Preto, University of São Paulo) between 1998 and 2000. Family members of duplicated patients were also included if they had been evaluated clinically and/or electrophysiologically. The duplication test was performed in all patients with chronic sensory and motor neuropathy and a median nerve conduction velocity below the limit value of 42 m/s [28]. Asymptomatic or very mild symptomatic patients with the same electrophysiology were also tested. Sporadic cases were defined by history and neurological examination of the parents. Most of them were also tested for the duplication.

After receiving informed consent, 10 ml of peripheral blood were collected, and DNA was extracted from leucocytes according to routine protocols. Duplication and location of the recombination event were established according to published methods [48, 49]. Haplotype studies with markers D17S122, D17S955, D17S921, D17S839, D17S1358 and D17S261were used to identify the origin of the duplication in patients whose parents tested normal.

A detailed clinical evaluation was performed according to our routine protocol. Briefly, sensation was tested with cotton wool, a disposable pin and a 128 Hz tuning fork. Abdomen and trunk were also screened. Abnormalities were classified as mild when the patient could feel and identify the stimulus, but less intense when compared with more proximal regions; moderate when the stimulus could be felt but could not be characterized, and severe if the stimulus was not felt.

Muscle strength was graded bilaterally from 0 to 5 according to the MRC scale. The abductor pollicis brevis (APB), first dorsal interosseous and wrist flexors and extensors defined the upper extremity distal group, while the first toe flexors and extensors and foot dorsiflexors and plantar flexors defined the lower extremity distal group. The muscles included in the proximal group were biceps, triceps and flexors and extensors of the shoulder in the upper extremity, and quadriceps, hamstrings and flexors and extensors of the hip in the lower extremities. For each muscle group defined above, MRC quantification was summed and used to arbitrarily characterize muscle performance as follows: 40 = normal strength, 39 to 30 = mild weakness, 29 to 20 = moderate weakness, 19 to 10 = important weakness, 9 to 0 = severe weakness. Functional status was evaluated using the following scale: 1 = no incapacity (able to run normally), 2 = unable to run but walking normally, 3 = walking abnormally but without help, 4 = able to walk only with assistance (cane or crutch), 5 = wheelchair bound, and 6 = bedridden.

Nerve conduction studies were performed using MEB 4200K (NIHON KODEN) or Keypoint (DANTEC) machines according to routine protocols. Sensory and motor components of the median and ulnar nerves were studied in the upper limbs. In the lower limbs, sensory fibers were evaluated in the sural and superficial peroneal nerves, while motor fibers were evaluated in the peroneal and posterior tibial nerves. Sensory action potentials (SAPs) were recorded with subdermal needle electrodes, while compound muscle action potentials (CMAP) were recorded with surface electrodes. Median and ulnar SAPs were recorded orthodromically while the SAPs of the sural and superficial peroneal nerves were recorded antidromically. SAP amplitude was measured from the first positive peak or baseline deflection to the negative peak, and CMAP amplitude from baseline to the negative peak.

This study was approved by the Ethics Committee of the School of Medicine of Ribeirão Preto, University of São Paulo.

Results

Genetic findings

Fifty-three unrelated index cases of hereditary demyelinating neuropathy were identified during the study period. The 17p11.2-p12 chromosome duplication was present in 42 (79%) index cases. In 77% of the duplicated cases, the unequal cross over took place in the hotspot region for recombinations located in the CMT1A-REP region.

In the duplicated families, a clear autosomal dominant inheritance was definable in only 8 cases (19%) and nine cases (22%) were sporadic. In one of the isolated cases haplotype studies identified a new mutation of paternal origin. Thirty-five (84%) of the families were Caucasian, 1 (3%) was of Japanese descent, and 5 (13%) were of African descent (Table 1).

Clinical findings

A total of 57 patients from the 42 families showing duplication were evaluated (Table 2), although not all data were available for all patients. The disease was perceived by the patient in 21 cases, by relatives in 28, and was diagnosed as a result of family screening, medical consultation or EMG evaluation for other health problems in 8

Table 1 Summary of the genetic data

	Families
CMT1 families	
Non duplicated CMT1	11
Dupl-CMT1A	42
Site of duplication	
Inside the "hot-spot" area at CMT1A-REP region	32
Outside the "hot-spot" area at CMT1A-REP region	10
Inheritance	
Dominant	32
autosomal dominant	*8*
Sporadic	9
Family history not available	1
Main descent	
Caucasian	33
African	6
Japanese	3

Table 2 Summary of the clinical findings

	Patients
Age of onset (years)	
0 to 10	33
10 to 20	3
20 to 30	6
30 to 40	5
40 to 50	1
Unaware of the disease	9
Manifestations of onset	
Walking abnormalities	17
Feet deformities	11
Poor performance in physical activities	7
Painful cramps	4
Floppy baby syndrome	3
Hand weakness and/or deformities	3
Abnormal feet sensation	1
Severe scoliosis	1
Congenital hip displasia	1
Weakness topography	
LL: distal; UL: normal	11
LL: distal; UL: distal	24
LL: distal and proximal; UL: distal	5
LL: distal and proximal; UL: distal and proximal	2
Muscle stretch reflexes	
All abolished	34
At least one reflex decreased or absent	23
Sensory abnormalities	
Intensity and quality	
no involvement	*7*
mild loss	*32*
moderate loss	*9*
severe loss	*9*
positive manifestations	*12*
Topography	
LL > UL	*39*
LL ~ UL	*9*
*Inconclusive**	*2*
Cranial nerve abnormalities	
Nystagmus	3
Decreased convergence	3
Abnormal pursuit movements	2
Orbicular oculi weakness	2
Dysphagia	2
Ptosis	1
Miotic pupils	1
Skeletal abnormalities	
Pes cavus	23
Pes cavus and hammer toes	12
Pes cavus and varus	3
Pes planus	1
Claw hands	3
Ulnar deviation of the hand	1
Kyphoscoliosis	3
Lordosis	1

LL lower limbs; *UL* upper limbs; * two young patients

cases. In most cases disease onset was in the first decade, including 7 patients who were abnormal since birth. Only 1 symptomatic case was diagnosed after the 4th decade. The most frequent manifestations at onset were walking abnormalities and/or foot deformities and/or poor performance during children's games (35/57). Uncommon manifestations at onset included floppy baby syndrome, pain and/or cramps, hypoesthesia, hand weakness and/or deformity, severe scoliosis, and congenital hip dysplasia.

Weakness was present in 48 patients (84 %) although a detailed description was available for only 42. The lower limbs were always more affected than the upper limbs, and in most cases the distal muscles were more impaired than the proximal muscles. However, in 2 severely affected cases, the proximal muscles were equally affected as the distal muscles. Diaphragmatic weakness was clinically detected in only two patients, and one displayed severe facial weakness. The last three patients also showed a marked limb weakness, characterizing a pattern of diffuse and severe muscular impairment. Atrophy accompanied the weakness, and in 5 patients calf hypertrophy was present.

All patients had abnormalities in muscle stretch reflexes, which were totally absent in 34 (60 %). The remaining ones showed a distal-to-proximal involvement, except two in whom knee reflexes were less affected than biceps and triceps reflexes. No patient showed increased reflexes. Apart from resting tremor of the upper limb observed in 6 patients, no other involuntary movement was noted.

Almost 80 % of the study population were unaware of any sensory abnormality, although on examination sensory deficits were found in 50 patients. In all a distal-to-proximal distribution, with distal predominance, was

present, but in 7 the proximal regions of the limbs were also affected. In 6 of them there was abdominal hypoesthesia, characterizing a diffuse sensory involvement. The upper and the lower limbs were impaired to a similar extent in only 9 patients. Pain, tactile and vibration sensation were those most affected, while joint position sense was mostly preserved (64%). These sensory abnormalities were considered to be severe in only 9. Positive sensory manifestations, including pain and paresthesias, were reported by 12 patients. In 5, a mechanical factor such as foot or ankle abnormality was the most probable underlying event; one patient was also diabetic, but in the remaining ones no specific cause other than the neuropathy could be found.

Only minor abnormalities were detected in the cranial nerves. Most were related to abnormal eye movements. Two patients complained of dysphagia, but no abnormality was found on examination.

Pes cavus was the most frequent skeletal abnormality either isolated (40%) or associated with other foot abnormalities. In two patients, the second and third metatarsi were abnormally shorter, while in a third patient retraction in extension of the second toe was found. The first two cases were father and son, and apparently this abnormality segregated out together with the neuropathy in their family. Hand abnormalities were considerably less frequent. Kyphoscoliosis was present in 3 patients, being severe in one. Prominent lordosis was found in one case. Palpable enlargement of the nerves was found in only 7 patients; in 4 the enlargement was generalized, and in the remaining 3 the ulnar nerves were the most affected ones.

Walking was normal in 20 patients (35%) but in 36 (63%) a steppage-gait was present. One patient was wheelchair-bound. Considering the functional index, 12 (21%) could run, 23 (40%) walked normally but could not run, 18 (31%) walked abnormally but unaided, 3 (5.8%) walked with canes, and one could not walk. Three patients also had limitations in their hands. Almost 60% of patients reported that the disease was stable or was worsening slowly while the remaining 23 (40%) considered the disease to be progressively worsening.

Uncommon manifestations of the neuropathy included troublesome pain (4 patients) and/or paresthesias (3 patients), severe hypoesthesia and/or foot ulceration (3 patients), severe and disproportionate hand impairments (2 patients), difficulty in swallowing (2 patients), severe proximal weakness (2 patients), and fasciculations (1 patient). Manifestations that were probably not directly related to the neuropathy were also found, including learning impediments in five patients (three siblings from consanguineous parents and two unrelated patients), and cryptorchidism in two unrelated patients.

Nerve conduction studies

The compound muscle action potentials (CMAP) (Table 3) of the median, ulnar and peroneal nerves were recorded in 95%, 92% and 48% of the nerves tested, respectively. Motor conduction velocities were always abnormal, ranging from 12.6 to 35 m/s, 10.6 to 32 m/s and 8.9 to 30.4 m/s, respectively. Sensory action potentials of the median, ulnar and sural nerves were recorded in 72%, 68% and 23% of the nerves tested. Sensory conduction velocities followed the same distribution pattern as recorded in the motor nerves: 11.8 to 23.8 m/s, 7.1 to 27.3 m/s and 11.8 to 27.3 m/s, respectively. No significant temporal dispersion or conduction block was detected.

Discussion

Dupl-CMT 1A is thought to have a worldwide distribution but, to the best of our knowledge, all studies have been restricted to populations from North America and Europe. In this report, we analyzed the characteristics of 57 Brazilian patients from 42 unrelated families that carried the duplication. Brice et al. [7] encountered the duplication in all 12 French families studied, the inclusion criteria being autosomal dominant inheritance and a median motor NCV $\leq$38 m/s. Similar findings were reported by Belloni et al. [4] in a study of 14 Italian families and 2 sporadic cases. MacMillan et al. [35] found the duplication in 11 of 12 Welsh families, and Ionasescu et al. [25] found the duplication in 94.8% of their dominant CMT1 patients. Wise et al. (1993) [55], studying 63 unrelated patients, detected the duplication in 68%, and in the collaborative European study [40], 70.7% of 881 patients were found to have the duplication. Our data support the idea that duplication is a universal disease mechanism present in other world regions besides Europe and North America. The male ancestry of the Brazilian population is mainly European, but the female lineage is Amerindian or African, revealing that although of different genetic heritage [13], the proportion of the disease in the Brazilian population is similar to that reported for Europe and North America. Similarly, in 77% of the 42 duplicated families, the duplication occurred in the "hot spot" region of the CMT1A [33, 44], again confirming the universality of the duplication mechanism [51].

Sex distribution was close to 1:1 as expected for an autosomal dominant disorder and as observed in other series. Most of our patients were white, but 13% were black or showed a predominantly black component, suggesting that the subpopulation of African descent may be affected like other populations, which is in contrast to the data presented by Aiyesimoju et al. [1], who found only 3 cases of CMT in patients of African descent over

Table 3 Nerve Conduction Studies

Nerve	Motor conduction studies					
	Median		Ulnar		Peroneal	
	MCV (m/s)	AMPL (mV)	MCV (m/s)	AMPL (mV)	MCV (m/s)	AMPL (mV)
Median	17.4	3.0	16.0	3.5	13.9	1.4
Medium	18.9 (37.9 %)	3.53 (92.9 %)	16.9 (33.8 %)	3.61 (94.9 %)	15.8 (39.6 %)	1.86 (66.4 %)
SD	5.45	2.7	4.28	2.22	4.9	1.65
Lowest	12.6 (25.2 %)	0.14 (3.6 %)	10.6 (21.2 %)	0.3 (7.9 %)	8.9 (22 %)	0.13 (4.6 %)
Higher	35.0 (70 %)	10.2 (268.4 %)	32.0 (64 %)	7.7 (202.6 %)	30.4 (76 %)	6.0 (214.6 %)
Normal	> 50.0	> 3.8	> 50.0	> 3.8	> 40	> 2.8
Number/NR	43/2	43/2	36/3	36/3	50/26	50/26
Nerve	Sensory conduction studies					
	Median		Ulnar		Sural	
	SCV (m/s)	AMPL (μV)	SCV (m/s)	AMPL (μV)	SCV (m/s)	AMPL (μV)
Median	18.2 (36.4 %)	2.25 (25 %)	18.7 (37.4 %)	2.5 (24.4 %)	15.8 (39.5 %)	2.7 (33.8 %)
Medium	18.0 (36 %)	2.24 (24.9 %)	17.8 (35.7 %)	3.2 (35.5 %)	18.1 (42.5 %)	2.7 (33.8 %)
SD	4.7	1.49	6.4	3.2	6.4	2.0
Lowest	11.8 (23.6 %)	0.3 (3.33 %)	7.1 (14.2 %)	0.2 (2.22 %)	11.8 (29.5 %)	0.5 (6.25 %)
Higher	23.8 (47.6 %)	4.2 (46.0 %)	27.3 (54.4 %)	11.6 (129 %)	27.3 (68.8 %)	4.9 (61.5 %)
Normal	> 50.0	> 9.0	> 50.0	> 9.0	> 40.0	> 8.0
Number/NR	43/31	43/31	34/23	34/23	6/26	6/26

MCV motor conduction velocity; *SCV* sensory conduction velocity; *AMPL* amplitude; *(%)* percentage of the lower limit of normality; *NR* no response

a period of 25 years. An autosomal dominant inheritance could be established in only 19 % of our cases and 22 % of the remaining ones were isolated cases. These factors should be considered when rationalizing for the genetic tests. In many situations, an autosomal dominant inheritance cannot be characterized, but this should not constitute a reason to exclude the duplication test [15]. In one of the isolated cases a new mutation of paternal origin was demonstrable, but no other families were available for such studies. Some of the remaining sporadic patients may also carry new mutations, but false paternity and asymptomatic relatives are also likely.

As in most other reports [18, 24, 49], disease onset was mainly related to poor physical performance. However, unexpected onset manifestations like severe scoliosis, hand abnormalities, pain, congenital hip displacement and the floppy baby syndrome were also observed.

Pain was usually a rare and mild event, but in four cases it motivated the patient to seek medical care. Dyck et al. [18] and Hoogendijk & de Visser [23], reported that pain in the lower limbs is frequent in CMT patients, mainly during or after exercise. Dyck et al. [18] noted that CMT 1 patients report burning or stabbing pain in the limbs, manifestations not present in other series. In contrast, Thomas et al. [49] attributed painful events to muscular or skeletal afflictions. Seventy percent of 617 patients with CMT reported by Carter et al. [12] complained of some kind of pain. In contrast to pain, sensory impairment is present in most patients, but is usually asymptomatic. In one of our patients, however, the first abnormality noticed was a severe loss of sensation, and in another, the most prominent manifestation was chronic foot ulceration. Although rare, similar observations of prominent or early sensory abnormalities have been made by other investigators.

Motor abnormalities predominated in most patients. Weakness may possibly be present at birth; although not personally examined by us, three of our patients were reported by family members to be floppy at birth. Overall, the cases were of mild weakness, and the subsequent evolution of the neuropathy was not unusual. In one case, the parents were consanguineous and mild mental retardation was also found; it is uncertain whether hypotonia in this patient was due solely to CMT. The floppy baby syndrome seems not to be reported in CMT1 [27]. Baker and Upton [3] described a floppy infant with CMT1 but manifestations of central nervous system impairment were also present.

As is usually the case [31], weakness in our patients followed a length-dependent pattern. Although rare, severe proximal impairment was observed, but it was never more intense than the distal weakness. Auer-Grumbalch et al. [2] described a patient in whom weakness was predominantly proximal but, in such cases, an associated disorder like fascioscapulohumeral muscular dystrophy should be considered, as described by Bütefisch et al. [10]. Calf hypertrophy is now a well accepted

manifestation of CMT [16, 49, 52] and was found in five of our patients. Postural tremor seems to be a frequent manifestation in CMT patients [11], being present in 6 of our patients, the clinical variant referred to as the "Roussy-Levi syndrome" [49].

When present, tendon jerks were hypoactive in a length-dependent pattern, except in two patients. There was no hyper-reflexia or extensor toe response, that eventually may be detected [9, 45, 54].

As is usually the case, pes cavus was the most frequent skeletal abnormality. Although scoliosis is sometimes described in CMT1A [24], it is found in less than 20 % of patients [25] and almost never as the presenting or principal feature of the disease. One of our patients suffered severe kyphoscoliosis. Incapacitating scoliosis is a manifestation of CMT4C [20, 30], a recessive and rare form of CMT associated with basal lamina onion bulbs. Another interesting finding was abnormal 2nd and/or 3rd toes in one isolated patient, running in a family, suggesting that both conditions are segregating together.

Functional evaluation revealed that the disease is in general relatively benign [5] although three of our patients required assistance to walk and one is wheelchair bound, facts not observed in some of the other series [15]. Diaphragmatic weakness was clinically evident in only two patients, causing severe incapacitation.

Motor and sensory nerve conduction studies followed the same patterns as described in other series [5, 8, 29, 31, 49]. Median and ulnar nerve conduction velocities were always below 38 m/s, a value proposed by Harding and Thomas [22, 29] as the limit between axonal and demyelinating hereditary neuropathies.

In summary, this is the first dupl-CMT1A population studied outside Australia, Europe and the United States. The genetic, clinical and neurophysiological characteristics of this Brazilian population are very similar, confirming the universality of the disease and its mechanisms. However, phenotypic variations, such as floppy baby syndrome, learning impairments, severe pain, disproportionate hand impediments, cryptorchidism, swallowing impediments, severe hypoesthesia and/or foot ulceration, and severe proximal weakness, have been observed and their mechanisms require further investigation.

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