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Journal of the Chinese Medical Association 75 (2012) 197–202

www.jcma-online.com

Original Article

Electrophysiological characterization of Charcot–Marie–Tooth disease type 1A in Taiwan

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Received August 31, 2011; accepted December 16, 2011

Abstract

Background: Charcot–Marie–Tooth disease type 1A (CMT1A) is the most common type of hereditary neuropathy. The demyelinating pathology of CMT1A results in significant nerve conduction slowing such that a nerve conduction study (NCS) is important in the clinical assessment of CMT1A. In this study, we analyzed and reported the electrophysiological features of a large Taiwanese cohort with CMT1A.

Methods: We retrospectively analyzed the NCS data of 106 Taiwanese patients with CMT1A. We also compared the electrophysiological parameters of the CMT1A patients with those of 20 patients with early-onset Charcot–Marie–Tooth disease type 1B (CMT1B).

Results: The patients with CMT1A had a significant but variable degree of slowed nerve conduction. The median motor nerve conduction velocities (MNCVs) varied from 10.0 to 37.3 m/s in the entire CMT1A cohort but were more concordant in patients within a family ($p < 0.001$). In each patient, the MNCVs among different nerves were concordant ($p < 0.001$), and the MNCVs tended to remain steady longitudinally. Moreover, younger patients had a slower MNCV than older patients within the CMT1A population ($p < 0.001$). The average median MNCV was significantly faster in the CMT1A patients than in the CMT1B patients (21.8 ± 6.2 m/s and 16.3 ± 3.6 m/s; $p < 0.001$).

Conclusion: This study provides basic electrophysiological knowledge about CMT1A in Taiwan. The findings also suggest that the electrophysiological variability in the CMT1A cohort may be at least partially attributable to unknown genetic factors. These data emphasize the role of MNCV in the clinical assessment of CMT1A. A median or ulnar MNCV below 38 m/s can be a sensitive criterion for supporting the diagnosis of CMT1A. A median MNCV can sometimes help to distinguish CMT1A from CMT1B, and CMT1A should be considered in patients with median MNCVs near or above 24 m/s. Moreover, the MNCV may to some degree reflect the severity of CMT1A.

Keywords: Charcot–Marie–Tooth disease; CMT1A; CMT1B; nerve conduction study

1. Introduction

Charcot–Marie–Tooth (CMT) disease, also called hereditary motor and sensory neuropathy, is the most common hereditary peripheral neuropathy, with an estimated prevalence of one in 2500.[1] The syndrome was first described by Jean-Martin Charcot and Pierre Marie in France and Henry Howard Tooth in England in 1886. The characteristic features include progressive distal muscle atrophy and weakness, decreased sensation, depressed tendon reflexes, and foot deformities.

The syndrome can be further classified according to the age at disease onset, inheritance patterns, and electrophysiological or pathological features. CMT type 1 (CMT1) is the most common type and consists of a genetically heterogeneous group

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1726-4901/$ - see front matter
doi:10.1016/j.jcma.2012.03.005

of autosomal dominant demyelinating neuropathies. Among them, CMT1A is the most frequent subtype, 53.6–70.7% of CMT patients belonging to the CMT1A group.[2–4] CMT1A is caused by a 1.5-Mb DNA duplication on chromosome 17p11.2–12 that includes the peripheral myelin protein 22 gene (*PMP22*).[5,6] CMT type 1B (CMT1B), another rarer type of CMT1, results from a mutation in the myelin protein zero gene (*MPZ*).[7]

Nerve conduction studies (NCSs) play an important role in diagnosing and assessing the severity of CMT1A. Patients with CMT1A usually have a median motor nerve conduction velocity (MNCV) of less than 38 m/s,[8] and slowing of nerve conduction can perfectly distinguish CMT1A patients from those that are unaffected.[9] Moreover, the muscle wasting and weakness seen in CMT1A patients can correlate well with compound muscle action potential (CMAP) amplitudes;[10] thus, NCSs can be used to monitor the clinical severity of CMT1A.

It is interesting that CMAP rather than MNCV correlates well with motor function in CMT1A patients.[10] This suggests that their disability might come from secondary axonal damage rather than demyelination,[11,12] although the principal neuropathological change in CMT1A is peripheral demyelination. The NCVs in patients with CMT1A are usually maximally slowed before age 5 years,[10] and precede the onset of weakness, also suggesting that demyelination is not the major determinant of disability in CMT1A.

Because a large degree of phenotypic variation is common in CMT1, NCSs may be more helpful than clinical examination in identifying CMT1A. Although NCSs play an important role in the clinical survey of CMT1A, there are as yet no referenced electrophysiological data on CMT1A in the Taiwanese population or other Chinese populations. In this study, we characterize and report the electrophysiological features of a large Taiwanese CMT1A cohort of Han-Chinese origin.

2. Methods

2.1. Subjects

We retrospectively analyzed the demographic and NCS data of a consecutive series of 106 Taiwanese patients of Han-Chinese origin with CMT1A that had been recruited in the previous 20 years from the Neurology Service, Taipei Veterans General Hospital, Taiwan. These 106 patients with CMT1A came from 81 families, and all underwent NCS at least once. All of the patients harbored a duplication of the 1.5-Mb DNA region on chromosome 17p11.2, as demonstrated by the short tandem repeat polymerase chain reaction method.[13] Twenty patients with *MPZ* mutations were enrolled as the CMT1B group, and most of these subjects had previously been described in an earlier study.[14]

NCSs were performed by standard techniques utilizing a Medelec MS25 electromyograph (Mistro, Surrey, U.K.) with surface electrode stimulations and recordings.[15] Distal and proximal motor latencies and CMAP amplitudes were recorded from the median, ulnar, peroneal, and tibial nerves in the subjects studied. Sensory nerve action potential (SNAP) amplitudes and distal latencies (DLs) were recorded from the median, ulnar, and sural nerves. NCVs were calculated by standard techniques. NCS data from the first study performed with the patients who underwent NCS more than once were included in our statistical analysis. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2011-06-17IC).

2.2. Statistical analysis

The mean and standard deviation of each electrophysiological parameter (DL, MNCV, and CMAP amplitude) were calculated for the median, ulnar, peroneal, and tibial nerves. For the patients with CMT1A, the MNCV and CMAP amplitudes of the median and ulnar nerves were compared between men and women using Student *t* tests. The CMT1A patients were further divided into two groups based on the cut-off value of 20 years of age. The MNCV and CMAP amplitudes of the median and ulnar nerves were then compared between the subjects older and younger than 20 years of age using Student *t* tests. Seven subjects underwent two NCSs at longitudinal follow-ups. The median MNCVs of each subject at follow-up and at the first visit were compared using the Wilcoxon signed rank test. The associations between age and MNCVs or CMAP amplitudes of different nerves were analyzed by Pearson's correlation. Similarly, we evaluated the relationships between median MNCVs and ulnar MNCVs, as well as between median and peroneal MNCVs.

Among the 106 CMT1A patients, 42 were consanguinities recruited from 17 families. We then compared the median MNCVs of the index case and the data of their relatives from the same family using Pearson's correlation. We also compared the electrophysiological data of the patients with CMT1A with those of the 20 patients with CMT1B using Student *t* tests. All of the statistical analyses were performed with Predictive Analytics Suite Workstation (PASW) statistics, version 18.0.0 (SPSS Inc., Chicago, IL, USA). A two-tailed $p < 0.05$ was defined as statistically significant.

3. Results

3.1. General findings

We analyzed the NCS data of the 106 patients with CMT1A. Fifty-three patients (50%) were male, and the mean age at examination was 39.58 ± 18.13 years (range 3–81 years). Eleven patients underwent more than one NCS (time interval 6–93 months). For the patients receiving multiple NCS examinations, the first NCS dataset was used for statistical analysis.

The median MNCV, CMAP amplitude, and motor latencies were the most frequently detectable electrophysiological parameters (95.28%), and the median MNCVs of the 106 CMT1A patients were all below 38 m/s (range 10.0–37.3 m/s). The MNCVs, CMAP amplitudes, and motor DLs of our study participants are shown in Table 1. The SNAP amplitudes were

Table 1
Motor nerve conduction findings in 106 patients with Charcot–Marie–Tooth disease type 1A.

	Range	Mean ± SD	Normal value
Median nerve ($n = 101$, undetectable = 5)			
DL (ms)	7.00–19.30	11.14 ± 2.14	< 4.80
MNCV (m/s)	10.00–37.30	21.76 ± 6.15	> 50.70
CMAP (mV)	0.10–10.00	3.83 ± 2.35	> 5.70
Ulnar nerve ($n = 98$, undetectable = 8)			
DL (ms)	4.80–17.50	8.26 ± 2.05	< 3.45
MNCV (m/s)	7.40–36.80	20.00 ± 5.57	> 46.70
CMAP (mV)	0.20–8.00	3.63 ± 1.85	> 6.00
Peroneal nerve ($n = 38$, undetectable = 68)			
DL (ms)	6.40–24.10	10.90 ± 3.36	< 6.00
MNCV (m/s)	9.60–28.20	18.54 ± 4.90	> 42.00
CMAP (mV)	0.10–3.50	1.13 ± 0.96	> 1.70
Tibial nerve ($n = 58$, undetectable = 48)			
DL (ms)	5.70–17.30	9.41 ± 2.83	< 7.10
MNCV (m/s)	11.40–33.70	20.57 ± 5.59	> 41.50
CMAP (mV)	0.10–6.60	1.62 ± 1.65	> 3.50

CMAP = compound muscle action potential; DL = distal latency; MNCV = motor nerve conduction velocity; SD = standard deviation.

abnormal in all patients, and they were undetectable in the median and ulnar nerves of 100 patients (95.24%). In the remaining five patients, the sensory DLs were 7.96 ± 1.94 ms in the median nerves and 8.83 ± 3.68 ms in the ulnar nerves, and the SNAP amplitudes were 2.34 ± 2.21 mcV in the median nerves and 5.53 ± 2.30 mcV in the ulnar nerves. The sural nerve SNAP amplitudes could not be determined in 105 patients (99.06%).

The median MNCV was significantly correlated to the ulnar or peroneal MNCV ($r = 0.835$ and 0.795, respectively; $p < 0.001$), indicating that the median MNCV was concordant with the ulnar or peroneal MNCV in CMT1A.

3.2. Gender

There was no significant difference in the MNCV and CMAP amplitudes for the median and ulnar nerves between the male and female patients (median MNCV, $p = 0.593$; median CMAP amplitudes, $p = 0.978$; ulnar MNCV, $p = 0.409$; ulnar CMAP amplitudes, $p = 0.903$).

3.3. Age at examination

The median and ulnar MNCVs positively correlated with patient age at the time of the NCS examinations ($r = 0.331$ and 0.471, respectively; $p \leq 0.001$; Fig. 1A). The CMAP amplitudes at the median nerves had an inverse relationship with age ($r = -0.267$, $p = 0.008$), while the ulnar CMAP amplitudes did not significantly correlate with age ($r = -0.045$, $p = 0.664$; Fig. 1B). We used an age of 20 years to dichotomize our patients into younger and older groups. The median and ulnar MNCVs were significantly lower in the younger group ($p \leq 0.001$; Table 2). However, there was no significant difference in the median and ulnar CMAP amplitudes between the two groups.

3.4. Longitudinal electrophysiological change

Eleven patients had more than one NCS (with time intervals from 6 to 93 months), and only seven of them had a detectable MNCV on two different NCS assessments. There were no significant longitudinal changes in the median MNCV and CMAP amplitudes of these seven patients in the two examinations ($p = 0.6$ and 0.735, respectively).

3.5. Intrafamilial electrophysiological variation

Forty-two patients from 17 families had at least one relative who also participated in this study. Three patients were excluded because their median MNCVs were undetectable. The mean median MNCV in the 16 families was 22.59 ± 6.02 m/s (range 11.3–34.7 m/s). Among each family, the average variation of the median MNCV was 3.15 ± 2.54 m/s (range 0.4–9.17 m/s). In spite of a small degree of intrafamilial variation, there was a moderate correlation ($r = 0.76$) between the median MNCVs of subjects from the same family ($p < 0.001$; Fig. 2).

3.6. Comparison with CMT1B patients

We compared the NCS parameters of the CMT1A patients with those of the 20 CMT1B subjects from our population. All those patients harboring *MPZ* mutations had early-onset neuropathy.[16] The comparison between CMT1A and CMT1B is shown in Table 3. Compared with the patients with CMT1B, the MNCVs of the median and ulnar nerves were significantly higher in patients with CMT1A ($p \leq 0.001$; Fig. 3).

4. Discussion

In this study, we performed an electrophysiological analysis of 106 patients with CMT1A and found that all of them had a significant but variable degree of slowed nerve conduction. The median MNCVs varied from 10.0 to 37.3 m/s in the whole CMT1A cohort, but were more concordant in patients within a family. In each patient, there was a concordance between different nerve MNCVs, and the MNCVs tended to remain steady longitudinally. Moreover, within the CMT1A population, younger patients had slower NCVs than older patients. Further, early-onset patients with CMT1B usually had lower median MNCVs than those with CMT1A. These findings may have the following implications.

First, the median or ulnar MNCV can be a sensitive parameter to support the diagnosis of CMT1A. Theoretically, CMT1A is a generalized demyelinating neuropathy with a uniform slowing of conduction, but in clinical practice not all nerve conduction is detectable. In our study, all the nerves of the 106 CMT1A patients had significantly decreased NCVs, but in many cases sensory or motor nerve conduction could not be appropriately elicited. Among the nerves

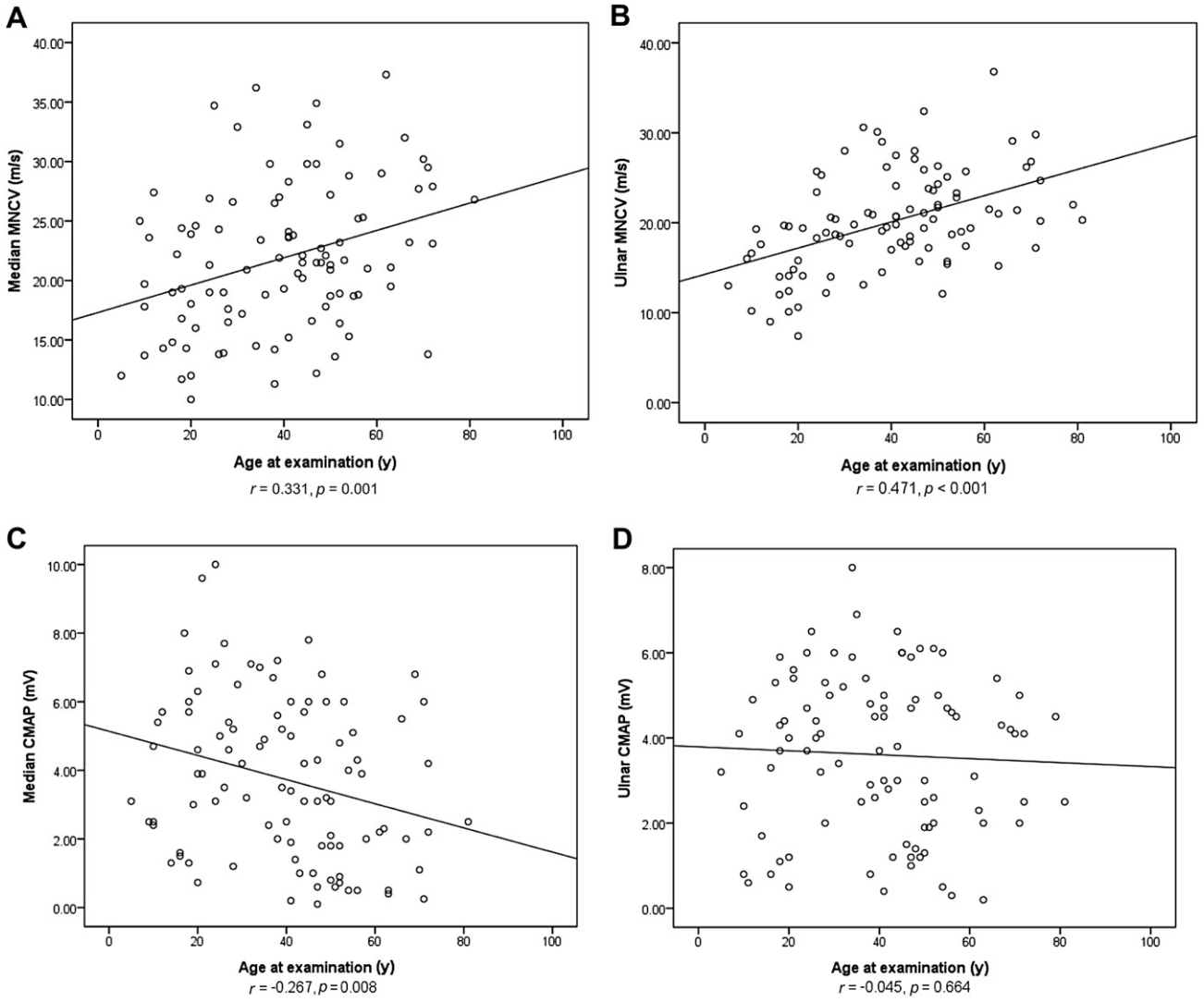

Fig. 1. Scatter plot diagrams with Pearson's correlation analysis between the age at examination and the median and ulnar MNCVs (A, B) and median and ulnar CMAP amplitudes (C, D). CMAP = compound muscle action potential; MNCV = motor nerve conduction velocity.

investigated in the clinical routine, only motor conduction for the median or ulnar nerve could be detected in more than 90% of the CMT1A patients, and the median or ulnar MNCVs were all below 38 m/s. The normal lower limits of median or ulnar MNCVs in our electromyography laboratory were 50.7 and 46.7 m/s, respectively. The diagnosis of CMT1A could be

Table 2
Electrophysiological comparison between two age groups.

	Younger group (≤ 20 years old)	Older group (> 20 years old)	*p*
Number of patients	22	84	
Median MNCV (m/s)	18.00 ± 5.13	22.83 ± 6.05	0.001*
Ulnar MNCV (m/s)	14.01 ± 3.73	21.53 ± 4.92	< 0.001*
Median CMAP (mV)	3.86 ± 2.15	3.72 ± 2.39	0.822
Ulnar CMAP (mV)	2.90 ± 1.79	3.77 ± 1.83	0.075

Data are shown as mean ± standard deviation.
*A $p \leq 0.05$ was statistically significant.
CMAP = compound muscle action potential; MNCV = motor nerve conduction velocity.

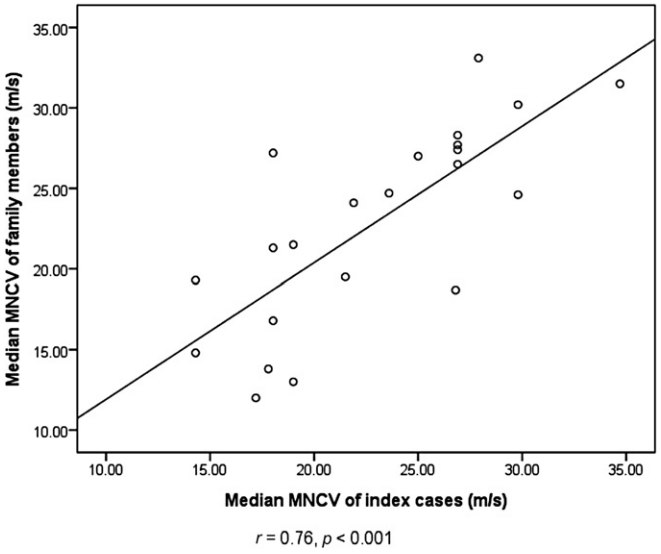

Fig. 2. The correlation of the median motor nerve conduction velocity (MNCV) between index cases and family members.

Table 3
Comparison between patients with Charcot–Marie–Tooth type 1A disease (CMT1A) with 17p11.2 duplication and early-onset type 1B disease (CMT1B) with *MPZ* mutation.

	CMT1A	CMT1B	*p*
Number of patients	106	20	
Age at examination	39.58 ± 18.13 (3–81)	36.15 ± 17.61 (9–77)	0.438
Median MNCV (m/s)	21.76 ± 6.15 (10.00–37.30)	16.28 ± 3.59 (8.90–24.00)	< 0.001*
Ulnar MNCV (m/s)	20.00 ± 5.57 (7.40–36.80)	15.49 ± 3.22 (9.40–23.30)	< 0.001*
Median CMAP (mV)	3.83 ± 2.35 (0.10–10.00)	3.93 ± 2.25 (0.40–9.80)	0.869
Ulnar CMAP (mV)	3.63 ± 1.85 (0.20–8.00)	3.34 ± 1.73 (0.2–6.4)	0.535

Data are shown as the mean ± standard deviation. Numbers in parentheses refer to ranges.
*A $p \leq 0.05$ was statistically significant.
CMAP = compound muscle action potential; MNCV = motor nerve conduction velocity.

excluded if the median or ulnar MNCV was greater than 38 m/s.

Second, NCVs in patients with CMT1A are also modified by other genetic factors in addition to the *PMP22* duplication. In addition to significantly slowed nerve conduction, a highly individual variation in NCVs was reported in several different CMT1A populations.[9,17] Our study revealed that NCVs in patients from the same family tended to be concordant despite a high variation between NCVs across the entire CMT1A population. Consequently, this suggests that NCV slowing is not solely determined by *PMP22* duplication, but is also modified by other genetic factors shared by the same family. Further study to identify these NCV-modifying genes in CMT1A might increase the knowledge of the pathophysiology of CMT1A and increase the options for developing new therapeutic strategies.

Third, the MNCVs may reflect the severity of the congenital myelin defects in the patients with CMT1A. Our study showed that MNCVs in patients with CMT1A tended to remain the same longitudinally, a phenomenon that has also been reported in CMT1A patients in other populations.[18–20]

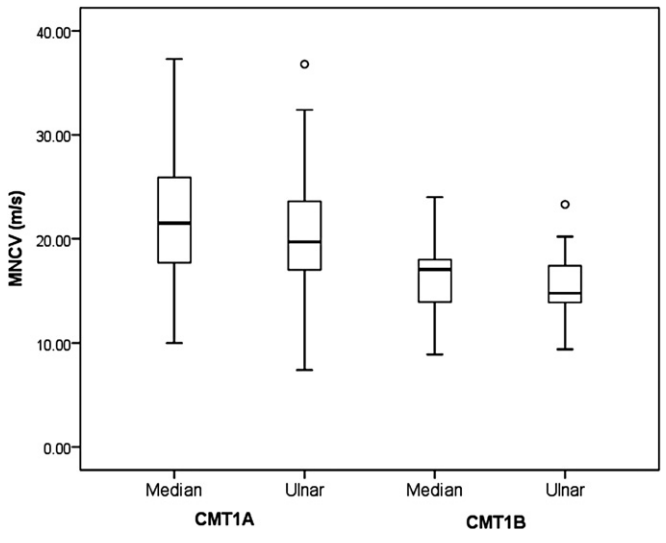

Fig. 3. The distribution of median and ulnar motor nerve conduction velocity (MNCV) in patients with Charcot–Marie–Tooth disease type 1A (CMT1A) and 1B (CMT1B). The means of the median and ulnar MNCVs in CMT1A patients were significantly higher than those in CMT1B patients. The box blot shows the median and the 1st and 3rd quartiles. The circles denote outliers.

Myelin plays an essential role in facilitating nerve conduction. Thus, the steady MNCV values could be representative of the intactness of the myelin. Although we do not have in this retrospective study precise data addressing patient age when clinical onset occurred, the patient age at the first NCS could be positively correlated to the age at clinical onset because patients with an earlier onset often sought medical help and underwent NCS earlier than those who had a later onset. Therefore, a lower MNCV in younger patients with CMT1A in our study could be interpreted as "CMT1A patients with an earlier clinical onset have lower MNCVs." In addition to an earlier clinical onset, a lower median MNCV is also associated with a more severe disease course.[17,18,21]

Compared with patients with CMT1A, those with early-onset CMT1B usually had lower MNCVs. The means of the median and ulnar MNCVs of the CMT1B patients were significantly lower than those of the CMT1A patients in our study, which was consistent with previous reports.[18,22] The ranges of the median MNCVs of our CMT1A and CMT1B patients were 10–37.3 m/s and 8.9–24 m/s, respectively. Therefore, CMT1B should be considered first in the CMT1 patients with median MNCVs near or below 10 m/s, and CMT1A should be considered in CMT1 patients with median MNCVs near or above 24 m/s in patients of Han-Chinese origin.

In conclusion, we analyzed and reported the electrophysiological features of a large Taiwanese cohort with CMT1A. In addition to providing basic knowledge on CMT1A in our population, our findings also suggest that unknown genetic factors may modify CMT1A, and emphasize the role of MNCVs in the clinical assessment of CMT1A as follows: a median or ulnar MNCV below 38 m/s can be a sensitive criterion for supporting the diagnosis of CMT1A, a median MNCV can sometimes help to distinguish CMT1A from CMT1B, and the MNCV may reflect the severity of CMT1A.

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