

Analysis of compound muscle action potential in patients with chronic inflammatory demyelinating polyneuropathy and Charcot-Marie-Tooth disease type 1A

Onur Akan^{1*}, Canan Emir¹

¹ Dept. of Neurology, University of Health Sciences, Prof.Dr. Cemil Taşcıoğlu City Hospital, Istanbul, TR

* Corresponding Author: Onur Akan E-mail: dronurakan@hotmail.com

ABSTRACT

Objective: To provide an additional contribution to the differential diagnosis of Charcot-Marie-Tooth disease type 1A (CMT1A) and chronic inflammatory demyelinating polyneuropathy (CIDP) by analyzing distal duration and proximal/distal amplitude and duration ratios on different nerves in these diseases that show demyelinating peripheral neuropathy features.

Material and Methods: We retrospectively reviewed the electromyography (EMG) findings of patients aged 18-80 years who were followed up with a diagnosis of acquired and hereditary demyelinating type polyneuropathy in the neuromuscular diseases outpatient clinic in our center. We analyzed the distal CMAP duration and amplitude, proximal and distal compound muscle action potential, and duration ratios on each nerve in the patient groups, separately.

Results: The CIDP group had significantly longer Peroneal nerve distal duration than the CMT1A group ($p=0.04$). Median, ulnar, and tibial nerve distal durations were similar between the groups ($p=0.84$, $p=0.86$, and $p=0.13$, respectively). The median nerve, ulnar nerve, and peroneal nerve proximal/distal amplitude ratios were not different between the CMT1A and CIDP groups ($p=0.99$, $p=0.38$, and $p=0.16$, respectively). The tibial nerve proximal/distal amplitude ratio in the CIDP group was lower than in the CMT1A group ($p=0.003$). Median, ulnar, peroneal, and tibial nerve proximal/distal duration ratios were statistically similar among the groups ($p=0.21$, $p=0.66$, $p=0.62$, and $p=0.46$, respectively).

Conclusion: This study may help to improve the management of challenging patients where there is an overlap between hereditary and inflammatory neuropathies. The different electrodiagnostic models of various acquired and hereditary demyelinating polyneuropathies should be clinically recognized.

Keywords: Compound muscle action potential, Duration, Demyelinating polyneuropathy

Research Article

Received 31-01-2020

Accepted 15-02-2021

Available Online: 17-02-2021

Published 24-02-2021

Distributed under
Creative Commons CC-BY-NC 4.0

OPEN ACCESS



INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune-induced, demyelinating polyneuropathy (PNP) with a chronic progressive nature, or relapses and remissions. The basic pathology is the removal of myelin from axons via macrophages, the most striking feature of which is multifocal demyelination. However, type, the number, and the location of demyelinating lesions vary between CIDP subgroups and patients (1). Charcot-Marie-Tooth (CMT) disease, i.e. hereditary sensory and motor neuropathies, includes genetically heterogeneous hereditary neuropathies among which CMT1A is the most common form with autosomal dominant inheritance, and duplication in 17 p11.2-12 regions encoded by the peripheral myelin protein 22 (PMP 22) genes cause the disease. The classic clinical picture is distal muscle weakness that begins in childhood or adolescence and progresses slowly. However, cases can occur in adulthood.

Despite the guidance of family history and clinical findings, difficulties may be experienced in the differential diagnosis of hereditary motor sensory neuropathies with CIDP (2, 3).

Electromyography (EMG) helps in the diagnosis of PNP by detecting findings specific to acquired demyelinating neuropathies, showing that nerves, and especially myelin sheaths, are affected in most cases.

However, 48-64% of patients with CIDP may not show typical signs such as segmental conduction slowdown, or severely prolonged terminal latency, or conduction blocks. CMT cases with nerve conduction blocks have also been reported, albeit rarely.

In this study, distal duration and proximal/distal amplitude ratios on different nerves were analyzed in nerve conduction studies in CIDP and CMT1A patient groups showing major demyelinating peripheral neuropathy features, and it was aimed to examine the electrophysiologic features that made an additional contribution to the differential diagnosis of these diseases.

For this purpose, we hypothesized that distal duration and proximal/distal amplitude ratios would differ from the hereditary polyneuropathy group in patients with acquired polyneuropathy.

MATERIAL AND METHODS

The EMG findings of those at age of 18-80 years who were followed up with a diagnosis of acquired and hereditary demyelinating type PNP, whose diagnoses were established through clinical, genetic, and advanced laboratory examinations in the neuromuscular diseases outpatient clinic in our center, were retrospectively analyzed. The diagnosis of all cases of CMT1A was genetically confirmed.

The diagnosis of CIDP was made according to nerve conduction studies, cerebrospinal fluid (CSF) examination, and clinical features after the clinical criteria of EFNS/PNS (4). Those with toxin exposure, vitamin B12 deficiency, and diabetic PNP, uremic PNP, and additional systemic diseases were not included in the study. Ethics committee approval was obtained before the study (Decision number: 2.04.2019 / 1230).

In the electrophysiologic examination, the motor responses obtained using standard supramaximal stimulation techniques and the superficial electrode of each participant were evaluated.

The proximal and distal CMAP, which were recorded using standard methods, of the median nerve with the abductor pollicis brevis, the ulnar nerve with the abductor digiti minimi, the tibial nerve with the abductor hallucis, and the peroneal nerve with the external digitorum brevis, were retrospectively reviewed.

The baseline to the negative peak value was defined as the amplitude value. Duration of CMAP was accepted as the negative peak duration at 500 mV sensitivity. Distal CMAP duration, proximal and distal CMAP ratios were analyzed separately in the examined nerves.

Ratios of distal and proximal amplitude were determined as the ratio of CMAP amplitude (mV) of elbow stimulation / CMAP amplitude (mV) of wrist stimulation for median and ulnar nerves, and the ratio of CMAP amplitude (mV) of knee stimulation / CMAP amplitude (mV) of ankle stimulation for peroneal and tibial nerves. Proximal and distal t duration ratios were similarly calculated by proportioning the proximal CMAP duration to the duration of distal CMAP in each nerve.

Statistical Analyses

In the study, the statistical analysis was done using SPSS 22.0 program (Chicago, IL). The Kolmogorov-Smirnov test was used to see if the data complied with normal distribution, and the analysis of correlations between numerical variables was evaluated using Pearson's correlation test. Descriptive results for variables with normal distribution are expressed as mean±standard deviation (SD).

The t-test and/or the Mann-Whitney U test were used to evaluate differences between groups. Categorical variables are expressed as ratios and percentages. The results were compared using the Chi-square test. $p < 0.05$ showed statistically significance in all tests.

RESULTS

A total of 22 patients with CMT1A and 26 with CIDP participated in the study. The 22 patients with CMT1A were aged between 18 and 80 years, 13 were female and nine were male. The mean disease duration was 7.5 ± 6.2 (range, 1-26) years, and the meantime from the onset of symptoms to diagnosis was 5.72 ± 6.67 (range, 1-28) years. The 24 patients CIDP were aged between 19 and 78 years, eight were female and 16 were male. The mean disease duration was 8.6 ± 6.1 (range, 1-26) years, the mean age at disease diagnosis was 49.8 ± 15.4 (range, 18-76) years, and the meantime from the onset of symptoms to diagnosis was 4.8 ± 4.6 (range, 1-15) years.

When the sex distribution, age, age during diagnosis, duration of the disease, and the interval between the start of symptoms and the diagnosis were compared, the CMT1A and CIDP groups showed no statistically significant difference ($p > 0.05$) (Table 1).

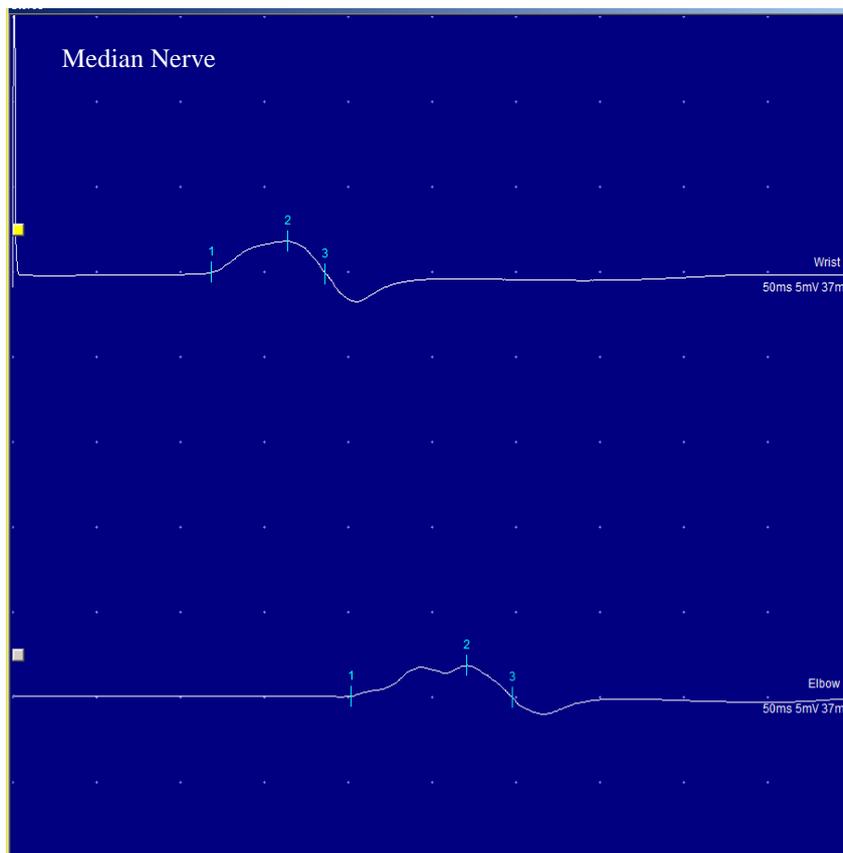
the CMT1A and CIDP groups did not show a difference in the ulnar, median, and peroneal nerve proximal/distal amplitude ratios, but the tibial nerve proximal/distal amplitude ratio was statistically lower in the CIDP group compared with the CMT1A group ($p=0.99$, $p=0.38$ $p=0.16$, and $p=0.003$, respectively).

Ulnar, median, tibial, peroneal and nerve proximal/distal duration ratios were statistically similar among the patient groups ($p=0.21$, $p=0.66$, $p=0.62$, and $p=0.46$, respectively). Motor response examples of the ulnar nerve, the median nerve, peroneal nerve, and tibial nerve in patients with CMT1A and CIDP are shown in Figures 1 and 2.

Table 1: Demographic features and EMG measurements of the CMT1A and CIDP groups

Parameter	CMT1A (n=22)	CIDP (n=26)	P
Age (years)	47.9±16.4	55±15.2	0.11
Sex			0.08
Female	13	8	
Male	9	18	
The time passed between symptom onset and diagnosis (years)	5.72±6.7	4.84±4.6	0.65
Age during diagnosis (years)	44.4±17.5	49.8±15.4	0.26
Disease duration (years)	7.5±6.3	8.9±6.2	0.39
Distal duration (mean)			
Median nerve	6.6 ±1.66	6.71±2.01	0.84
Ulnar nerve	7.21±1.51	7.23±1.02	0.86
Tibial nerve	4.85±2.94	7.99±4.86	0.13
Peroneal nerve	4.28±2.2	7.03±1.44	0.04
Proximal/distal Amplitude ratio			
Median nerve	0.80±0.17	0.80±0.19	0.99
Ulnar nerve	0.80±0.11	0.74±0.17	0.38
Tibial nerve	0.78±0.18	0.52±0.24	0.003
Peroneal nerve	0.80±0.17	0.66±0.27	0.16
Proximal/distal duration ratio			
Median nerve	1.42±0.61	1.20±0.31	0.21
Ulnar nerve	1.19±0.16	1.16±0.17	0.66
Tibial nerve	1.49±0.58	1.24±0.38	0.62
Peroneal nerve	1.20±0.23	1.13±0.21	0.46

Figure 1: Examples of the median nerve, ulnar nerve, peroneal nerve, and tibial nerve motor responses in a patient with CMT1A



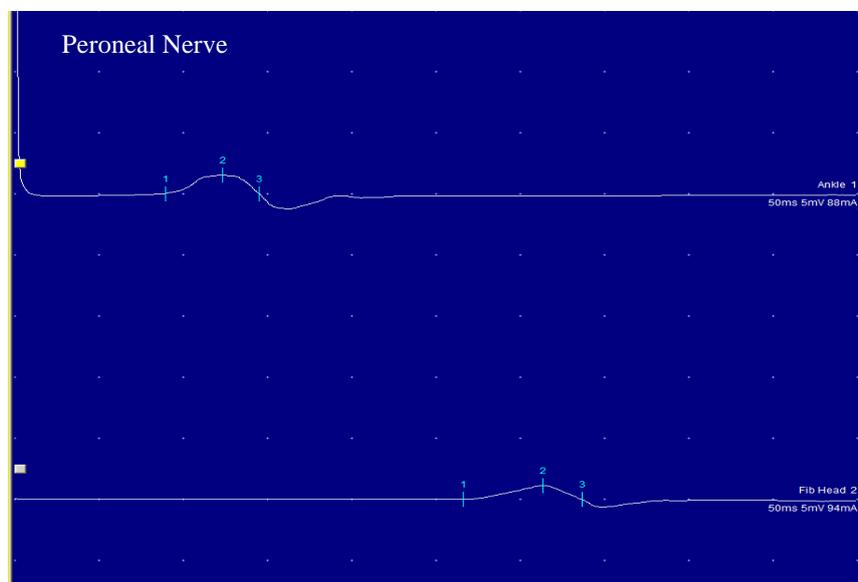
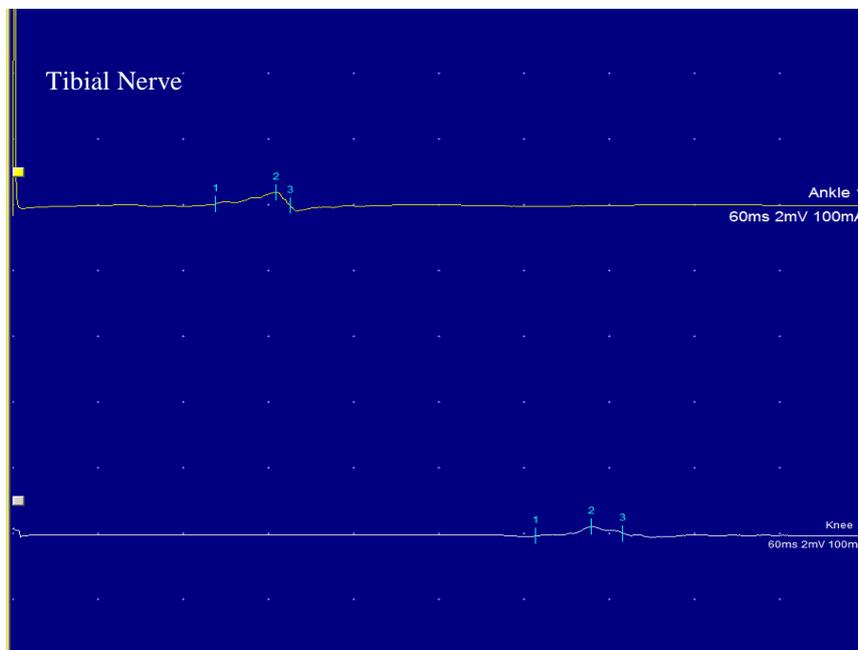
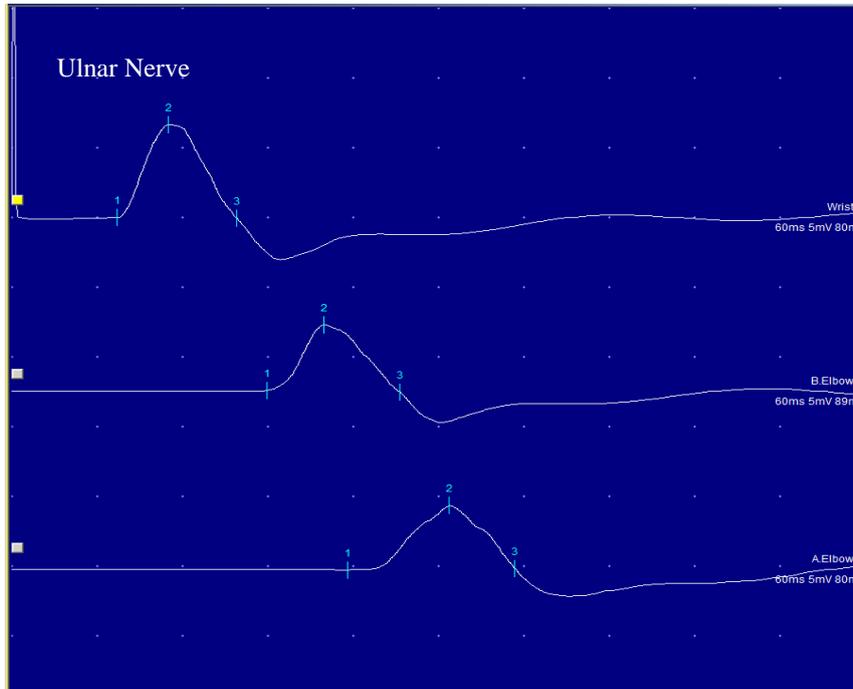
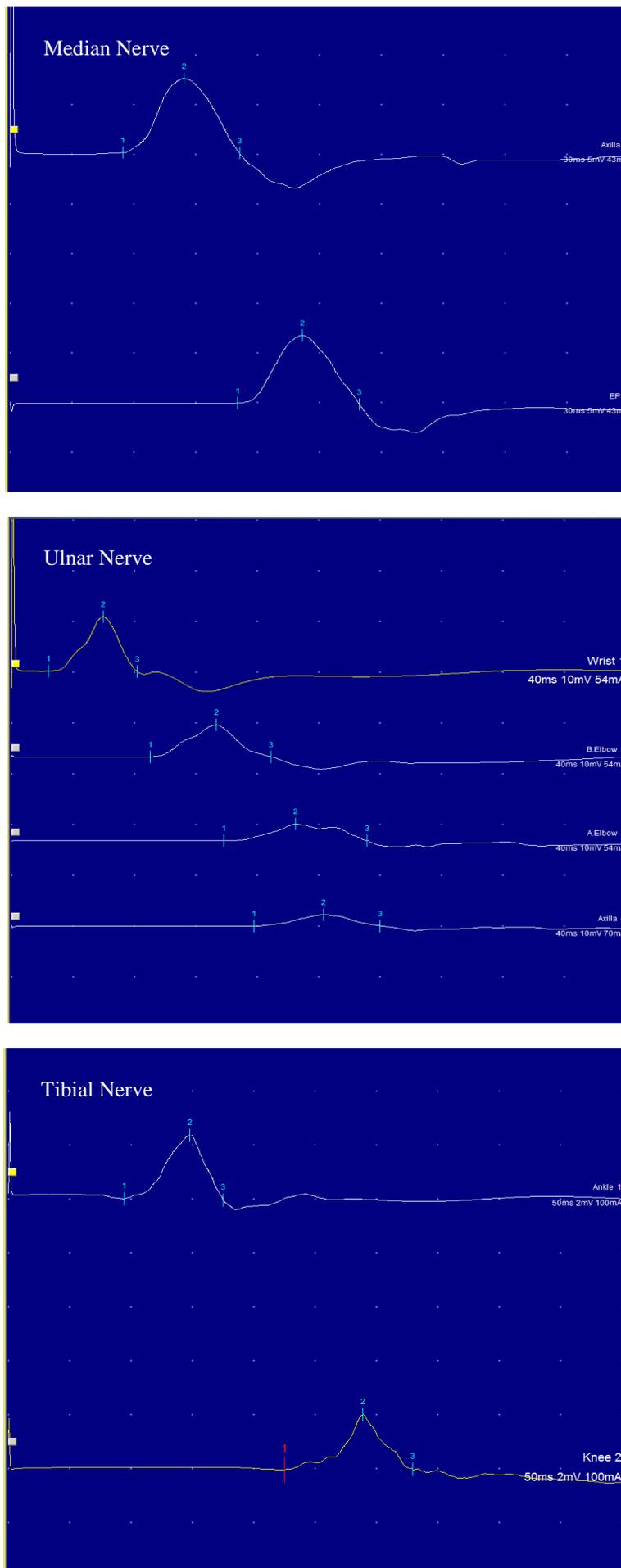
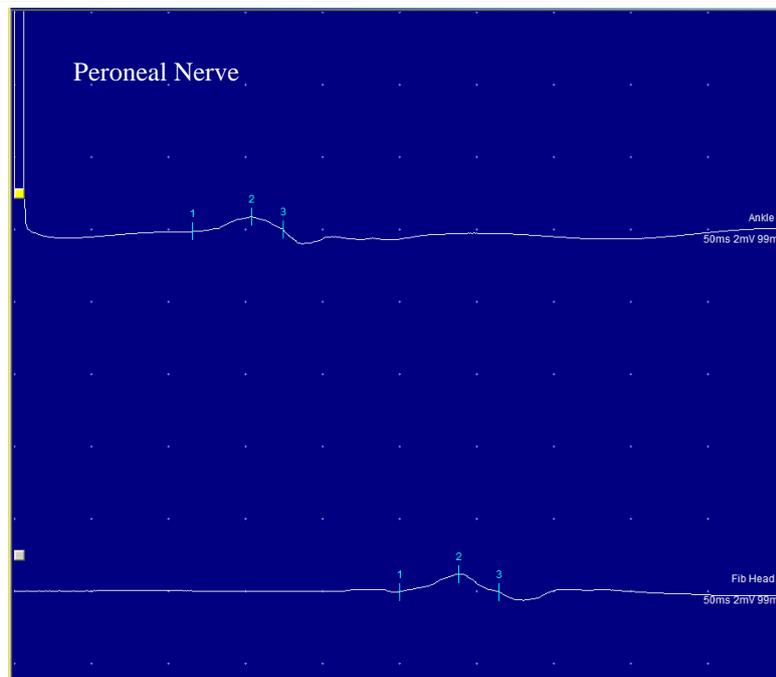


Figure 2: median nerve, ulnar nerve, peroneal nerve, and tibial nerve motor response examples in a patient with CIDP





DISCUSSION

This study aimed to investigate hereditary and acquired demyelinating polyneuropathies as the different electrodiagnostic parameters. In our study, we found that the mean distal duration of the peroneal nerve was statistically significantly longer in the CIDP group compared with the CMT1A group. The groups had similar mean distal durations for the ulnar, tibial nerves, and median. The CIDP group had statistically lower tibial nerve proximal/distal amplitude ratio in the CIDP group than the CMT1A group had.

Tankisi et al. compared CMAP amplitude and durations in 132 patients with demyelinating polyneuropathy and 53 patients with axonal polyneuropathy and found the CMAP duration longer in demyelinating PNPs than the axonal PNPs (5). They emphasized that distal CMAP duration was a useful marker for reflecting distal demyelination. In this study, we compared the negative peak durations in demyelinating polyneuropathy subgroups instead of axonal/demyelinating polyneuropathies. We demonstrated that the CIDP group had longer peroneal motor nerve distal CMAP than the hereditary polyneuropathies. Likewise, our findings may indicate that CIDP has distal demyelination.

Our study supports previous studies suggesting elongated CMAP duration in CIDP. This study only found that the patient groups showed a difference in terms of distal duration of the peroneal nerve, and longer duration of the CIDP group. We found no difference in distal CMAP duration between the CMT1A and CIDP groups for the median, ulnar, and tibial nerves. One reason is that amplitude due to phase cancellation decreases. Another possibility may be inaccurate measurement due to low CMAP amplitude. If we had studied total distal CMAP duration instead of negative peak duration, perhaps a difference could be found.

Although both disease groups cause demyelinating polyneuropathy, there are differences in transmission characteristics.

Some patients with CMT1A underwent histopathologic examinations showing that all fiber sizes decreased as the most prominent ones in large fibers (6). There is evidence of axonal atrophy, as well as significant demyelination in nerve biopsies. Conduction velocities may be apparently slowed down due to significant demyelination all over the peripheral nervous system. In CMT1A, wave morphology is well preserved without evidence of temporal dispersion or conduction block by stimulating the distal and proximal parts (6). Various segments of each nerve and similar nerves are slowed down uniformly. However, nerve fiber of the peripheral nerves in acquired polyneuropathies such as CIDP may be impacted in various segments. Segmental demyelination and remyelination are the most important histopathologic changes in CIDP (6). The pathologic process is performed resulting in disruption of myelin (paranodal and segmental demyelination), impairing the salutatory conduction (7). Findings about asymmetric nerve conduction may be often shown in CIDP Patients, despite no clinically significant asymmetry. Besides, multifocal conduction blocks and excessive temporal dispersion in non-entrapment regions are typical for acquired demyelinating polyneuropathies (7). However, increased temporal dispersion can be seen in very rare hereditary polyneuropathies such as Charcot-Marie-Tooth disease type X (CMTX). In addition, very rarely, acquired demyelinating polyneuropathy findings such as newly developed Guillain Barré syndrome can be added to CMT1A cases. Therefore, such distinction may be relatively difficult.

Thaisetthawatkul et al. performed receiver operating characteristic (ROC) analysis of the tibial, median, ulnar, and peroneal nerve distal CMAP duration of 23 patients with CIDP, 54 patients who had non-neuropathic syndrome of musculoskeletal pain, 34 with diabetic polyneuropathy, 34 with amyotrophic lateral sclerosis (ALS), and (8), the mean distal CMAP duration in CIDP was longer than in the other groups.

They reported sensitivity and specificity of the distal CMAP dispersion as CIDP electrophysiologic tool. Although a different disease group was studied in our study, distal CMAP duration was found to be longer in the CIDP group. Our findings support the view that distal CMAP duration is a preferable measure of distal demyelination in CIDP.

A review of the electrophysiologic data of 471 participants (61 with ALS, 145 normal controls, 205 with other axonal neuropathies, and 60 patients with CIDP) by Iose et al. found the duration of distal CMAP to be a useful index for detection of distal demyelination (9). Distal CMAP duration was especially prolonged especially in the lower extremities, as the most prominent findings in the peroneal nerve. Our study showed significant prolongation of distal CMAP in the peroneal nerve in the CIDP group. Due to the effect of CIDP on the slow and fast conducting fibers at different rates and non-involvement of motor fibers in the demyelinated areas during the same period, different effects may occur in different nerves. Nodera et al. found prolonged CMAP duration in 34% of patients with CIDP in their study on 35 patients with CIDP and 30 normal controls in CMAP (T) durations recorded from the tibialis anterior muscle. They also found the longevity of CMAP duration which was recorded from the tibialis anterior muscle in 42% of patients with normal duration of CMAP which was recorded from the extensor digitorum brevis and 28% of patients who had normal CMAP duration which was recorded from abductor hallucis (10). They emphasized the usefulness of determining the duration of tibialis anterior CMAP due to a significant axonal loss.

Few studies reviewed the literature on proximal-distal CMAP dispersion and distal CMAP in patients who had hereditary polyneuropathies. Stanton et al. evaluated 33 CIDP patients and 91 patients who had hereditary neuropathies (17 HNPP, 31 CMT1A, and 10 CMTX). They calculated the percentage decreases in CMAP amplitude and percentage increases in CMAP duration between the distal and proximal stimulation zones for each nerve in the forearm and foreleg segments to detect conduction block or temporal dispersion. It has been demonstrated that dispersion of distal CMAP is more common in CIDP than in inherited neuropathies (11). In addition, they found the distal CMAP dispersion was almost more prevalent in CMT1A compared with other hereditary neuropathies. They found that the CIDP group had significantly longer mean distal CMAP duration than the group with hereditary neuropathies. Our study also supports this finding.

Normal individuals showed reduced amplitude of motor response in proximal stimulations. Typically, the CMAP amplitude decreases slightly as the stimulus point moves proximally. With increasing the distance of transmission, the slow-conveying fibers were slower than the fast-conveying fibers. CMAP amplitude decreases due to the phase cancellation and temporal dispersion (7). Conduction blocks and dispersion are common in acquired forms of demyelinating polyneuropathy. More proximal stimulation reduces amplitudes of CMAP due to higher conduction blocks and temporal dispersion along some fibers (7). Temporal dispersion in demyelination is caused by abnormal conduction velocity disruptions between individual axons of a nerve. Long distance of the transmission reduces amplitude of

CMAP. While the elongation in the latency reflects the reduced speed of the fastest transmitting fibers, the duration of distal CMAP reflects the temporal dispersion between the slow and fast transmitting distal motor fibers.

Distal and proximal muscle recordings are compared to identify primary demyelination to effectively contribute to routine electrophysiologic studies to evaluate the polyneuropathy (12). In our study, we found that the tibial nerve proximal/distal amplitude ratio was lower in the CIDP group than the CMT1A group. The CIDP and CMT1A patient groups did not show any difference in terms of ulnar nerve, median nerve, and peroneal nerve proximal/distal amplitude ratio. In addition, our study found the similarity of the proximal/distal ratios for all nerves in the CMT1A group, while showing a difference of the rates in the CIDP group whose values between nerves had a wide range. Therefore, the previous studies support our findings that CMT1A patients showed homogeneous characteristics of polyneuropathy and CIDP patients show partial and focal decreases in nerve conduction and blocks of velocities conduction.

A retrospective analysis of NCS results of 30 CMT1 patients, 35 CIDP patients, and 77 healthy controls by Kang et al. In the qualitative analysis of proximal-distal CMAP amplitude ratios, showed lower values for the CIDP group in all tested nerves compared with the group with CMT1 (13). They stated that values close to 1 in proximal/distal ratios showed smaller differences in amplitudes between proximal and distal segments. Amplitude in all peripheral nerves was relatively equally reduced in the CMT1 group, while the CIDP group's findings showed the conduction blocks of which amplitude was significantly reduced in the proximal segments. Amplitude in all peripheral nerves was reduced relatively equally in the CMT1 group while the CIDP group's findings indicated that conduction blocks may have significantly reduced amplitude in the proximal segments as compared with the distal segments.

In this study, proximal and distal CMAP duration ratios were analyzed for the first time. We expect this ratio to be high in the acquired group, assuming that the speeds of fast and slow transmitting fibers would be significantly affected differently with increasing the transmission distance. However, we found no significant differences between the patient groups in terms of duration ratios. One reason may be that we calculated the negative peak duration. CMAP amplitude may be possibly lost since the secondary axonal damage accompanies the disease.

This study has some limitations. The first limitation is the relatively small number of subjects and the retrospective nature of our study. Prospective studies involving larger CIDP and CMT1A patient groups are needed. Perhaps, one can investigate the guiding role of analyses before and after immunotherapy in a larger sample. The strength of the study is the use of distal CMAP duration and proximal/distal amplitude ratio to distinguish between acquired and hereditary demyelinating polyneuropathies. In the future, studies that provide optimum integration with a larger patient group to existing electrophysiologic criteria are needed.

The data in our study support new efforts aimed to improve the performance of CIDP electrodiagnostic criteria. It cannot be used alone to distinguish between the hereditary demyelinating polyneuropathy and acquired demyelinating polyneuropathy though it can sometimes electrophysiologically differentiate from CMT1A. In this way, an approach to increasing the diagnostic capacity can be provided in patients with demyelinating polyneuropathy with severe secondary axonal involvement and few inducible motor responses, who have difficulty in the distinction between hereditary/acquired, severe secondary axonal involvement and few excitable motor responses can be recorded.

CONCLUSION

This study may benefit the diagnosis of patients with hereditary and inflammatory polyneuropathy with common features. Different electrodiagnostic models of hereditary and acquired demyelinating polyneuropathies should be clinically recognized, contributing to the diagnosis and treatment of these patients.

Author contributions: OA, CE; Literature search and study design, patient examinations, data collection and analyzes OA; Writing article and revisions

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical issues: All authors declare originality of research.

REFERENCES

- Lewis RA, Sumner AJ, Shy ME. Electrophysiological features of inherited demyelinating neuropathies: A reappraisal in the era of molecular diagnosis. *Muscle Nerve*. 2000;23(10):1472-87.
- Rajabally YA, Adams D, Latour P, Attarian S. Hereditary and inflammatory neuropathies: a review of reported associations, mimics and misdiagnoses. *J Neurol Neurosurg Psychiatry*. 2016;87(10):1051-60.
- Potulska-Chromik A, Ryniewicz B, Aragon-Gawinska K, Kabzinska D, Seroka A, Lipowska M, vd. Are electrophysiological criteria useful in distinguishing childhood demyelinating neuropathies? *J Peripher Nerv Syst JPNS*. 2016;21(1):22-6.
- CL, Leger JM, Nebil-Orazio E, Pollard J, Sommer C, van Doorn PA, van Schaik IN. European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society-first revision. *Eur J Neurol*. 2010;17: 356-363.
- Tankisi H, Otto M, Pugdahl K, Johnsen B, Fuglsang-Frederiksen A. Correlation between compound muscle action potential amplitude and duration in axonal and demyelinating polyneuropathy. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2012;123(10):2099-105.
- Daniel Dumitru, Anthony A. Amato, Machiel J. Zwarts. *Electrodiagnostic medicine*. Second edition. Philadelphia.2002.
- David C. Preston, Barbara E. Shapiro. *Electromyography and neuromuscular disorders. Clinical-electrophysiologic correlations*. Second edition. Philadelphia. 2005.
- Thaisetthawatkul P., Logigian E.L., Herrmann D.N.: Dispersion of the distal compound muscle action potential as a diagnostic criterion for chronic inflammatory demyelinating polyneuropathy. *Neurology* 2002; 59: pp. 1526-1532.
- Isose S., Kuwabara S., Kokubun N., Sato Y., Mori M., Shibuya K., et. al.: The Tokyo Metropolitan Neuromuscular Electrodiagnosis Study Group. Utility of the distal compound muscle action potential duration for diagnosis of demyelinating neuropathies. *J Peripher Nerv Syst* 2009; 14: pp. 151-158.
- Nodera H, Latov N, Carey B, Langsdorf J, Bedoya V, Tacheva S, Chin RL. Prolongation of the tibialis anterior duration in chronic inflammatory demyelinating polyneuropathy. *Clin Neurophysiol*.2012; 123(82):393-398
- Stanton M, Pannoni V, Lewis RA, Logigian EL, Naguib D, Shy ME, vd. Dispersion of compound muscle action potential in hereditary neuropathies and chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2006;34(4):417-22.
- Raynor EM, Ross MH, Shefner JM, Preston DC. Differentiation between axonal and demyelinating neuropathies: identical segments recorded from proximal and distal muscles. *Muscle Nerve*. 1995;18(4):402-8.
- Kang JH, Kim HJ, Lee ER. Electrophysiological evaluation of chronic inflammatory demyelinating polyneuropathy and charcot-marie-tooth type 1: dispersion and correlation analysis. *J Phys Ther Sci*. 2013;25(10):1265-8.