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Central motor and sensory pathway involvement in an X-linked Charcot-Marie-Tooth family

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Abstract

The aim of the present study was to investigate the subclinical involvement of the central nervous system (CNS) in an X-linked Charcot-Marie-Toth (CMTX) family.

Material and methods : Seven subjects, all members of one family with a C.462T > G connexin 32 (Cx32) mutation were investigated by Blink reflex, Somatosensory evoked potentials (SEP) and Transcranial magnetic stimulation (TMS). There were five clinically symptomatic for CMT neuropathy (four male and one female) and two asymptomatic (female) subjects.

Results : Subclinical CNS involvement was observed in all, symptomatic and asymptomatic subjects.

Conclusion : This is the largest CMTX neuropathy family investigated for CNS involvement. Electrophysiological involvement of the CNS in every examined member of this family was observed, raising the question of a more systematic involvement of the CNS in CMTX disease.

Introduction

Charcot-Marie-Tooth (CMT) is the most frequent inherited neuropathy. X-linked CMT (CMTX) is the second more frequent form after CMT1A, with a frequency about 20% (Ionasescu VV 1995). It is due to mutations in the gap junction protein 1 gene (GJB1), mapped to chromosome Xq13.1 (CX32). More than 290 different mutations of this gene have been described (www.Molgen.ua.ac.be/CMTMutations/DataSourse/MutByGene.cfm). CX32 is expressed both in the peripheral and the central nervous system. Signs of CNS involvement have been reported in a few CMTX patients (Marques *et al.*, 1999 ; Taylor *et al.*, 2003) Moreover, the use of modern imaging and electrophysiological methods has provided evidence of occasional subclinical CNS involvement in some other cases (Bahr *et al.*, 1999 ; Nicholson and Garth, 1998 ; Panas *et al.* , 1998 ; Paulson *et al.*, 2002). We describe the findings of an electrophysiological investigation of the central motor and sensory pathways in seven members of one family with a C.462T > G CX32 mutation.

Material and methods

Seven probants (4 male and 3 female), all members of the same family, were investigated by DNA analysis and electrophysiological tests. They were five symptomatic (four male and one female) and two asymptomatic (female) subjects. All symptomatic subjects had clinical features typical of CMT disease (distal muscle weakness and atrophy, foot drop, sensory symptoms and deficit, pes cavus, absent tendon reflexes). Figure 1 shows the family pedigree. The median age of patients was 44 years (21-64), the median age at onset and the median duration of the symptoms were 22.4 years (11-43) and 23.6 (11-40) years respectively. Tendon reflexes were absent in all but one patient (case 3) in whom all tendon reflexes were brisk, except the Achilles.

Central nervous system investigation comprised : 1. Blink reflex responses to stimuli delivered through a pair of surface electrodes to the supraorbital nerve were recorded from orbicularis oculi with concentric needle electrodes 2. Tibial nerve somatosensory evoked potentials (SEP) recorded after stimulation of the nerve at the internal malleolus. 3. Transcranial magnetic stimulation (TMS) using a Magstim 200 apparatus and a regular double coil. Motor evoked potentials (MEP) were recorded from flexor hallucis brevis from the side with the higher compound muscle action potential (CMAP) amplitude on peripheral stimulation. In four patients in whom CMAP from the foot muscles could not be elicited, TMS responses were recorded from thenar muscles. The peripheral motor conduction time (PMCT) and the central motor conduction time (CMCT) were calculated using the faster out of 15 F-waves and the formulas PMCT = $(F + M + 1) \times {}^1/_2$ and CMCT= total motor conduction time (TMCT)-PMCT. Routine Nerve conduction studies (NCS) and needle EMG were performed by standard techniques. and a Nihon Kohden, Neuropack Σ apparatus. Skin temperature was maintained between 31-33 °C.

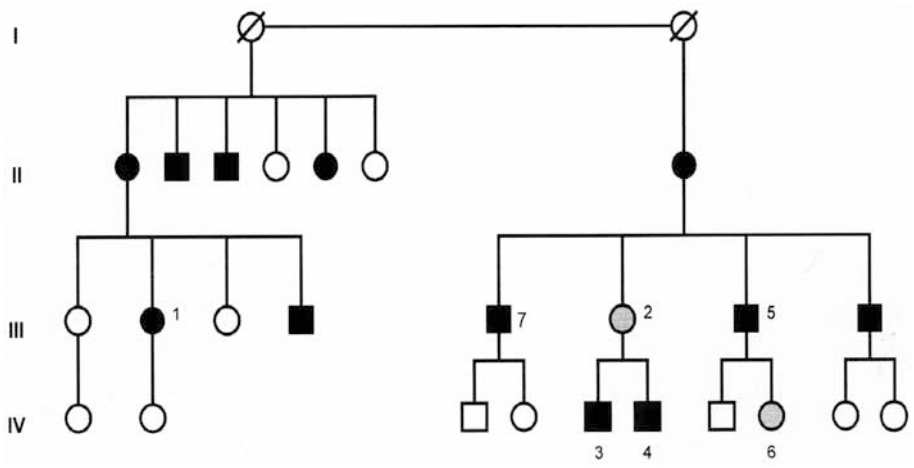

FIG. 1. — Family's pedigree. Circles = females, Squares = males, Black = clinically affected, Gray = clinically healthy, positive for the mutation.

Table 1

Central nervous system findings in CMTX patients

			Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	N.V. (X+2.5SD)
Sex/age			F/52	F/57	M/24	M/33	M/55	F/26	M/64	
Blink Reflex	Stim R	R1(msec)	10	10.6	**13.4**	**13.6**	**15.4**	10.8	**13.4**	12.52
		R2 R	37	36.6	**42.4**	**43.8**	**43.6**	38.2	**51.2**	40.23
		R2 L	38.2	39.2	**47.2**	40.4	**46.4**	38.2	**51**	40.48
	Stim.L	R1	10.2	10.6	**13.2**	**13.6**	12.6	10.8	**13**	12.69
		R2 R	35.6	36	**43.2**	**44.6**	**42.6**	38.2	**44.4**	40.48
		R2 L	34.8	36.2	**45.8**	38.8	**43.6**	39.6	**40.6**	40.23
SEP		N21(msec)	**55**	**29**	_	_	_	**27.8**	_	25.19
		P40	**95.6**	**55.4**	_	_	**92.4**	**49.8**	_	44.15
		N50	**105**	**66.2**	_	_	_	**60.2**	_	52.2
		P40/N50(μV)	**0.2**	1.5	_	_	_	1	_	0.5-6.2
TMS-CMCT(ms)	FHB			14.9				11		15.4
	APB		**21.6**		**53.9**	**13.8**	7.6		5.6	8.06

SEP : Somatosensory evoked potentials, TMS-CMCT : Transcranial magnetic stimulation-Central motor conduction time, FHB : Flexor hallucis brevis, APB : Abductor pollicis brevis. Abnormal values in bold.

All the results were compared to the normal values of our laboratory.

Brain MRI was performed in two patients (case 3 and 4) with abnormal Blink reflex, TMS and SEP and was normal.

Results

The Tyr 154 Stop mutation was detected : All 7 subjects had a T to G transversion at position 462, resulting in a stop codon.

Table 1 summarizes the electrophysiological investigation of CNS. Abnormally prolonged CMCT was found in three symptomatic (case 1, 3, 4) subjects. SEPs showed prolonged latency over central segments in two symptomatic (case 1, 5) and in the two asymptomatic subjects (case 2, 6). In the other three symptomatic subjects no responses could be recorded. Blink reflex showed bilaterally prolonged R1 and R2 responses in four symptomatic patients (case 3, 4, 5, 7) with normal distal motor latency of the facial nerve. NCS were compatible with demyelinating neuropathy.

Discussion

An extensive electrophysiological study of the central nervous system in seven CMTX subjects of the same family, five symptomatic and two asymptomatic, with the same CX32 mutation was performed.

All symptomatic subjects in our study presented subclinical involvement of the CNS motor and sensory pathway. The two asymptomatic female

subjects presented involvement of the central sensory pathway. In one of the two clinically symptomatic for CMT disease brothers (case 3) the brisk tendon reflexes (except Achilles) alludes to central motor neuron involvement, and it was the only clinical sign for CNS involvement.

In CMTX female subjects are usually asymptomatic (Rouger *et al.*, 1997), but symptomatic or oligosymptomatic females are not infrequently encountered (Dubourg *et al.*, 2001).This could be attributed to the non-random inactivation of the normal X chromosome in a higher percentage of cells. Cx32 is expressed by Schwann cells and CMTX is a demyelinating neuropathy with secondary axonal loss (Anzini *et al.*, 1997 ; Scherer *et al.*, 1998 ; Scherer and Fischbeck, 1999) although demyelination is accompanied by mild reduction of CV (Anzini *et al.*, 1997).

Central nervous system symptoms in the form of pyramidal signs have been described by Marques *et al.* (Marques *et al.*, 1999) in two identical twins with CMTX. Hearing loss has also been reported by Matsuyama *et al.* (2001) and transient central nervous system abnormalities by Paulson *et al.* (2002). Central motor pathway were found involved in both,CMT1A (Sartucci *et al.*, 1997) and CMTX patients (Bahr, 1999). Panas *et al.* (1998) using electrophysiological and MRI techniques described CNS involvement in 4 patients with CX32 mutations. Prolonged BAEPs were found in most of the Cx32 mutations studied by Nicholson and Garth (1998), including one subject with Tyr154 Stop mutation.

The pathogenesis of CNS involvement is not fully understood. Cx32 is also expressed in oligodendrocytes (Dermietzel *et al.*, 1997) and is essential as a channel-forming protein. A toxic effect of some Cx32 mutations on oligodendrocytes and dominant-negative interactions with other connexins expressed by oligodendrocytes, like Cx29 have been suggested (Kleopa *et al.*, 2002). Taylor *et al.* (2003) also proposed that the disruption of gap junction communication between oligodendrocytes and astrocytes could be another explanation for CNS symptoms. Cx32 mutations may also interrump the direct diffusion of ions and small molecules directly across the myelin sheath in the incisures and paranodes, leading to demyelination (Bone *et al.*, 1997).

Besides the systematic presence of CNS involvement in our patients, the abnormal electrophysiological findings in the two asymptomatic subjects indicate that CNS involvement occurs early in the course of the disease and probably simultaneously with that of the PNS. However, this involvement remains unsuspected as the expression of CNS symptoms is obscured by the reduction of tendon reflexes, muscle atrophy and sensory impairment due to the lesion of the peripheral nerves. In one of our patients,although the severe involvement of the peripheral nervous system, tendon reflexes were brisk, a finding alluding to central motor pathway involvement. The abnormal clinical, electrophysiological and MRI findings in both CMT1A and CMTX patients indicates that CMT is a disease not related to the PNS only (Taylor *et al.*, 2003).

In conclusion, electrophysiological evidence of subclinical involvement of the CNS has been demonstrated in all subjects in this study, and this is the largest CMTX neuropathy family electrophysiologically investigated for central nervous system involvement. If CMTX is occasionally complicated by CNS impairment or is overall characterized by CNS involvement of variable degree, remains to be clarified. To this purpose, a systematic, neurophysiologic investigation of the CNS is recommended in CMTX subjects.

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