Different distributions of nerve demyelination in chronic acquired multifocal polyneuropathies

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Abstract
Background: Multifocal motor neuropathy (MMN), Lewis-Sumner syndrome (LSS), and many chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs) are representative of acquired multifocal polyneuropathy and are characterized by conduction block (CB). This retrospective study aimed to investigate the demyelinating distribution and the selective vulnerability of MMN, LSS, and CIDP with CB (CIDP-CB) in nerves.

Methods: Fifteen LSS subjects (107 nerves), 24 MMN subjects (176 nerves), and 17 CIDP-CB subjects (110 nerves) were included. Their clinical information was recorded, blood and cerebrospinal fluid tests were conducted, and nerve conductions of the median, ulnar, radial, peroneal, and tibial nerves were evaluated. CB, temporal dispersion, distal motor latency (DML), and F-wave latency were recorded, and nerve conduction velocity, terminal latency index, and modified F-wave ratio were calculated.

Results: CB was more likely to occur around the elbow in CIDP-CB than in MMN (78.6% vs. 6.8%, \(P < 0.01\)) but less likely to occur between the wrist and the elbow than in LSS (10.7% vs. 39.3%, \(P < 0.05\)). Tibial nerve CB was most frequently observed in MMN (47.4%, \(P < 0.05\)). CIDP-CB was characterized by a prolonged DML in all nerves, and slow motor nerve velocity of the upper limb was significant when CB nerves were excluded (\(P < 0.05\)).

Conclusions: We report the different distributions of segmental and diffuse demyelination of the ulnar and tibial nerves in LSS, MMN, and CIDP-CB. These distinct distributions could help in differentiating among these conditions.

Keywords: Multifocal motor neuropathy; Lewis-Sumner syndrome; Chronic inflammatory demyelinating neuropathy; Conduction block; Demyelination

Introduction
The pathological features of peripheral nerve myelin lesions are known as diffuse and focal demyelination. As a hallmark of peripheral nerve focal demyelination, conduction blocks (CBs) have been observed in both acquired and hereditary demyelinating neuropathies.\(^1\)\(^-\)\(^4\) Multifocal motor neuropathy (MMN) and Lewis-Sumner syndrome (LSS) are the most representative chronic acquired focal neuropathies, while many of the classic chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs) also present with CB.\(^5\)\(^-\)\(^6\)\(^-\)\(^7\) Distinct from common peripheral neuropathies, the motor impairments in these focal neuropathies are clinically non-uniform, that is, non-length dependent and asymmetric.\(^6\)\(^-\)\(^7\) Their limb onset selectivity is well known,\(^8\) although reciprocal differentiation is not efficient. Differing nerve involvement among demyelinating polyneuropathies was proposed in a morphological study, in which the authors suggested different demyelination distributions and selective vulnerability of nerves.\(^9\)\(^-\)\(^10\) This phenomenon has been observed in other neuropathies,\(^10\)^\(^-\)\(^11\) but it has not been fully studied in focal demyelination by electrophysiology methods. Thus, in this study, by using many well-established electrophysiological indicators, for example, distal motor latency (DML), terminal latency index (TLI), F-wave latency, and nerve conduction velocity (NCV) as well as CB, we aimed to investigate the demyelinating distribution and selectivity of nerves and segments in patients with LSS, MMN, and CIDP with CB (CIDP-CB).

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Methods

Subjects

This was a retrospective cross-sectional study performed under the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Renji Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent for data and sample collection was obtained from the patients on admission.

Fifteen LSS subjects, 24 MMN subjects and 17 CIDP-CB subjects admitted to the Renji Hospital, Shanghai Jiao Tong University School of Medicine from 2013 to 2017 were included in the study. A total of 107 nerves of LSS subjects, 176 nerves of MMN subjects, and 110 nerves of CIDP-CB subjects were analyzed. The LSS and CIDP diagnoses were based on the 2010 European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines on CIDP,[12] and the MMN diagnosis was based on the 2010 EFNS/PNS guidelines on MMN.[13] The exclusion criteria were peripheral neuropathy family history; alcohol abuse; toxic and neurotoxic exposure; tumor; metabolic disorders including pathoglycemia (diabetic mellitus and impaired glucose tolerance); and paraproteinemia (monoclonal gamma-globulin related polyneuropathy).

Clinical profiles and examinations

General information on gender, age, and height were recorded. Detailed clinical history was investigated to collect disease duration and onset and to determine neurological manifestations of weakness, numbness, and atrophy. Meticulous physical examinations were performed to determine the tendon reflex as well as other positive neurological signs. Routine blood tests, liver and kidney function, blood electrolytes, thyroid function, vitamin B12, folic acid, and blood glucose were evaluated to ensure that patients met the inclusion and exclusion criteria. Gangliosidosis antibody examination was semi-quantitative by blot and was fulfilled by the KingMed Diagnostics (Guangdong, China). A panel of various kinds of anti-gangliosidosis (GM1, GM2, GM3, GD1a, GD1b, GQ1b, GD1b) was used, and a positive result was determined by the visible band in the GM1 area. Blood immunofixation electrophoresis was tested for subjects to meet the exclusion terms. Lumbar puncture was performed under the informed consent of subjects, and cerebrospinal fluid (CSF) was quantitatively analyzed to determine albumin protein concentration.

Nerve conduction

All subjects received a nerve conduction test by Keypoint. All nerves were examined in a quiet room with a temperature >20° C. Surface electrodes were used to record the wave forms of fully relaxed muscles after stimulation. Median, ulnar, radial, peroneal, peroneal superficial, tibial, and sural nerves were selected for evaluation (sensory nerve data are not shown). Multiple sites were stimulated to ensure that sufficient data were collected for each nerve and to calculate velocities. For the median nerve, recording was placed on the abductor pollicis brevis, and stimulation was conducted on the wrist and the elbow. For ulnar nerve recording, the abductor digiti quinti was placed, and stimulation was applied at the wrist, below the elbow, above the elbow, and at Erb point. For radial nerve recording, the extensor indicis proprius was recorded, and stimulation was applied at the forearm, below the elbow and on the upper arm. For the peroneal nerve, the extensor digitorum brevis was recorded, and stimulation was applied at the ankle, below the fibular head and above the fibular head. For the tibial nerve, the abductor hallucis was recorded, and stimulation was applied on the ankle and the popliteal fossa. The normal values and ranges used in our laboratory were adopted.

Negative peak amplitude, curve area, and duration were recorded to determine CB and temporal dispersion (TD). A definite CB was defined as area reduction upon proximal vs. distal stimulation of at least 50%, a distal compound muscle action potential (CMAP) >20% of the lower limit of normal and >1 mV, and increase in proximal to distal CMAP duration must be ≤30%. An additional 60% or greater amplitude reduction between proximal and distal stimulation was applied to the tibial nerve.[14] Nerve variants, especially Martin-Gruber anastomosis, were carefully excluded by additional stimulation. TD was defined as a >30% duration increase between the proximal and distal CMAP.[12]

Take-off latency and distance were recorded, and NCV was thus calculated. Distal distance (dD), DML, and NCV were used to calculate TLI by the following formula: TLI = (dD/DML)/NCV. F-waves were recorded during a bout of stimulation of distal muscle, and the first F-wave latency was determined. DML, proximal motor latency (PML), which is the latency recorded from the second stimulation site from the distal region, and F-wave latency was used to calculate the modified F-wave ratio (MFR) by the formula $ MFR = \frac{(F + DML2 \times PML-1)\times2}{(PML-DML)} $.

Statistical analysis

Normally distributed data were described as the mean ($\bar{x}$) ± standard deviation, and skewed distribution data were described as the median (25% percentile–75% percentile). Particularly, data of the same type in a table row were kept the same description for comparability. Chi-square tests were used to analyze the proportion and composition of different groups with Bonferroni correction. One-way analysis of variance and group t-test were used for data with a normal distribution and a standard homogeneity of variance; otherwise, the Kruskal-Wallis test with Bonferroni correction was chosen instead. All statistical analyses were performed by using Stata 15.1 (StataCorp, College Station, TX, USA), and $ P < 0.05$ indicated significant differences.

Results

General information of subjects

Gender, age, and height were commensurate among the different groups ($ P > 0.05$). Intragroup gender composi-
Onset

Upper and Lower Limbs

Gender

Hyporexia

Hyporeflexia

Weakness

Atrophy

CSF Albumin Protein (mg/dl)\(^\ast,\dagger\)

Positive anti-GM1\(^\ast,\dagger\)

The DML of all nerves was significantly prolonged in the CIDP-CB group (\(P < 0.05\)), while only the TLI of the ulnar nerve was prolonged with a value of 0.40 (0.36–0.51) in the LSS group (\(P < 0.05\)). No F-wave latency or MFR difference was found in any nerve. Only ulnar NCV differences were found between the CIDP-CB group and the MMN group (\(P < 0.05\)). When nerves with CB were excluded, a significantly mild decrease (\(P < 0.05\)) in upper limb NCV was observed in the CIDP-CB group, i.e., a median nerve value of 44.45 (35.3–50.9) m/s and an ulnar nerve value of 51.3 (39.4–54.8) m/s. The lower limb CMAP was smaller in the CIDP-CB group (\(P = 0.01\)). Electrophysiological findings of the indicators are shown in Table 3.

Discussion

Despite our broadening understanding of LSS, MMN, and CIDP, the diagnostic borders for discriminating these conditions remain unclear. Sensory involvement has been regarded as a useful tool for differentiating these conditions.\(^{[1,4]}\) However, recent studies, for example, MMN with sensory involvement or CIDP-CB with pure upper limb demyelination, emphasized the overlap of diagnoses in these three similar acquired focal demyelinating neuropathies,\(^{[13,17]}\) which could probably confuse the diagnoses and prompt further investigation of their motor demyelinating features for precise differentiation. Using electrophysiological indicators, we presented a horizontal comparison of LSS, MMN, and CIDP-CB nerves.

Clinically, MMN and LSS are characterized by male predominance, upper limb onset, and different sensory involvement.\(^{[6,18,20]}\) In this study, we also found a male predominant composition in the MMN group and the LSS group, which was different from that in the CIDP-CB group. A high upper limb onset proportion and rare sensory involvement in MMN were also proven and could help in differentiating CIDP-CB. In addition, we found that MMN presented slowly progressive long duration, low

Table 1: General and clinical profiles of LSS, MMN, and CIDP-CB subjects.

| Characteristics          | LSS \((n = 15)\) | MMN \((n = 24)\) | CIDP-CB \((n = 17)\) | \(P\) value |
|--------------------------|-----------------|-----------------|---------------------|-----------|
| Gender                   |                 |                 |                     | 0.501     |
| Female                   | 3 (20.0)        | 5 (20.8)        | 6 (35.3)            |           |
| Male                     | 12 (80.0)       | 19 (79.2)       | 11 (64.7)           |           |
| Age (years)              | 44.2 ± 15.1     | 42.7 ± 12.5     | 51.6 ± 16.4         | 0.142     |
| Height (cm)              | 169.0 ± 7.3     | 168.0 ± 5.7     | 164.6 ± 8.7         | 0.183     |
| Disease Duration (months)\(^\ast,\dagger\) | 10 (3–12)       | 24 (12–39)      | 6 (5–12)            | 0.033     |
| Onset                    |                 |                 |                     |           |
| Upper and Lower Limbs    |                 |                 |                     |           |
| Upper Limbs\(^\dagger\)  | 10 (66.7)       | 16 (66.7)       | 5 (29.4)            | 0.036     |
| Lower Limbs              | 2 (13.3)        | 2 (8.3)         | 3 (17.6)            | 0.693     |
| Weakness                 | 6 (40.0)        | 9 (37.5)        | 9 (52.9)            | 0.084     |
| Atrophy                  | 5 (33.3)        | 5 (33.3)        | 1 (58.5)            | 0.093     |
| Hyporeflexia             | 15 (100)        | 24 (100)        | 17 (100)            | NA        |
| CSF Albumin Protein (mg/dl)\(^\ast,\dagger\) | 629.9 ± 184.0   | 398.5 ± 171.6   | 995.2 ± 416.9       | <0.001    |
| Positive anti-GM1\(^\ast,\dagger\) | 2 (13.3)        | 18 (75)         | 2 (11.8)            | <0.001    |

Data are presented as n (%), median (range), or mean ± standard deviation. \(* P < 0.05\) between LSS subjects and MMN subjects. \(\dagger P < 0.05\) between MMN subjects and CIDP-CB subjects. \(\ddagger P < 0.05\) between LSS subjects and CIDP-CB subjects. LSS: Lewis-Sumner syndrome; MMN: Multifocal motor neuropathy; CIDP-CB: Chronic inflammatory demyelinating polyradiculoneuropathy with conduction block; CSF: Cerebrospinal fluid; GM1: Monosialotetrahexosyl ganglioside; NA: Not applicable.

CB was more likely to occur around the elbow in the CIDP-CB group (78.6% vs. 6.8%, \(P < 0.01\)) but less likely to occur between the wrist and the elbow than in the LSS group (10.7% vs. 39.3%, \(P < 0.05\)). CB was found in nearly half of the tibial nerves examined in the MMN group, and it was significant (47.4%, \(P < 0.01\)). No significant difference in CB occurrence was found in other sites. TD was found in 7 of 107 nerves in the LSS group, in 12 of 176 nerves in the MMN group and in 8 of 110 nerves in the CIDP-CB group. The comparison was statistically insignificant (\(P = 0.977\)). The CB distribution is shown in Table 2. Typical waveforms of ulnar CB in LSS, ulnar CB in CIDP-CB, and tibial CB in MMN are shown in Figure 1. The hotspot graph of the incidence of CB is shown in Figure 2.

Conduction indicators of nerves

The DML of all nerves was significantly prolonged in the CIDP-CB group (\(P < 0.05\)), while only the TLI of the ulnar nerve was prolonged with a value of 0.40 (0.36–0.51) in the LSS group (\(P < 0.05\)). No F-wave latency or MFR difference was found in any nerve. Only ulnar NCV differences were found between the CIDP-CB group and the MMN group (\(P < 0.05\)). When nerves with CB were excluded, a significantly mild decrease (\(P < 0.05\)) in upper limb NCV was observed in the CIDP-CB group, i.e., a median nerve value of 44.45 (35.3–50.9) m/s and an ulnar nerve value of 51.3 (39.4–54.8) m/s. The lower limb CMAP was smaller in the CIDP-CB group (\(P = 0.01\)). Electrophysiological findings of the indicators are shown in Table 3.
CSF protein, and frequent positive anti-GM1, while LSS and CIDP presented progressive duration, moderate-high CSF protein, and rare positive anti-GM1. The clinical findings were consistent with those of previous studies.[21,22]

The selective vulnerability of nerves is particularly interesting and controversial in focal neuropathy. The ulnar nerve has been suggested to be useful in diagnosing acute demyelinating neuropathy,[23] while another study found no difference in CB distribution.[24] In this study, the wrist-to-elbow segment of ulnar nerve conduction, which is a non-entrapment site, was more likely to be blocked in LSS than in CIDP-CB. Consistently, focal demyelination in the forearm segment of the ulnar nerve has been suggested to be a sign of immune-mediated demyelinating neuropathy and is commonly associated with LSS, with an even higher proportion (59%) than in this study (39.3%).[25] Morphological studies by ultrasound revealed markedly larger (poor) nerves at the non-entrapment sites of the upper limbs.[26,27] Our findings strengthen the conclusion that forearm CB in the ulnar nerve implies a diagnosis of immunemediated demyelinating neuropathy, especially LSS. The opposite was found regarding the segment around the elbow of the ulnar nerve, which indicated that CB is more likely to occur in CIDP-CB than in MMN. As the segment around the elbow is a common entrapment site, the conclusion was drawn based on the fact that the three groups shared commensurate general information and risk of compression. The CB presented here could both reflect the selectivity of direct inflammatory attack or the liability of compression induced by inflammatory processes,[28] while the latter assumption tended to be recognized in a variety of acquired neuropathies.[29] However, previous studies do not support the assumption that CIDP increases the risk of entrapment,[30,31] thus strengthening the direct inflammatory attack theory. On the other hand, the finding could partially be attributed to the relatively “healthy” non-blocked segments in MMN, as inhomogeneous and regional nerve enlargement is more common in MMN by ultrasound.[32,33] We also observed the CB distribution characteristic of frequent tibial nerve CB in MMN. The results indicated that although the upper limb is more frequently affected in MMN, as mentioned above,
Table 3: Electrophysiological findings of peripheral nerve demyelination among LSS, MMN, and CIDP-CB nerves.

| Indicators and nerves | LSS          | MMN          | CIDP-CB       | P value |
|-----------------------|--------------|--------------|---------------|---------|
| DML (ms)              |              |              |               |         |
| Median                | 3.4 (3.15–3.8) | 3.67 (3.2–4.24) | 4.75 (3.5–5.4) | 0.001   |
| Ulnar                 | 2.71 (2.5–3.07) | 2.75 (2.35–3.11) | 3.87 (2.62–4.38) | 0.004   |
| Peroneal†             | 4.3 (3.7–5.17) | 4.75 (4.3–5.5) | 5.9 (4.6–7.1) | 0.004   |
| Tibial†               | 4.31 (3.86–5.19) | 4.4 (3.65–5.3) | 5.65 (4.51–6.70) | 0.047   |
| TLI                   |              |              |               |         |
| Median                | 0.16 (0.3–0.4) | 0.34 (0.26–0.39) | 0.29 (0.25–0.39) | 0.334   |
| Ulnar†                | 0.40 (0.36–0.51) | 0.35 (0.30–0.41) | 0.36 (0.29–0.42) | 0.038   |
| Peroneal†             | 0.41 (0.33–0.46) | 0.44 (0.32–0.52) | 0.36 (0.28–0.47) | 0.267   |
| Tibial†               | 0.42 (0.36–0.50) | 0.43 (0.37–0.51) | 0.35 (0.29–0.48) | 0.172   |
| F-wave latency (ms)   |              |              |               |         |
| Median                | 29.95 (28.4–NP) | 48.7 (29.15–NP) | 39.6 (30.3–57.3) | 0.595   |
| Ulnar                 | 32.35 (27.9–NP) | 33.7 (27.1–NP) | 45.25 (33.1–NP) | 0.243   |
| Peroneal              | 54.9 (48.3–NP) | 66.75 (51.5–NP) | 69.8 (58.6–NP) | 0.141   |
| Tibial                | 52.8 (49.45–67) | 51.5 (70.3–NP) | 55.15 (51.75–70.15) | 0.236   |
| MFR                   |              |              |               |         |
| Median                | 1.81 (1.65–NP) | 2.81 (1.87–NP) | 1.84 (1.51–2.63) | 0.050   |
| Ulnar                 | 2.16 (1.76–NP) | 3.06 (2.36–NP) | 3.03 (2.32–NP) | 0.147   |
| Peroneal              | 3.19 (2.21–NP) | 3.69 (2.42–NP) | 4.53 (2.88–NP) | 0.519   |
| Tibial                | 1.92 (1.49–2.29) | 2.25 (1.63–NP) | 2.09 (1.63–2.82) | 0.479   |
| MCV (m/s)             |              |              |               |         |
| Median                | 48.5 (41–53.2) | 49.65 (36.75–55.8) | 39.40 (33.1–49.20) | 0.070   |
| Ulnar                 | 50.95 (41.4–53.8) | 54.15 (45–59.8) | 51.15 (32.60–54.45) | 0.027   |
| Peroneal              | 42.3 (39.2–45.7) | 40.4 (36.5–44.15) | 42.65 (34–45.9) | 0.518   |
| Tibial                | 43.4 (39.8–45.6) | 43.3 (39.1–46.3) | 42.5 (36.85–46.1) | 0.768   |
| MCV (nerves without CB) (m/s) |     |              |               |         |
| Median                | 52.4 (51.3–55.4) | 54.8 (53–59) | 44.45 (35.3–50.9) | 0.003   |
| Ulnar                 | 52.2 (49.1–55.1) | 57.25 (51.7–60.5) | 51.3 (39.4–54.8) | 0.017   |
| Peroneal              | 42.8 (40.2–45.7) | 41.3 (37.4–44.5) | 43.95 (39.75–46) | 0.353   |
| Tibial                | 43.7 (42.05–45.6) | 46.1 (39.1–48.3) | 43.4 (40.8–46.8) | 0.637   |
| Distal CMAP (mV)      |              |              |               |         |
| Median                | 6.3 (5.1–8.2) | 6.55 (3.4–9.4) | 5.3 (3.5–6.6) | 0.471   |
| Ulnar                 | 7 (4.9–7.65) | 7.65 (4.35–8.95) | 5.6 (3.5–7.5) | 0.393   |
| Peroneal              | 2.8 (1.3–3.9) | 3.3 (1–4.9) | 1.57 (0.03–2.68) | 0.014   |
| Tibial                 | 7.85 (4.9–10.1) | 7.3 (3.7–10.5) | 3.5 (3.3–6) | 0.010   |

The results are shown as median (range). No. of nerves: LSS, Median = 29, Ulnar = 28, Peroneal = 23, Tibial = 20; MMN, Median = 44, Ulnar = 44, Peroneal = 38, Tibial = 38; CIDP-CB, Median = 30, Ulnar = 28, Peroneal = 23, Tibial = 25. \( * P < 0.05 \) between LSS nerves and MMN nerves. \( † P < 0.05 \) between LSS nerves and CIDP-CB nerves. \( ‡ P < 0.05 \) between MMN nerves and CIDP-CB nerves. LSS, Lewis-Sumner syndrome; MMN: Multifocal motor neuropathy; CIDP-CB: Chronic inflammatory demyelinating polyradiculoneuropathy with conduction block; DML: Distal motor latency; TLI: Terminal latency index; MFR: Modified F-wave ratio; MCV: Motor conduction velocity; CB: Conduction block; CMAP: Compound muscle action potential; NP: No potential elicited.
superimposing tibial nerve focal demyelination implies inclination of MMN diagnosis, which has not yet been reported. The tibial nerve could also be involved in the onset of MMN and was hypothesized to be particularly involved in MMN. As we demonstrated in the conduction study that the distal CMAP, representing axonal degeneration, was significant in the lower limb in CIDP-CB, which to a certain degree could mask the presence of CB; however, the selectivity still could not be fully explained. These findings suggest that ulnar and tibial CB may be critical in differentiation and, to our knowledge, have not been highlighted in chronic focal demyelinating diseases.

The mechanism of nerve and segment selectivity of chronic focal demyelinating diseases has not been fully investigated. No study has answered the question of how the ulnar or tibial nerve is particularly involved. Recently, a common etiology discovered in demyelinating diseases with CB was the detection of autoantibodies, for example, anti-neurofascin 140/186 and anti-neurofascin 155. As a target, neurofascin expression in node and paranode sites determines the impairment pattern of conduction failure and is associated with CB. CB could be restored after long-term treatment. A reasonable hypothesis is that the uneven distribution of nerve expression of neurofascin or other paranode targets may contribute to the selectivity. However, a similar unsettled confusion is why the motor nerve is selectively attacked in MMN, while studies have found that sensory and motor nerves express similar quantities of GD1a and GM1 gangliosides. It has been postulated that both the fine specificity and ganglioside orientation/exposure in the tissues contribute to target recognition. In future studies, we might extend the idea to demyelinating selectivity and look for similar underlying immuno-attack targets.

Distal vulnerability was previously suggested in typical CIDP while CIDP-CB as a subtype has rarely been analyzed and compared. Although prolonged DML in all CIDP-CB nerves was in accordance with the distal predominant pattern, the similar TLI values, comparing the distal and middle segments, of most nerves among groups implied that the distal impairments might commensurate with the middle segment when the existence of CB was taken into consideration. The CB also masked the different diffuse demyelination of the median nerve, as only the ulnar nerve motor nerve velocity (MCV) was lower in CIDP-CB. When nerves with CB were excluded, an upper limb MCV decrease in CIDP-CB emerged. The results of conduction velocity comparison with or without CB are also consistent with the conclusions in a recent study. In the conduction study, we proved that CIDP-CB showed many common features with typical CIDP compared with MMN, highlighting its diffuse demyelination feature in median and ulnar nerves.

Conclusions
We report the different distributions of segmental and diffuse demyelination of the ulnar and tibial nerves in LSS, MMN, and CIDP-CB and proved more diffuse demyelinating features in CIDP-CB, distinguishing it from LSS and MMN. The different nerve demyelination distributions and patterns could help in differentiating these conditions. This study was limited by insufficient proximal and distal conduction data and a small sample size. A prospective cohort study for evaluating the immunological mechanisms is anticipated in the future.

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Conflicts of interest
None.

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