NERVE ULTRASOUND FINDINGS IN A COHORT OF PATIENTS WITH MPZ-RELATED CHARCOT-MARIE-TOOTH NEUROPATHIES

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BACKGROUND

Nerve high-resolution ultrasound (US) is a sensitive technique for distinguishing Charcot-Marie-Tooth (CMT) 1A associated with the common 17p12 duplication (PMP22 trisomy) from chronic inflammatory demyelinating polyneuropathy (CIDP). US data in other genetic CMT subtypes, such as those related to Myelin Protein Zero (MPZ), are scanty and undefined. MPZ-related CMTs are the third genetic subtype of CMT and represent a spectrum of neuropathies, which include de-hypomyelinating CMT 3, demyelinating CMT 1B, intermediate CMT (CMT) and axonal (usually late-onset) CMT 2J/I.

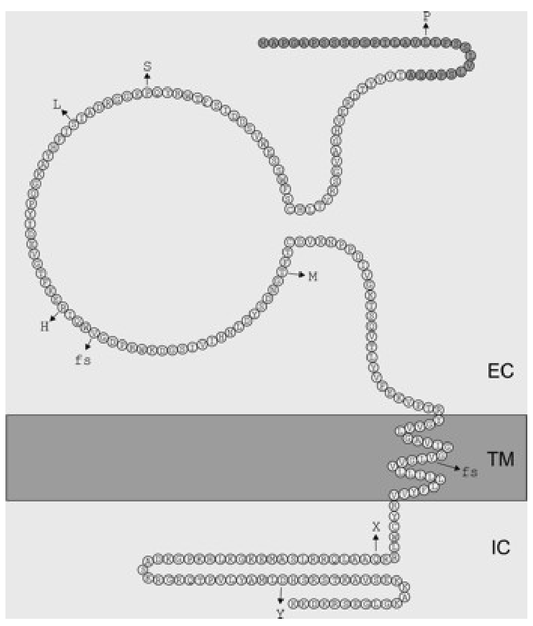
AIMS OF THE STUDY

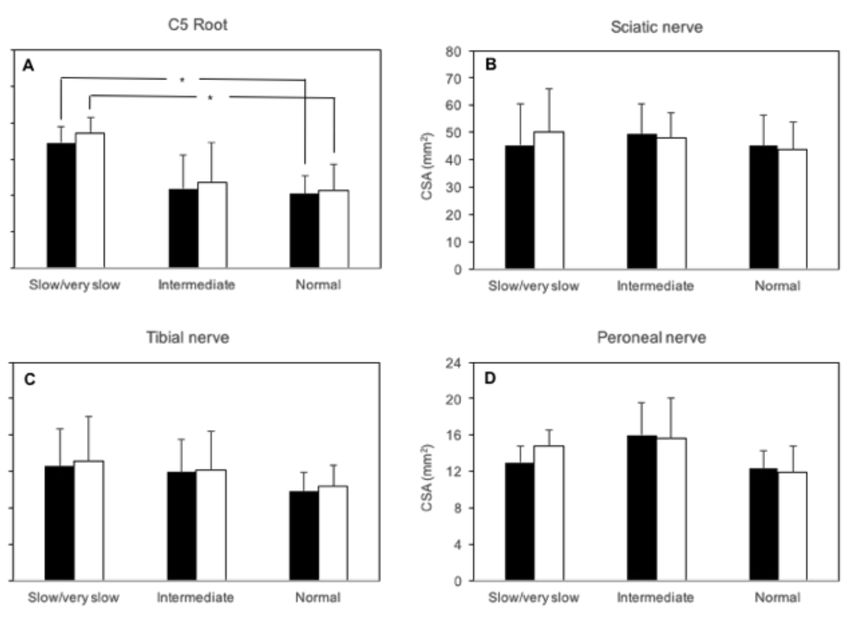
To explore the US features of peripheral nerve in a cohort of CMT patients with various MPZ genotypes and variable phenotypes defined according to standard neurophysiological or pathological criteria (in patients with archive nerve biopsies available) criteria. To correlate US data to clinical, and nerve conduction study (NCS) measures.

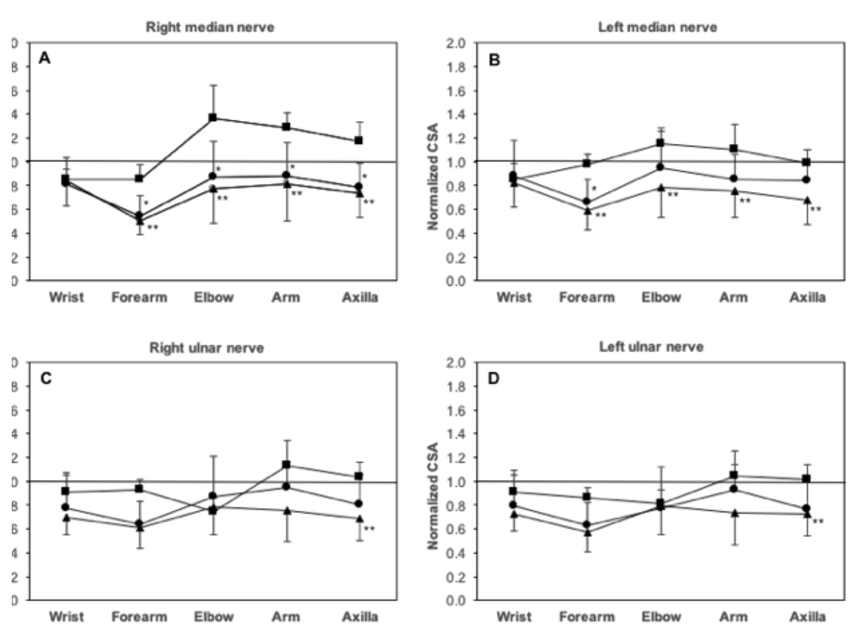
SUBJECTS AND METHODS

Participants. 25 patients from 18 families (12 males, 13 females, mean age 53.8, SD 17.0, range 13-77) with genetically confirmed diagnosis of MPZ-related CMT.
Clinical evaluation. The clinical severity of the peripheral neuropathy was measured with the CMT neuropathy score version 2 (CMTNS2).
Electrodiagnostic study. The distal motor latency (DML, ms), compound muscle action potential (CMAP) amplitude (mV), and motor nerve conduction velocity (MNCV, m/s) were measured in the median, ulnar, and peroneal nerve. The sensory nerve action potential (SNAP) amplitude (μV) and sensory nerve conduction velocity (SNCV, m/s) were measured in the radial, median, ulnar and sural nerve. The ulnar NCS of the patients were classified as normal (ulnar NCS > 45 m/s), intermediate (35-45 m/s), slow (25-35 m/s) and very slow (< 25 m/s).
Nerve ultrasound. Nerve US was performed with a Xario 200 (Toshiba Medical Systems Europe, Zoetermeer, Holland) equipped with a high-frequency bandwidth linear-array transducer. The median and ulnar nerve were identified by their location (Peer and Bodner, 2008), visualized over their whole course from the wrist to the axilla, and their cross sectional area (CSA) was measured at the wrist, mid-forearm, elbow, mid-arm, and axilla. The sciatic nerve was visualized from the thigh to its division into the tibial and peroneal nerve, which were both imaged. Three separate CSA measurements were averaged at each nerve site. The cut-off values for abnormal nerve enlargement were derived from the normative data of our laboratory and defined as the upper limit (i.e. mean + 2SD) of CSA. Normalized CSA was measured as the CSA/(upper limit of normal CSA values) ratio for each site tested.
Statistics. All tests were carried with the IBM SPSS version 20.0 statistical package. The non-parametric Kruskal–Wallis H test was used for continuous variables and the chi squared test for dichotomous ones. C5 root, sciatic, peroneal, and tibial US data were explored with the non-parametric Kruskal–Wallis H test and post-hoc Mann-Whitney U test with Bonferroni's correction. Median and ulnar nerve US findings were explored with a repeated measures ANOVA (within-subjects factor SITE, between-subjects factors SUBGROUPS and SIDE) and post-hoc t-test with Bonferroni's correction. The correlations between clinical, NCS, and US data were tested with the Spearman's ρ correlation coefficient. $P < 0.05$ (two-tailed) was taken as the significance threshold for all the tests.

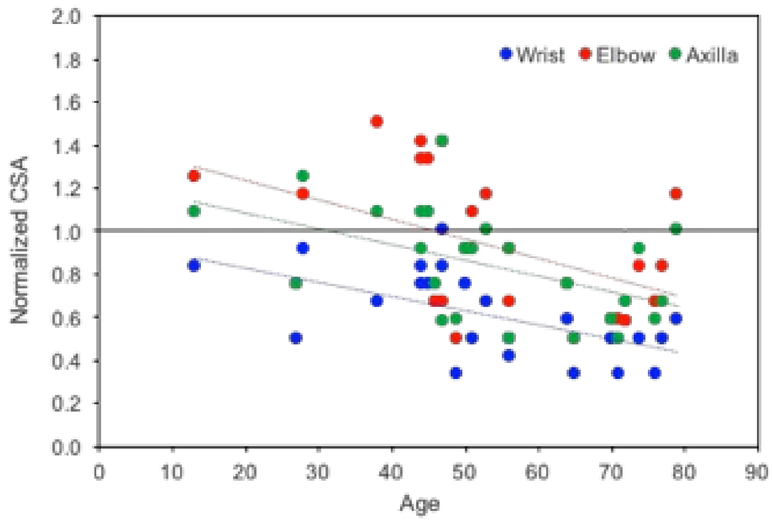
RESULTS

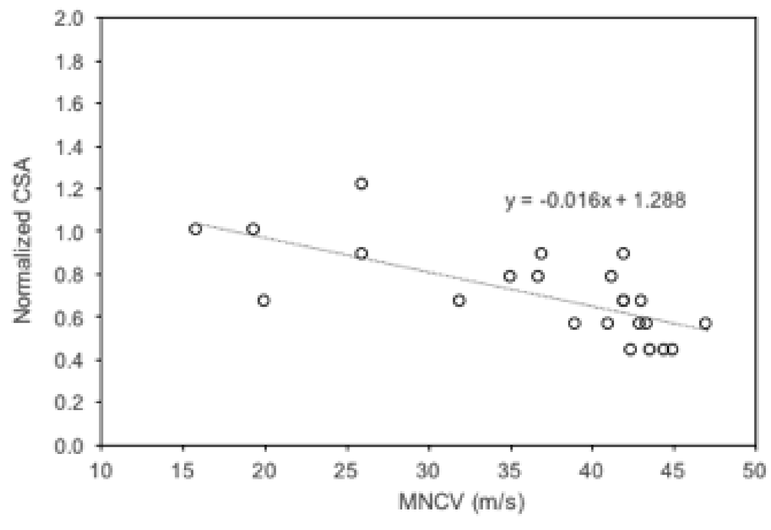






Pt	Family	Sex	Age	Onset	Age	CMTNS2	Mutation	NCV class	Nerve biopsy
1	I	F	46	Infantile	40	10	Leu17Pro	Normal	No
2	I	M	45	Infantile	44	19	Leu17Pro	Intermediate	No
3	II	F	70	Infantile	65	9	Pro70Ser	Normal	No
4	III	F	54	Adult	48		Ser78Leu	Very slow	Dem, OB+
5	IV	F	44	Adult	43		Ser78Leu	Very slow	No
6	IV	F	13	Infantile	2	7	Ser78Leu	Very slow	Dem, OB+
7	V	F	28	Juvenile	28	4	Arg98His	Slow	Dem, OB++
8	VI	F	79	Adult	64	21	Val102fs	Normal	Dem, OB-
9	VI	F	56	Adult	55	4	Val102fs	Normal	No
10	VI	M	50	Adult	48	6	Val102fs	Intermediate	No
11	VI	M	27	Juvenile	26	2	Val102fs	Normal	No
12	VII	F	77	Adult	63	16	Thr124Met	Normal	Axonal
13	VIII	M	47	Adult	38	15	Thr124Met	Slow	Axonal
14	IX	F	45	Juvenile	26	6	Val165fs	Intermediate	Dem, OB+
15	X	M	72	Adult		6	Val165fs	Intermediate	No
16	X	M	47	Infantile	15	3	Val165fs	Intermediate	No
17	XI	F	50	Adult	46	9	Gly187stop	Normal	No
18	XII	F	76	Adult	66	9	Asp224Tyr	Intermediate	No
19	XIII	M	74	Adult	73		Asp224Tyr	Intermediate	No
20	XIV	M	71	Adult	38	14	Asp224Tyr	Intermediate	Mixed
21	XIV	F	65	Juvenile	55	16	Asp224Tyr	Normal	No
22	XV	M	65	Adult	59	11	Asp224Tyr	Normal	No
23	XVI	M	56	Adult	52		Asp224Tyr	Intermediate	No
24	XVII	M	51	Adult	42	3	Asp224Tyr	Normal	No
25	XVIII	M	38	Adult	33	9	Asp224Tyr	Normal	Mixed





CONCLUSIONS

To the best of our knowledge, this is the first report to examine a large group of patients with MPZ-related CMT, different mutations and various MNCV phenotypes with a combined clinical, NCS, US and nerve biopsy approach.

The main new findings of the present study, were as follows:
a)median nerve and C5 root US differentiated slow/very slow MNCV patients, who showed slightly enlarged CSA, from those with intermediate and normal MNCV, who had normal CSA;
b)CSA borders for ulnar, sciatic, tibial and peroneal nerve US data were more blurred between the three groups;
c)median and ulnar nerve CSA was negatively correlated with age (i.e. smaller nerves in older patients);
d)median CSA at the forearm was negatively correlated with MNCV.

Nerve US, in addition to NCS might facilitate targeted gene analysis (Noto et al., 2015) and might be helpful for better understanding of pathogenesis of inherited neuropathies. Future studies should confirm our findings through a multicenter approach, and better define the US boundaries between MPZ-related CMT, other CMTs, and acquired polyneuropathies.