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Review Article

CMT1A and T2DM versus CMT1A Alone: A Retrospective Comparison of Nerve Conduction Values and Terminal Latency Index

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Abstract

Objective: To investigate the effects of concurrent Charcot-Marie-Tooth type 1A (CMT1A) and type 2 Diabetes mellitus (T2DM) on median nerve conduction parameters and terminal latency index.

Design: Retrospective Chart Review

Setting: The Neuromuscular Disease Clinic at McMaster University Medical Centre.

Participants: From 80 cases of CMT1A identified in a database, 8 had concurrent T2DM, and of which 7 were analyzed for this study. One patient did not have nerve conduction parameters and was therefore excluded. A total of 20 age-matched CMT1A patients without T2DM were used for controls.

Main Outcome Measures: Median nerve conduction parameters including CMAP amplitude, conduction velocity and terminal motor latency were compared between our two groups. A median terminal latency index value was also calculated for all patients and compared between groups.

Results: Patients with CMT1A and T2DM had significantly lower CMAP amplitudes (5.24±0.76 mV vs. 2.60±1.01, $p<0.037$). Conduction velocity, terminal motor latency, and terminal latency index were similar

Conclusions: This study has demonstrated that the presence of T2DM in CMT1A patients is associated with reduced CMAP amplitudes with no effect on terminal latency index.

Keywords: Charcot-Marie-Tooth Disease; Diabetes Mellitus, Type 2; Neural Conduction

Abbreviations
CMT: Charcot-Marie-Tooth;
CMT1A: Charcot-Marie-Tooth type 1A;
T2DM: Type 2 Diabetes Mellitus;
CTS: Carpal Tunnel Syndrome;
MTLI: Median Terminal Latency Index ;
NCV: Nerve Conduction Velocity;
CMAP: Compound Muscle Action Potential;
TML: Terminal Motor Latency;
CMTNS: Charcot-Marie-Tooth Neuropathy Score

Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy (prevalence of 36:100 000) [1]. CMT type 1A (CMT1A) is the most frequently occurring dysmyelinating subtype (80%) and is caused by a duplication of PMP22 (peripheral myelin protein 22) on the short arm of chromosome 17[2,3]. While PMP22 is expressed primarily on Schwann cells, the progressive motor deficits reflect an evolving length-dependent axonopathy [4]. Most patients with CMT1A manifest distal weakness, sensory loss, and muscle atrophy affecting the lower extremities to a greater extent than the upper extremities, with proximal musculature rarely involved [4].

Type 2 Diabetes mellitus (T2DM) is a leading cause of neuropathy in the Western world [5]. The prevalence of neuropathy in type 2 diabetic patients may be as high as 45% [6]. Sensory loss is the most common manifestation, yet motor nerve impairment, such as distal weakness, can also occur. Several pathogenic mechanisms have been proposed to explain the axonal neuropathy of T2DM, but no single hypothesis has proven conclusive. Diagnosis of diabetic neuropathy may be based on presenting symptoms like paresthesias or painful dysesthesias (e.g. burning or tingling feet), unsteady gait, and postural instability, with co-existing hyperglycemia [5].

Despite CMT1A and T2DM being the most common causes of genetic and metabolic neuropathies, their coexistence is relatively rare. Therefore, patients manifesting both conditions offer a unique opportunity to examine potential interaction. The concept of "double-crush" neuropathy is relevant as these patients may develop median nerve entrapment neuropathy due to the genetic-metabolic interaction between CMT1A and T2DM [7]. Clinically, this may present with symptoms of carpal tunnel syndrome. We were unable; however, to find any studies that investigated entrapment neuropathy in patients with concomitant CMT1A and T2DM.

Median nerve terminal latency index (mTLI) has been shown to have a sensitivity of 90.1% in assessing carpal tunnel syndrome (CTS), and can show the effect on median nerve motor fibres in mild CTS cases [8]. We have evaluated the effects of T2DM on CMT1A with regards to electrophysiological parameters and mTLI to determine whether there is an increased propensity for axonopathy or entrapment neuropathy.

Methods

We conducted a retrospective review of a CMT database from the Neuromuscular Disorders Clinic at McMaster University. This database contains clinical and electrophysiological data on more than 300 patients with CMT, 80 of which have documented CMT1A confirmed through genetic testing. For the purposes of this study, only subjects with genetic confirmation of PMP22 duplication or a 1st degree relative with known CMT1A and nerve conduction values supporting a CMT1 diagnosis were included.

During the clinical intake process, the presence of diabetes was evaluated in all patients and confirmed by glucose testing if necessary. Within the database, there were a total of 8 patients with a concomitant diagnosis of CMT1A and T2DM. Unfortunately there was one patient for whom electro diagnostic values were not recorded and they were therefore excluded. For the purpose of comparison, we randomly selected age-matched, non-diabetic control patients with CMT1A (n=20; Group A). Group B consisted of the patients with both CMT1A and T2DM (n=7).

The Hamilton Integrated Research Ethics Board aproved this retrospective review.

Nerve Conduction

The nerve conduction velocity (NCV), compound muscle action potential (CMAP) amplitude, and terminal motor latency (TML) were recorded for various combinations of the ulnar, peroneal, tibial, sural and median nerves. Temperature was maintained at 34^0C in the hands and feet for all visits. Surface electrodes were used in all studies. Nerve conduction data pertaining to the median nerve was collected most consistently among patients and was thus extracted for the purpose of this study. When data was available for both median nerves, the nerve with the lowest conduction velocity was used.

Median nerve terminal latency index (mTLI) was calculated based on the formula used by Uzar et al as follows:

mTLI = distal distance (mm)/(mNCV (m/s) x mTML (ms))

Statistical Analysis

Statistical analysis was performed using Microsoft Excel (2007). Categories for each group were compared using their means and reported with standard error of the means. Statistical significance was evaluated using a single-tailed, paired T-Test.

Results

Cohort Age

The mean age for Group A was 48.70±2.71 and for Group B was 51.00±7.84 ($p<0.362$).

Nerve Conduction Parameters

The mean median nerve conduction velocity in Group A was 21.98±2.03 m/s versus 20.71±1.39 m/s in Group B ($p<0.363$). The mean median nerve terminal motor latency was 10.08±0.65 ms versus 9.96±1.00 ms for Groups A and B respectively ($p<0.463$). Neither of these nerve conduc-

nerve conduction parameters showed a difference between the two groups that met statistical significance. The median nerve compound muscle action potential amplitude for Group A was 5.24±0.76 mV versus 2.60±1.01 mV for Group B. This was a significant difference (p<0.037).

Terminal Latency Index

As previously described, the median nerve terminal latency index was calculated for each patient in both groups. The mean for Group A was 0.420±0.03 and the mean for Group B was 0.434±0.07. There was no significant difference noted between the two groups (p<0.402).

Table 1. Comparison of median nerve electrophysiological parameters and terminal latency index between CMT1A patients with and without diabetes.

	CMT1A (N=20)	CMT1A + T2DM (N=7)	P value
NCV	21.98±2.03	20.71±1.39	0.363
TML	10.08±0.65	9.96±1.00	0.463
CMAP	5.24±0.76	2.60±1.01	**0.037**
TLI	0.420±0.03	0.434±0.07	0.402

CMT1A-Charcot-Marie-Tooth disease type 1A; T2DM-Type 2 Diabetes Mellitus; NCV-Nerve Conduction Velocity; CMAP-Compound Muscle Action Potentials; TML-Terminal Motor Latency; TLI-Terminal Latency Index.

Discussion

This retrospective database analysis of patients with CMT1A has demonstrated that peripheral neuropathy is more severe in diabetic patients with CMT1A than in those without diabetes. Significant decreases were identified in CMAP amplitude in patients with both CMT1A and T2DM, and no significant differences in conduction velocity or terminal motor latency. Given the decreased amplitudes, this suggests a more advanced axonal loss in patients with both CMT1A and T2DM than patients with CMT1A alone [9,10]. These observations indicate the importance of close glycemic monitoring of CMT1A patients, and also pose further questions on the pathogenic mechanisms present with these two diseases.

There is a growing body of evidence investigating the additive effect of T2DM on CMT1A. Sheth et al. used a composite score, the CMT neuropathy score (CMTNS), which involved history, neurological examination, and clinical neurophysiological information. Their study yielded a significant increase in CMTNS in patients with T2DM and CMT1A versus CMT1A controls. They found a trend for CMT1A patients with diabetes to have low compound muscle action potential amplitudes and sensory nerve action potentials, although these did not reach statistical significance. Despite these amplitude differences there was no significant difference in nerve conduction velocities between the two groups [9]. Ursino et al investigated the influence of medical comorbidities on CMT1A patients. Their results supported previous findings of increased CMTNS scores in patients with T2DM as well as decreased CMAP amplitudes but no effect on motor nerve conduction velocities [10]. The results of this study are in keeping with the previous retrospective Treviews by both Sheth et al and Ursino et al.

In their study of median terminal latency index in carpal tunnel syndrome, Simovic and Weinberg summarized normative data from previous studies and found a normal mTLI to be ≥0.34 [11]. Our study found no significant difference in the median nerve terminal latency index between the two groups. In our groups, mTLI means were 0.420±0.03 and 0.434±0.07, suggesting that neither group met the criteria for median nerve entrapment. The concept of an axonal double crush is borne out by our results; however, this does not appear to be the case at the most common site of entrapment. We postulate whether this could be because individuals with CMT are less likely to engage in repetitive activities. Furthermore, it is not known if, for a given volume of repetitive hand-based work, CMT patients are more vulnerable to developing median nerve dysfunction at the carpal tunnel.

There have been many proposed mechanisms for diagnosing median nerve entrapment using electrodiagnostic parameters [12]. These include, but are not limited to, prolonged median motor distal latency, median-ulnar latency comparisons, and sensory latency differentials [12]. As evidenced by our data set, the terminal motor latencies of patients with demyelinating peripheral neuropathies may be significantly prolonged. This makes previously determined standard values difficult to use in the diagnosis of median nerve entrapment with concomitant demyelinating neuropathy. Terminal latency index, calculated from distal motor latency, distal distance and proximal motor conduction velocities, are electrophysiological parameters used to identify abnormalities in the distal segment of the motor nerve [8]. The proximal velocity dictates the expected latency through the terminal segment such that the slower the forearm conduction velocity, the longer the expected terminal motor latency. Therefore, only when the TML is more prolonged than expected based on the forearm velocity, do we invoke additional pathology at the carpal tunnel. When there is a demyelinating neuropathy, we propose that traditional methods of diagnosis using standard values for terminal motor latency or proximal segment conduction velocity may be inaccurate. To our knowledge, there have not been any studies to develop a set of expected terminal motor latencies in patients with demyelinating disease. This may represent an area of potential future research.

Study Limitations

A potential confounding variable was that our sample size for Group B was seven patients, which we recognize to be small, yet similar studies have also produced similarly small sample sizes due to the rareness of this condition. Unfortunately, we do not have historical or physical examination data pertaining specifically to symptoms of carpal tunnel syndrome in our patient groups. We also acknowledge that because this was a retrospective review of patients with CMT1A from our database, that we lack a

control group with age-matched T2DM without CMT1A. Our results were obtained retrospectively and will need to be confirmed in a larger prospective study. Following CMT1A patients who subsequently develop T2DM will allow for measuring of the changes in various nerve function parameters on an individual basis and possibly help to further clarify the pathophysiologic mechanisms involved.

Conclusions

Patients with CMT1A and T2DM show signs of more severe neuropathy than patients with CMT1A alone. This is manifested in decreased CMAP amplitudes, suggesting further axonal loss. There was no difference in median terminal latency index values, terminal motor latency, or conduction velocity between the two groups. Further research is needed to elicit mechanisms for nerve destruction in diabetic neuropathy and the interaction with dysmyelinating neuropathies. Further research is also needed to develop a set of reference values for patients with dysmyelinating hereditary neuropathies.

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