NERVE CONDUCTION VELOCITY IN CMT1A: WHAT ELSE CAN WE TELL?

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ABSTRACT

Objective. The aim of the present study was to analyze the large amount of electrophysiological data collected in the ascorbic acid trial in Italy and the UK (CMT-TRIAAL/CMT-TRAUK).

Methods. We analyzed baseline electrophysiological data from 271 patients. Electrophysiological recordings were taken from the motor ulnar, median, and peroneal nerves and the sensory ulnar nerve. Distal motor latency (DML), motor (MNCV) and sensory (SNCV) nerve conduction velocity, and amplitudes of compound motor action potentials (CMAPs) and sensory action potentials were assessed. Electrophysiological findings were correlated with age of patients at examination and Charcot–Marie-Tooth Examination Score (CMTES).

Results. Nerve conduction velocity (NCV) was markedly and uniformly reduced. CMAP amplitudes were overall reduced but more severely in lower limbs. DML decreased and MNCV and SNCV increased with age of patients, whereas CMAP amplitudes worsened with age and also correlated with CMTES.

Conclusions. This is the largest sample of electrophysiological data obtained so far from CMT1A patients. Axonal degeneration as assessed by means of CMAP amplitude reflected clinical impairment and was consistent with a slowly progressive length-dependent neuropathy. All patients typically had markedly slowed NCV that however slightly increased with age of patients. The improvement of NCV might depend on myelin thickness remodeling that occurs during the adult life of CMT1A patients.

INTRODUCTION

Charcot-Marie-Tooth (CMT) disease is the most frequent neurologic hereditary disorder and is characterised by clinical and genetic heterogeneity. Motor nerve conduction velocity (MNCV) enables separation of dysmyelinating (CMT1) from axonal (CMT2) CMT on the basis of a 38 m/sec cut-off value in upper limb nerves [1]. CMT1A is the most common form of CMT and is characterized by low MNCV, the electrophysiological surrogate marker for myelin integrity. In CMT1A, MNCV is uniformly reduced in all nerves and values less than 38 m/s are highly diagnostic [2,3]. This electrophysiological hallmark, fully penetrant since the first years of life [4-6], remains fairly stable through the life [7-9] and does not correlate with disability whereas CMAP amplitude that is a surrogate marker of axonal degeneration, does [3].

Recently, the ascorbic acid trial in Italy and the UK allowed us to collect and analyze electrophysiological data from a large cohort of CMT1A patients [10].

The aim of the present study was to further analyze the large amount of data collected in the trial and to use this data to gain insights into the pathophysiology of nerve conduction velocity in CMT1A.

PATIENTS AND METHODS

Data were obtained from the baseline electrophysiological evaluation of 271 patients recruited in the CMT-TRIAAL (CMT Trial with Ascorbic Acid Long Term, EudraCT 2006-000032- 27)/CMT-TRAUK (CMT Trial with Ascorbic Acid UK, ISRCTN61074476) [10]: 108 males and 163 females, mean age 41.8 $\pm$ 13.2 years, range 18-70 years.

Electrophysiological recordings were taken from the motor ulnar, median, and peroneal nerves (non-dominant side) and the sensory ulnar nerve (non-dominant side and antidromic technique). Distal motor latency (DML), motor (MNCV) and sensory (SNCV) nerve conduction velocity, and amplitudes (base-line to negative peak) of compound motor action potentials (CMAPs) and sensory action potentials (SAPs) were assessed.

CMAP was recorded, by using a pair of surface electrodes with belly-tendon arrangement, from abductor digiti minimi muscle for ulnar nerve, abductor pollicis brevis muscle for median nerve, and extensor digitorum brevis muscle for peroneal nerve. Standardized distal distances for DML were used: ulnar and median nerves = 7 cm and peroneal nerve = 9 cm. The following nerve segments were used for calculating MNCV: below elbow to wrist for ulnar nerve, elbow to wrist for median nerve, and fibular head to ankle for peroneal nerve.

For SAP recording ring electrodes were placed around the proximal (cathode) and distal (anode) interphalangeal joint of fifth finger. SNCV was measured along the ulnar nerve from the wrist to fifth finger. Foot and hand skin temperature was checked and kept at 32‑34°C.

To ensure supra-threshold stimulation, when no distal CMAP was recordable or when the amplitude of proximal CMAP was less than 50% compared to distal CMAP amplitude, the intensity of electrical stimulus was increased until 100 mA and if necessary the duration of electrical stimulus was increased until 0.5 ms.

Electrophysiological procedures were established by a neurophysiology committee and to ensure the quality of NCS performed in multiple institutions, all neurophysiological recordings were revised by the Center of Naples (by LS, FM and CP).

Standard Protocol Approvals, Registrations and Patient Consents

The protocol was approved by the institutional review board at every site, and patients gave written informed consent before any study-related procedures. This study is registered, numbers ISRCTN61074476 (CMT-TRAUK) and EudraCT 2006-000032-27 (CMTTRIAAL). CMT-TRIAAL and CMT-TRAUK shared a common protocol but have different names and registration numbers because funding was separate in Italy and the UK.

Statistical Analysis

Statistical analysis was performed using STATA 12.1 for Windows (StataCorp LP, USA).

The Pearson or the Spearman coefficient with Bonferroni-adjusted significance level were used, for parametric or non-parametric data respectively, to investigate the correlations among

electrophysiological (i.e. DML, MNCV, SNCV, CMAP and SAP) and clinical (age and Charcot–Marie-Tooth Examination Score - CMTES) variables. Multiple regression model was applied to assess the independent associations between electrophysiological variables and CMTES; mean MNCV and CMAP amplitude summatory of the three explored nerves (ulnar, median and peroneal) were the independent variables and CMTES was the dependent variable.

Moreover, in order to evaluate MNCV changes over 2 years we looked at the longitudinal data of CMT-TRIAAL/CMT-TRAUK. We applied ANOVA model for repeated measures with Time (four levels: baseline, 6, 12, 18 and 24 months) as within subject factor and Group of treatment (two levels: placebo and ascorbic acid) as between subject factor. A p value of < 0.05 was considered significant.

RESULTS

Electrophysiological data from 271 CMT1A patients are reported in table 1.

DML, MNCV and SNCV were abnormal in all patients.

Nerve conduction velocity (NCV) slowing ranged from 4 to 38 m/sec. Mean value of both MNCV and SNCV was around 20 m/sec.

MNCV slowing was concordant among the three explored nerves (ulnar/median, $r = 0.7519$, $p < 0.0001$; ulnar/peroneal, $r = 0.6412$, $p < 0.0001$; median/peroneal, $r = 0.6405$, $p < 0.0001$).

Moreover, MNCV slowing, was concordant between distal and proximal nerve segments (DML/MNCV in ulnar nerve, $r = -0.5045$, $p < 0.0001$; DML/MNCV in median nerve, $r = -0.3667$, $p < 0.0001$; DML/MNCV in peroneal nerve, $r = -0.2950$, $p = 0.01$).

Temporal dispersion was not reported. A reduction of proximal CMAP amplitude >50% compared with distal CMAP amplitude (consistent with partial conduction block) was occasionally observed (26 out of 574 evaluable nerves = 4.5%).

Distal CMAP amplitudes were overall reduced but more severely in lower limbs. No distal CMAP was recordable in 7/268 (2.6%) patients in the ulnar nerve, in 13/268 (5.9%) patients in the median nerve and in 194/264 (73.4%) patients in the peroneal nerve.

No SAP was recordable in 215/267 (80.5%) patients in the ulnar nerve.

Correlations between electrophysiological and clinical data

Correlations and their significance are reported in table 1.

Briefly, DML decreased with age in ulnar and peroneal nerves while in median nerve DML did not change with age.

MNCV increased with age in ulnar and median nerves (Figure 1) as well as SNCV increased with age in ulnar nerve.

MNCV did not change over 2 years of follow up (F= 2.098; p = 0.079). Treatment did not influence MNCV over 2 years of follow-up (F= 0.791; p = 0.531).

Distal CMAP amplitude decreased with age in ulnar and median nerves while in peroneal nerve CMAP amplitude showed only a tendency ($p = 0.06$) to decrease with age.

Clinical disability, as assessed by CMTES, worsened with age ($rho = 0.2760$, $p < 0.0001$).

Moreover, CMTES correlated inversely with CMAP and SAP amplitudes and only partially with MNCV. However, multiple regression analysis showed that only CMAP amplitude correlated with CMTES (coefficient = - 0.37; 95% CI = - 0.48 - 0.27; $p <$ 0.001).

Overall, NCV increased and DML decreased with age, whereas CMAP amplitudes, a surrogate marker of axonal degeneration, showed a slight decline with age and correlated with clinical disability, as well.

DISCUSSION

In this study, we analyzed the largest sample of electrophysiological data obtained so far from CMT1A patients.

All patients had marked and uniform NCV slowing. Moreover, axonal degeneration as assessed by means of CMAP amplitude reflected clinical impairment and was consistent with a slowly progressive length-dependent neuropathy. Distal CMAP amplitude deteriorated with age in the ulnar and the median nerves but not in the peroneal nerve. This latter finding has been likely influenced by the high prevalence of unrecordable CMAPs in the peroneal nerve that may have resulted in a floor effect.

Somewhat unexpectedly, we found that NCV increased with age of CMT1A patients. Consistently, DML decreased with age, even though only in the ulnar and peroneal nerves and not in the median nerve. The possible coexistence of a carpal tunnel syndrome, that is the most common entrapment neuropathy in the general population, may have influenced the lack of correlation for the median nerve.

It is of interest that although these findings have already been noted in previous reports [2,11], the current notion is that NCV does not significantly change through the life in CMT1A patients [7-9]. Birouk and colleagues found in their large sample of CMT1A patients that NCV increased with age and they interpreted the more evident lower NCV in younger patients as expression of early diagnosis in younger CMT1A patients due to their more severe symptoms [2]. However, the deterioration of clinical disability with age makes unlikely in our population that a more severe clinical impairment may have influenced the results of slower NCV in young patients. Therefore, we believe that our NCV findings can be rather expression of patients' age *per se*.

It is well known that NCV slowing in CMT1A reflects myelin abnormalities.

The NCV that is typically uniformly reduced and fully penetrant from the first years of life [4-6] supports the view that CMT1A may be mainly a dysmyelinating neuropathy rather than a demyelinating neuropathy. The latter is expected to cause temporal dispersion and conduction block, in addition to non-uniform and variable NCV slowing.

In keeping with such electrophysiological features, pathological evidence supports that a developmental abnormality in internode formation resulting in uniformly shortened internodes may

have a major role in NCV slowing in CMT1A [12,13]. Abnormalities of nodal-paranodal regions might play an additional role in NCV slowing but this remains to be determined [12,13].

In addition, altered myelin thickness provides a further explanation for NCV slowing in dys-myelinating neuropathies [14-18]. Experimental models showed that reduced expression of Neuregulin 1 (Nrg1), a master regulator of myelin thickness, causes a reduction of myelin thickness resulting in reduced NCV [16,17]. On the other hand, Fledrich and colleagues have observed that the overexpression of Nrg1 in CMT1A rats does not restore myelin sheath thickness and accordingly does not modify the impaired NCV [18].

Interestingly, an increased myelin sheath thickness (expressed as reduced g-ratio) has been demonstrated in sural nerve biopsies from young CMT1A patients [19-21]. At the same time, neuropathological data demonstrated that this myelin thickness tends to decrease (g-ratio increases) with age of patients [21,22].

All these data taken together might provide a possible explanation for the correlation between NCV and age of patients. The reduction of over-thick myelin that results in an improvement of g-ratio (toward its optimal value for conduction velocity) [23] could lead to an increase of NCV. However, NCV remains always markedly reduced in CMT1A patients, and this fits well with the shortened internodal lengths that persist stable through adult life [12,13].

Over-thick myelin is also a possible trigger for demyelination that might further influence NCV slowing. However, the increase of NCV and the lack of temporal dispersion suggest that de-remyelinating phenomena may be less relevant than other myelin abnormalities in the pathophysiology of NCV slowing in CMT1A. This also puts in question repetitive de-remyelination as the cause of onion bulbs that are a prominent pathological feature of CMT1A. Indeed, although onion bulbs occur in diseases that exhibit repeated de-remyelination (e.g. chronic inflammatory demyelinating neuropathy), our NCV findings are rather in keeping with the assumption that onion bulbs in CMT1A are expression of an altered Schwann cell differentiation that results in onion bulb-like arrangement of Schwann cells around the axon [24].

In conclusion, the strength of this study is the large sample of patients, though we are aware that much of the data we present especially with regards to changes with aging is cross sectional. A prospective study would be certainly more appropriate, but in practice difficult to do, in evaluating the changes of NCV over the life of patients. Longitudinal analysis of data from CMT-TRIAAL/CMT-TRAUK demonstrates that 2 years of follow-up are a too short time to detect changes of NCV in both treated and placebo group. However, in the ascorbic acid trial in a pediatric CMT1A cohort although there was not a statistical significance, a marked improvement of MNCV in the median nerve was observed in some patients treated with ascorbic acid [25]. This finding might indicate partial restoration of peripheral nerve myelin (e.g. myelin thickness) suggesting that NCV could represent, at least in children, a useful outcome in clinical trial in CMT1A.
Therefore, we believe that our observation offers additional insights into the pathophysiology of NCV slowing in CMT1A. The observed improvement of NCV, which anyway remains markedly reduced, highlights the role of myelin thickness remodeling in NCV changes. On the other hand, the reduced NCV, that represents the electrophysiological hallmark of CMT1A, may primarily reflect the abnormally developed shorter internodes.

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Figure 1

Scatterplot with correlation analysis between age and motor nerve conduction velocity (MNCV) of ulnar and median nerve.

Table 1. Correlation between electrophysiological and clinical data

Variables	Mean ± SD (range)	Normal values	Correlation with age *r* (*p* value)	Correlation with CMTES *rho* (*p* value)
DML (ms)				
Ulnar nerve (n = 261)	7.6 ± 1.7 (4-15.8)	≤ 3.3 ms (x 7 cm)	**- 0.2374 (<0.001)**	0.0840 (NS)
Median nerve (n = 255)	10.0 ± 2.1 (5.6-19.9)	≤ 4.1 ms (x 7 cm)	- 0.0571 (NS)	**0.2203 (<0.01)**
Peroneal nerve (n = 70)	10.9 ± 3.1 (6.3-20.7)	≤ 5 ms (x 9 cm)	**- 0.3657 (0.01)**	0.0816 (NS)
MNCV (m/sec)				
Ulnar nerve (n = 255)	19.8 ± 4.8 (4-33.6)	≥ 50 m/sec	**0.2779 (<0.0001)**	**- 0.1967 (0.01)**
Median nerve (n = 249)	21.0 ± 5.0 (5.2-38)	≥ 50 m/sec	**0.2531 (<0.001)**	- 0.1560 (NS)
Peroneal nerve (n = 70)	19.8 ± 4.9 (12-32.3)	≥ 41 m/sec	0.1852 (NS)	- 0.1452 (NS)
Mean MNCV	20.3 ± 4.5 (5.5-33.4)		**0.2975 (<0.0001)**	- 0.1552 (NS)
dCMAP (mV)				
Ulnar nerve (n = 268)	3.3 ± 2.0 (0-9.5)	≥ 5 mV	**- 0.1655 (0.03)**	**- 0.4250 (<0.0001)**
Median nerve (n = 268)	3.2 ± 2.2 (0-11.6)	≥ 5 mV	**- 0.3149 (<0.0001)**	**- 0.3590 (<0.0001)**
Peroneal nerve (n = 264)	0.2 ± 0.6 (0-5.2)	≥ 3 mV	- 0.1569 (NS)	**- 0.4297 (<0.0001)**
dCMAP summatory	6.7 ± 4.0 (0-19.2)		**- 0.2701 (<0.0001)**	**- 0.4339 (<0.0001)**
SAP (μV)				
Ulnar nerve (n = 267)	0.9 ± 2.3 (0-16)	≥ 6 μV	- 0.0316 (NS)	**- 0.1733 (0.01)**
SNCV (m/sec)				
Ulnar nerve (n = 45)	20.2 ± 4.9 (10.9-37.1)	≥ 50 m/sec	**0.3896 (0.02)**	- 0.2747 (NS)

CMTES = Charcot–Marie–Tooth Examination Score; DML = distal motor latency; MNCV/SNCV = motor/sensory nerve conduction velocity; dCMAP = distal compound motor action potential; SAP = sensory action potential; NA = not applicable; significant values are reported in bold.