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Electrophysiological Evaluation of Chronic Inflammatory Demyelinating Polyneuropathy and Charcot-Marie-Tooth Type 1: Dispersion and Correlation Analysis

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Abstract. [Purpose] The purpose of this study was to analyze and compare electrophysiological characteristics observed in nerve conduction studies (NCS) of chronic inflammatory demyelinating polyneuropathy (CIDP) and Charcot-Marie-Tooth disease type 1 (CMT 1). [Subjects] A differential diagnosis of acquired and congenital demyelinating neuropathies was based on a study of 35 patients with NCS-confirmed CIDP and 30 patients with CMT 1 genetically proven by peripheral myelin protein-22 (PMP-22) gene analysis, pulsed-field gel electrophoresis (PFGE), and Southern blot analysis. [Methods] We analyzed values collected in motor nerve conduction studies. We conducted dispersion analysis of the amplitudes of the compound muscle action potential (CMAP) of various nerve types and correlation coefficient analysis of the motor nerve conduction velocity (MNCV). [Results] We found that CIDP and CMT 1 were clearly attributable to severe polyneuropathy. In dispersion analysis, CIDP showed greater differences in proximal-to-distal amplitude ratios. Moreover, CMT 1 showed relatively high correlations compared to CIDP based on correlation coefficient analysis of MNCV. [Conclusion] The results of this study suggest that CIDP showed greater asymmetry than CMT 1 in MNCV and CMAP amplitudes.
Key words: Chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease type 1, Dispersion and correlation analysis

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INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated relapsing and remitting or progressive demyelinating polyneuropathy[1, 2)], which occurs mainly in adults aged 40 to 60 years; the disease occurs rarely in children[3–5)]. In CIDP, differential diagnoses based on hereditary motor sensory neuropathy, also called Charcot-Marie-Tooth disease (CMT)—peripheral nervous system diseases observed more frequently in children—are important[6)]. CIDP is associated with dysaesthesia, reduced focal motor nerve conduction velocity, multiple conduction blocks, and prolonged terminal latency[3, 7–11)]. In contrast, CMT presents symmetrically reduced motor nerve conduction velocities in all peripheral nerves without any conduction block[12, 13)]. However, 48 to 64% of CIDP patients do not exhibit typical findings, such as conduction blocks, segmentally reduced conduction velocity, or severely prolonged terminal latency and reversal; CMT cases showing nerve conduction blocks have been reported only rarely[14, 15)].

The most basic pathological finding of CIDP is myelin removal from axons by macrophages[16, 17)]. Demyelination results in conduction blocks or delayed conduction velocity and clinically, muscle weakness and sensory loss. CMT is the most frequently observed disorder among the hereditary nervous diseases and follows autosomal dominant heredity patterns in most cases[13)], with unmyelinated nerve fibers not commonly invaded. CMT type 1 (CMT 1), which is the most common type of CMT, is characterized by demyelinating neuropathy that invades both motor nerves and sensory nerves[18)]. In most cases, CMT 1 is attributable to the duplication and point mutation of the PMP-22 gene[19)]. Although genetic testing is essential to confirm CMT 1, electrodiagnostic evaluations conducted prior to testing can prove useful in genetic counseling, the selection of subjects or candidate genes in molecular genetic studies, and the identification of patients with no symptoms[20–23)]. The diagnosis of CIDP is based on clinical features, analysis of cerebrospinal fluid, and pathological findings[24)]. Nerve conduction studies (NCS) are also important in diagnosing both CIDP and CMT 1[13, 18, 25–28)].

In this study, the results of NCS of patients definitely diagnosed as having CIDP or CMT 1 were used to analyze the dispersion of the ratio of amplitude reduction in proximal sites compared to distal sites in various nerves. In addition, to compare the patterns of nerve conduction delays and determine whether the patterns were consistent in the two diseases, we conducted correlation analyses of the nerve conduction velocities of each nerve and segment. By

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performing dispersion and correlation analyses of the electrophysiological characteristics of CIDP and CMT 1, and identifying features of major demyelinating peripheral neuropathies clinically considered important, this study aims to aid the differential diagnoses of these diseases.

SUBJECTS AND METHODS

Subjects

The results of NCS of 65 patients with confirmed diagnoses of CIDP or CMT, and 77 persons in a normal control group were retrospectively analyzed. All subjects were informed about the purpose and procedure of the study and provided their written informed consent prior to participation. This study was approved by the research ethics committee of Kyungwoon University.

The patient groups satisfied the following conditions: The CIDP group included 35 patients who had been diagnosed with CIDP based on NCS and clinical manifestations, including abnormal increases in cerebrospinal fluid proteins of 2 months' duration. The CMT 1 group included 30 patients who showed duplication of the PMP-22 gene of the short arm of chromosome 17 in molecular genetic studies (PMP-22 gene analysis, PFGE-Southern blot) or were diagnosed as having CMT 1 based on family history or clinical analyses. The control group included 77 patients who had no history, clinical symptoms, or signs of neuropathy, and had been diagnosed as normal based on the results of NCS.

Methods

In NCS, the motor nerves, median nerves, and ulnar nerves in the upper limbs were examined by segment; the peroneal nerve and the posterior tibial nerve in the lower limbs were also assessed. The median nerve was stimulated at the wrist, elbow, and axilla. The ulnar nerve was stimulated at the wrist, below the elbow, and at the axilla. The peroneal nerve was stimulated at the ankle and fibular head, and the tibial nerve was stimulated at the ankle and popliteal fossa. For motor nerves, the compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) amplitudes obtained by supramaxial stimulations were analyzed by segment. The MNCV was measured in m/sec, and the amplitude was determined in millivolts (mV) by measuring the distance from the negative peak to the positive peak. All patients were studied using the same electromyography (EMG) unit. NCS were performed using standard EMG equipment (Viking IV, Nicolet, USA). A 20-mm round attachment type surface electrode was used; the measurements were based on the method and reference values proposed by Oh[29]. The equipment set-up was as follows: a filter frequency range of 2 Hz to 10 kHz, a sweep speed of 5 msec, a sensitivity of 5 mV. Although the filter frequency range was not adjusted, some conditions were altered based on the characteristics of the waveforms so that appropriate waveforms could be obtained.

Data on the proximal-to-distal CMAP amplitude ratios were obtained from the motor NCS of the median nerves, ulnar nerves, peroneal nerves, and posterior tibial nerves in the control, CIDP, and CMT 1 groups. The average CMAP amplitude values were compared, and the tendencies of individual amplitude ratios were qualitatively analyzed.

In correlation analysis of MNCV in the CIDP and CMT 1 groups, correlations between the upper limbs, the lower limbs, the upper limbs and the lower limbs, and the proximal segments and the distal segments were analyzed.

The NCS results were analyzed using the SAS 9.1 for Windows statistics package. The level of statistical significance was chosen as 0.05. To determine the uniformity of abnormal findings in each of the CIDP and CMT 1 groups, Spearman's correlation analysis was conducted of motor nerve conduction velocities between the upper limbs, the lower limbs, the upper limbs and the lower limbs, and the proximal and distal segments. When analyzing the correlations, values with a nerve conduction velocity of zero were excluded, and the statistical significances of the correlation coefficients were compared and tested in the two groups using Fisher's Z test.

RESULTS

Table 1 presents demographic data of the study groups and information on the number of examinations conducted on the various nerve types. As shown in Table 2, the CIDP group exhibited the lowest values of proximal/distal CMAP amplitude ratios (P/D ratio) in all the nerves tested. The P/D ratio of the posterior tibial nerve was larger than those of the other nerves. In dispersion analysis of each P/D ratio

Table 1. Demographic data of control, CIDP, and CMT 1 Groups

Group	Control (Number)	CIDP (Number)	CMT 1 (Number)
Men	40	16	18
Women	37	19	12
Median motor nerve	91	75	40
Ulnar motor nerve	89	71	39
Peroneal nerve	77	91	62
Posterior tibial nerve	74	90	61

Both upper limbs and one lower limb, or one upper limb and both lower limbs of each patient were examined. Abbreviations: chronic inflammatory demyelinating polyneuropathy (CIDP), Charcot-Marie-Tooth disease type 1 (CMT 1).

Table 2. Average value of proximal/distal CMAP amplitude ratios (P/D ratios)

Nerve	Control	CIDP	CMT 1
Median	0.96	0.77	0.85
Ulnar	0.95	0.76	0.85
Peroneal	0.90	0.68	0.75
Posterior tibial	0.77	0.58	0.67

The proximal/distal amplitude ratios were calculated as follows: Median and ulnar nerve: CMAP amplitude of elbow stimulation (mV)/CMAP amplitude of wrist stimulation (mV); Peroneal and posterior tibial nerve: CMAP amplitude of knee stimulation (mV)/CMAP amplitude of ankle stimulation (mV). The CIDP group showed lower P/D values than the CMT 1 group in all nerves tested.

individual values were more widely dispersed in the CIDP and CMT 1 groups than in the control group. In particular, values in the CIDP group were widely dispersed in both the upper limbs and the lower limbs.

In Spearman's correlation analyses positive linear correlations were apparent in both the CIDP and CMT 1 groups. In particular, the CMT 1 group exhibited relatively high correlations compared with the CIDP group in MNCV. Table 3 presents the results of Fisher's Z test of the significance of correlation coefficients between the two groups. Compared with the CIDP group, the CMT 1 group showed higher correlations and significant differences between the upper limbs (class 1), the proximal segments and the distal segments (class 2, 3), and the upper limbs and the lower limbs (class 6).

DISCUSSION

Various factors, such as metabolic diseases, immune-mediated disorders, and genetic defects can adversely affect the peripheral nervous system and eventually result in histological and physiological changes, which trigger peripheral neuropathy. Peripheral neuropathy can give rise to diverse diseases depending on the area affected. NCS are widely used for differential diagnoses and classification of these diseases[30–34]. In NCS, the electrophysiological functions of the peripheral nerves are determined. Such studies can be divided into motor nerve conduction analyses and sensory and mixed nerve conduction analyses. By analyzing characteristics of the nerve, such as terminal latency, conduction velocity, and amplitude, physiological functioning can be assessed.

In this study, dispersion and correlation analyses of the electrophysiological properties of CIDP and CMT 1 showing characteristics of major demyelinating peripheral neuropathy clinically considered important were conducted on nerves and nerve segments with the aim of aiding the differential diagnoses of these diseases. Qualitative analysis of the proximal-to-distal CMAP amplitude ratios show that compared to the CMT 1 group, the CIDP group exhibited lower values for all nerves tested (Table 2) and a tendency for individual values to be widely dispersed. Proximal/distal ratios closer to 1 signify smaller differences in amplitudes between the distal segments and proximal segments. The CMT 1 group showed relatively equal reductions in amplitude in all the peripheral nerves, whereas findings in the CIDP group suggest the possibility of conduction blocks, which are significant amplitude reductions in proximal segments compared to distal segments. In analyses of the various nerves, the posterior tibial nerves in the control group were also mainly distributed between 0.5–1. We attribute this result to the location of the posterior tibial nerves, which are sited more deeply than the other nerves, and thus show, a high propensity to resist stimulation. To determine whether the abnormalities detected in the CIDP and CMT 1 groups occurred uniformly among the different nerves and segments, correlation analyses were conducted, with motor nerve conduction velocities serving as the variable. We found statistically significant differences among all of the motor nerves (Table 3). Compared to the CIDP group, all cases of the CMT 1 group showed higher correlations between the upper limbs, the upper limb and the lower limb. Overall, the results suggest that the CMT 1 group exhibited more uniform characteristics of neuropathies. This finding is in agreement with previous studies of CIDP that have suggested that CIDP is characterized by focal and partial reductions in nerve conduction velocities and conduction blocks. Consistent with previous studies, our results also suggest that, in contrast to acquired demyelinating disorder, CMT 1 exhibits uniform patterns[6, 12, 13, 18, 25, 26, 30, 35–39]. Dispersion and correlation analyses of patients in the CMT 1 and CIDP groups, known to have severe demyelinating peripheral neuropathy, revealed there were more uniform abnormal findings in the CMT 1 group. However, larger numbers of samples will be necessary to confirm this finding.

Depending on the severity of neuropathy, the results of nerve conduction studies may yield diverse findings, even within the same disease. Moreover, both CIDP and CMT 1 may present with and without typical findings. Thus, when

Table 3. Spearman's correlation analysis and Fisher's Z test of motor nerve conduction velocity

	Nerve (segment)		Spearman R-value	
	Variable 1	Variable 2	CIDP	CMT 1
Class 1	Median	Ulnar	0.76	0.99*
Class 2	Median (distal segment)	Median (proximal segment)	0.82	0.96*
Class 3	Ulnar (distal segment)	Ulnar (proximal segment)	0.55	0.98*
Class 4	Median	Peroneal	0.80	0.84
Class 5	Ulnar	Peroneal	0.62	0.86
Class 6	Ulnar	Post. tibial	0.77	0.96*
Class 7	Peroneal	Post. tibial	0.84	0.88

Fisher's Z test (* Significant difference, $p < 0.05$); Class 1: $p < 0.0001$, Class 2: $p = 0.0302$, Class 3: $p < 0.0001$, Class 6: $p = 0.0125$. Variable 1, 2: motor nerve conduction velocity of each nerve; Median N. and Ulnar N: conduction velocity of wrist to elbow; peroneal N: Conduction velocity of ankle to fibular head; posterior tibial N: Conduction velocity of ankle to popliteal fossa. Distal segment of median and ulnar nerve: Conduction velocity of wrist to elbow, proximal segment of median and ulnar nerve: Conduction velocity of elbow to axilla. The CMT 1 group showed higher correlation coefficients and significant differences than the CIDP group.

arriving at a diagnosis, it is essential to consider clinical findings and the results of other examinations. Although NCS are widely used in differential diagnosis and classification of peripheral neuropathy, various factors, such as patients' ages, temperatures, heights, and postures in daily life all impact the results. If sufficient consideration is given to these factors and corrections are made, the accuracy and precision of NCS studies can be further improved.

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