Axonal damage determines clinical disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): A prospective cohort study of different CIDP subtypes and disease stages

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Abstract

**Background and purpose:** Monitoring of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is challenging in daily medical practice because the interrelationship between clinical disability, CIDP subtype, and neuronal degeneration is still elusive. The aim of this prospective cohort study was to investigate the role of different electrophysiological variables in CIDP monitoring.

**Methods:** Comprehensive bilateral nerve conduction studies (NCS) and structured clinical examinations were performed in 95 patients with typical CIDP and CIDP variants (age at inclusion 58.6 ± 11.6 years; median [range] inflammatory neuropathy cause and treatment overall disability score (INCAT-ODSS) 3 [0–9]), at time of first diagnosis in 25 of these patients (based on data from the prospective Immune-mediated Neuropathies Biobank registry). After 12 months, 33 patients underwent follow-up examination. Typical CIDP patients and patients with CIDP variants were characterized electrophysiologically and each individual NCS variable and the overall sum score for axonal damage and demyelination were then correlated to clinical disability scores (INCAT-ODSS, modified Medical Research Council (MRS) sum score, and INCAT sensory score).

**Results:** As opposed to demyelination markers, the NCS axonal damage variable correlated strongly with disability at both first diagnosis and advanced disease stages in cross-sectional and longitudinal analyses. Distal compound muscle action potential amplitudes of the upper limbs were found to have the strongest correlation with overall clinical function. Typical CIDP patients and patients with CIDP variants were characterized electrophysiologically and each individual NCS variable and the overall sum score for axonal damage and demyelination were then correlated to clinical disability scores (INCAT-ODSS, modified Medical Research Council (MRS) sum score, and INCAT sensory score).

**Conclusions:** Total disability is largely determined by the degree of axonal damage, especially in typical CIDP. Although most patients have symptoms predominantly in...
The study was conducted within the prospective Immune-mediated Neuropathies Biobank (INHIBIT) registry (Ethics Committee of Ruhr University Bochum vote-no. 18-6534-BR, registered DRKS00024494) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave written informed consent prior to their inclusion in the study.

Nerve conduction studies

All NCS were performed with the same device (Dantec™ Keypoint® Focus EMG device; Natus Medical GmbH, Planegg, Germany) using the standard techniques of percutaneous supramaximal stimulation and surface electrode in standardized conditions at a skin temperature of at least 33°C at the palm and 30°C at the external malleolus. Bilateral NCS were performed on the median (motor and sensory), ulnar (motor and sensory), radial (sensory), tibial (motor), peroneal (motor and sensory), and sural nerves (sensory) in all patients. In motor NCS, the variables included CMAP negative peak amplitude (measured from baseline to peak), distal motor latency (DML), distal CMAP negative peak duration, nerve conduction velocity (NCV), conduction block, temporal dispersion, minimal F-wave latency, and F-wave persistence. Motor NCV was assessed in the wrist to elbow segments for the median nerve, wrist to elbow and across the elbow for the ulnar nerve, ankle to fibular head and across the fibular head for the peroneal nerve, and ankle to popliteal fossa for the posterior tibial nerve. Sensory nerve conduction was measured orthodromically in the median, ulnar and peroneal nerves, and antidromically in the sural and radial nerves. Sensory NCS included sensory nerve action potential (SNAP) negative peak amplitude, NCV and distal sensory latency. SNAP was calculated after averaging at least 10 responses.

The degree of overall axonal damage in each patient was defined by the amount of nerves with reduced distal CMAP amplitudes. We used the reference values from Stöhr [10]. We created an ordinal scale, beginning with no axonal damage in any limb (0), then allocating scores for sensory involvement of the lower limbs (mild, 1), sensorimotor involvement of the lower limbs (moderate, 2), sensorimotor involvement of the lower limbs plus sensible involvement of the upper limbs (severe, 3), and sensorimotor involvement of the upper and lower limbs (very severe, 4). Six patients were not included here as they had predominant axonal involvement of the upper limbs, which is not measurable with this score.

Signs of demyelination were defined with regard to the EFNS/PNS criteria [2] in order to generate dichotomous variables. The

INTRODUCTION

Nerve conduction studies (NCS) represent the “gold standard” in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and are central to the criteria used by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) [1,2]. An extensive initial electrophysiological examination protocol is required to provide convincing evidence of demyelination. However, the role of NCS in the monitoring of CIDP patients is still under discussion. NCS can be misleading in severe disease courses, with low distal compound muscle action potential (CMAP) amplitudes suggestive of increased axonal damage [3–5]. Bearing in mind that more than 25% of CIDP patients do not adequately respond to first-line treatment and are at risk of disease progression, adequate monitoring has an important role to play in daily clinical practice [5–7]. Furthermore, several studies have demonstrated that different pathoanatomical features of CIDP variants, such as distal acquired demyelinating symmetric neuropathy (DADS) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), are relevant in diagnosis and monitoring [8]. It is unknown how well the degree of demyelination or axonal damage correlates with physical disability in different subtypes and stages of CIDP. The aim of the present prospective cohort study, therefore, was to consider to what extent NCS are suitable for monitoring and determining disease-related disability in such patients.

METHODS

Patients

In a single-centre prospective observational cohort study (St. Josef-Hospital, University Hospital Bochum) 95 patients with CIDP were analysed with regard to demographic, clinical, serological and electrophysiological data (overall cohort). A total of 25 patients had their first diagnosis within the 6-month period before inclusion in the study (mean time: 2.32 ± 2.32 months) and formed the initial diagnosis (ID) group. The remaining 70 patients were already diagnosed with CIDP before inclusion. Patients were diagnosed in accordance with the EFNS/PNS diagnostic criteria [2]. Atypical CIDP variants were further differentiated in accordance with Doneddu et al. [9] including DADS, MADSAM, pure sensory CIDP and pure motor CIDP. In addition to cross-sectional analysis of the whole cohort, follow-up examination was performed in 33 patients 12 months after inclusion. Patients with evidence of myelin-associated antibody (MAG) or antibodies associated with nodo-paranodopathy were not included.

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KEYWORDS

axonal damage, chronic inflammatory demyelinating polyradiculoneuropathy, CIDP variants, distal CMAP amplitude, monitoring
degree of overall demyelination in each patient was defined based on the number of different motor neurons involved (from 0 to 4 different nerves: median, ulnar, peroneal or tibial nerve).

Electromyographic examination

Electromyography was not conducted as part of this prospective study; however, results from electromyographic examinations on clinical indication were collected. The tibialis anterior muscle was analysed in each patient with regard to pathological spontaneous activity (PSA), as shown elsewhere [11].

Outcome analyses

Clinical disability was evaluated using the inflammatory neuropathy cause and treatment overall disability score (INCAT-ODSS) [12], the INCAT sensory score (ISS) [13], and the modified Medical Research Council (MRC) sum score [14,15] at the time of inclusion and 12 months afterwards if applicable.

Statistics

Statistical analysis was performed using IBM® SPSS Statistics (version 26.0.0.0). Demographic and clinical characteristics were compared between groups using Student’s t-test for numerical normally distributed variables and the Mann–Whitney test or chi-squared test for nominal variables. Analysis of variance for numerical normally distributed variables or Kruskal–Wallis analysis for nominal variables was used if three or more groups were compared. Pearson correlation for numerical normally distributed and Spearman’s correlation for nominal variables were used to correlate two variables. For longitudinal data, the differences between baseline and 12-month follow-up distal CMAP amplitude (Δdistal CMAP amplitude) or SNAP amplitude (ΔSNAP amplitude) and the differences between baseline and 12-month follow-up INCAT-ODSS (ΔINCAT-ODSS), modified MRC sum score (Δmodified MRC sum score), or INCAT-ISS (ΔINCAT- ISS) were correlated. Quantitative data are presented as mean values ± standard deviation or median and range values. For all analyses, the threshold for statistical significance was set at p < 0.05.

RESULTS

Demographic and clinical data

The mean age at onset was 58.6 ± 11.6 years and the time between onset of symptoms and study inclusion was 72.7 ± 58.5 months (female to male patient ratio 1:3.75). In the ID group, the mean disease duration from onset of symptoms to study inclusion was 31.0 ± 32.8 months. According to the electrophysiological EFNS/PNS criteria, 80% of the patients were diagnosed with definite, 3% with probable, and 17% with possible CIDP. At the time of inclusion in the study, 18 patients had not received immunotherapy; 69 patients received first-line immunotherapy, and 36 of these received a further second-line therapy. Eight patients were treated with a second-line therapy only.

At the time of inclusion in the study, the median (range) total INCAT-ODSS and modified MRC sum score were 3 (0–9) and 72 (37.5–80), respectively, in the overall cohort, and 3 (1–9) and 76 (38–80), respectively, in the ID group. Stratification of INCAT-ODSS by upper and lower limbs showed that 52.8% of the overall cohort and 64% of the ID group had a higher INCAT-ODSS in the lower limbs, while only 12.9% and 4%, respectively, had the opposite.

Distal CMAP as a marker for axonal damage

To provide evidence that distal CMAP amplitudes are suitable markers for axonal damage, we reviewed the presence of PSA and creatine kinase levels with regard to CMAP amplitudes. Electromyographic examinations in the tibial anterior muscle were performed in 37 patients at the same time as the electroneurography. Patients who had PSA had significantly lower distal CMAP amplitudes in the peroneal nerve compared to patients without PSA (24 vs. 13 patients: 0.16 ± 0.42 vs. 0.84 ± 1.39 mV; p = 0.028). Creatine kinase levels correlated inversely with distal CMAP amplitudes in the ulnar (r = −0.151, p = 0.045), tibial (r = −0.16, p = 0.034), and peroneal nerves (r = −0.255, p = 0.003; time from electroneurography to blood sample 40 ± 108 days).

Axonal damage is a reliable marker of clinical disability

Assessment of overall axonal damage using an ordinal five-step score (none to very severe) showed that no patients had either no or mild axonal damage in the overall cohort or in the ID group. Most of the patients in the overall cohort and the ID group experienced very severe (52.8%) or severe (56.0%) axonal damage, respectively. In the overall cohort, the group with very severe axonal damage had a significantly higher INCAT-ODSS compared to the group with moderate or severe damage (2 [0–4] vs. 2 [0–8] vs. 4 [2–9]; p < 0.001 [Figure 1a]). In the ID group, this was also evident for patients with very severe axonal damage compared to severe axonal damage (2 [1–8] vs. 5 [2–9]; p = 0.034 [Figure 1b]). Importantly, neither mean age nor mean disease duration (time from symptoms to inclusion) differed significantly between the severity groups.

The distal CMAP amplitudes of all analysed nerves significantly correlated to INCAT-ODSS, modified MRC sum score, and INCAT sensory sum score (Figure 2). The ulnar nerve had the highest
correlation coefficient with each of the measured outcome variables ($r = -0.468$, $r = 0.344$, $r = -0.344$, respectively; each $p < 0.001$). None of the distal CMAP amplitudes in any of the measured nerves significantly correlated to patient age. Only tibial nerve distal CMAP amplitude correlated weakly with time from onset to inclusion ($r = -0.186$, $p = 0.012$).

In longitudinal disease course analysis, $\Delta$distal CMAP amplitudes of the median and tibial nerves correlated significantly to $\Delta$INCAT-ODSS ($r = -0.423$, $r = -0.450$; each $p < 0.001$) and $\Delta$modified MRC sum score ($r = 0.273$, $p = 0.028$ and $r = 0.264$, $p = 0.032$, respectively), $\Delta$distal CMAP amplitude of the peroneal nerve correlated significantly to $\Delta$modified MRC sum score ($r = 0.261$, $p = 0.037$), and $\Delta$distal CMAP amplitudes of the radial nerve correlated significantly to $\Delta$INCAT-ODSS ($r = -0.025$, $p = 0.037$ [Figure 3]).

**Demyelination does not correlate with disability**

Similarly to axonal damage, overall degree of demyelination was also scored using an ordinal four-step score depending on the number of affected motor nerves. Most patients had demyelinating signs in two motor nerves (42%, 40/95), while 20% of patients (19/95) had these in one, 26% (25/95) in three, and 12% (11/95) in four motor nerves. There was no significant association between number of demyelinated nerves and INCAT-ODSS, age, or disease duration (Figure 1c).

**Sensory and motor upper limb involvement determines disability**

Even though all distal CMAP and SNAP amplitudes significantly correlated with the disability markers (Figure 2), the correlation coefficients for the upper limbs were higher compared to those for the lower limbs. The strongest correlations were found between ulnar nerve distal CMAP amplitude and both INCAT-ODSS ($r = -0.468$, $p < 0.001$) and modified MRC sum score ($r = 0.334$, $p < 0.001$), and between ulnar nerve SNAP amplitude and INCAT-SS ($r = -0.344$, $p < 0.001$). In this context, 57.9% and 52.6% of the measured motor nerves of the lower limbs had an amplitude <1 mV in the overall cohort and the ID group, in contrast to 3.8% and 0%, respectively, for the upper limbs.

**CIDP variants differ in degree of axonal loss and subsequent clinical disability**

In total, 48% of all patients (46/95) were diagnosed with typical CIDP, while patients diagnosed with DADS (57%, 28/49) or MADSAM (27%, 13/49) were the largest subgroups within the atypical CIDP variants. The CIDP subgroups did not differ significantly with regard to age or disease duration. However, patients with DADS and MADSAM had a significantly lower median INCAT-ODSS at inclusion compared to those with typical CIDP (2 [0–6] vs. 3 [2–8] vs. 4 [0–8]; $p < 0.001$). In contrast to typical CIDP and DADS patients, MADSAM patients had a higher median INCAT-ODSS for the upper (2, 0–3) than for the lower limbs (1 [0–6]). Moreover, patients with DADS had a significantly higher median modified MRC sum score compared to typical CIDP patients at inclusion (78.5 [56–80] vs. 67.25 [37.5–80]; $p < 0.001$ [Table 1]).

A detailed analysis of every electroneurographic variable stratified by CIDP subtype is presented in Table S1. The most important findings were as follows.

Typical CIDP patients had a high degree of axonal damage, especially in the lower limbs. In all measured nerves, distal CMAP and SNAP amplitudes were lower compared to those in DADS patients, which reached significance for distal CMAP amplitudes of the median and ulnar nerves (each $p < 0.001$) and SNAP amplitudes of the radial ($p = 0.041$) and peroneal nerves ($p < 0.001$).

In contrast, MADSAM patients had greater axonal damage in the upper limbs compared to patients with other CIDP subtypes, as
shown by a significantly lower distal CMAP amplitude in the ulnar nerve in comparison to that in DADS patients ($p = 0.031$), but a significantly higher distal CMAP amplitude of the tibial nerve (each $p < 0.001$) and a higher SNAP amplitude of the sural nerve ($p = 0.002$, $p = 0.013$) in comparison to typical CIDP and DADS patients. These results were very similar, when the number of non-excitable nerves (distal CMAP with an amplitude <1 mV) were compared among the CIDP subgroups.

The distal CMAP amplitudes of the ulnar, tibial and peroneal nerves in patients with typical CIDP correlated to INCAT-ODSS ($r = -0.421, p < 0.001; r = -0.225, p = 0.036; r = -0.348, p = 0.001$, respectively; Table 2). In line with the relatively mild reduction in distal CMAP amplitudes in patients with DADS and concordant low INCAT-ODSS, distal CMAP amplitude of the median nerve was the only variable that significantly correlated to INCAT-ODSS ($r = 0.321, p = 0.018$). In MADSAM patients, distal CMAP amplitudes

FIGURE 2 The distal compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes of all nerves correlated with clinical disability. The distal CMAP amplitudes of the median, ulnar, tibial, and peroneal nerves showed a significant inverse correlation with inflammatory neuropathy cause and treatment overall disability score (INCAT-ODSS) (a), with the correlation of ulnar nerve distal CMAP amplitude with INCAT-ODSS being the highest. A similar correlation was shown in regard to the modified Medical Research Council (MRC) sum score (b) and INCAT sensory score (c).
FIGURE 3  The distal compound muscle action potential (CMAP) amplitude correlated with disability in long-term analysis. The difference between baseline and 12-month follow-up distal CMAP amplitudes of the median (a) and tibial (b) or sensory nerve action potential (SNAP) amplitude of the radial nerve (c) correlated significantly inversely to the difference between baseline and 12-month follow-up inflammatory neuropathy cause and treatment overall disability score (INCAT-ODSS). The difference between baseline and 12-month follow-up distal CMAP amplitudes and baseline and 12-month follow-up modified Medical Research Council (MRC) sum score correlated significantly in the median (d), tibial (e), and peroneal (f) nerves. All other measured nerves did not show a significant correlation.

TABLE 1  Clinical characteristics of the different chronic inflammatory demyelinating polyradiculoneuropathy subtypes

|                     | Total, N = 95 | Typical CIDP, n = 46 | DADS, n = 28 | MADSAM, n = 13 | Other atypical CIDP, n = 8 | p value |
|---------------------|---------------|-----------------------|--------------|----------------|---------------------------|---------|
| Gender, male:female | 2.8:1         | 13.1                  | 12.1         | 0.61           |                           |         |
| Age at inclusion, years | 59.4 ± 11.1 | 59.3 ± 9.7            | 58.7 ± 11.9  | 51.4 ± 17.5    | 0.982                     |         |
| Age at onset, years  | 52.8 ± 11.9   | 53.5 ± 10.4           | 52.1 ± 10.9  | 47.1 ± 17.4    | 0.844                     |         |
| Age at initial diagnosis, years | 54.9 ± 11.6 | 57.6 ± 8.4            | 55.9 ± 11.8  | 49.4 ± 18.2    | 0.579                     |         |
| Disease duration, months | 77.2 ± 58.5 | 69.4 ± 57             | 77.2 ± 66    | 50.6 ± 50.1    | 0.727                     |         |
| Median (range) INCAT-ODSS upper limbs | 2 (0–3) | 1 (0–2)               | 2 (0–3)      | 2 (0–3)       | <0.001; <0.001; <0.001 |
| Median (range) INCAT-ODSS lower limbs | 2 (0–5) | 2 (0–4)               | 1 (0–6)      | 2 (2–6)       | 0.024; 0.030 ^a         |
| Median (range) INCAT-ODSS total | 4 (0–8) | 2 (0–6)               | 3 (2–8)      | 4 (2–9)       | <0.001; <0.001; 0.05 ^c  |
| Median (range) modified MRC sum score | 67.3 (37.5–80) | 78.5 (56–80)           | 72 (38–80)   | 77 (49–80)    | <0.001; <0.001 ^d            |
| Median (range) INCAT sensory sum score | 7 (0–20) | 5 (0–14)               | 3 (0–15)     | 8 (1–15)      | 0.041                     |

Note: Data are mean ± standard deviation, unless otherwise stated. DADS and MADSAM patients had a significantly lower median INCAT-ODSS at inclusion compared to typical CIDP patients. Moreover, patients with DADS had a significantly higher median modified MRC sum score compared to typical CIDP patients.

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DADS, distal acquired demyelinating symmetric neuropathy; INCAT-ODSS, inflammatory neuropathy cause and treatment overall disability score; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MRC, Medical Research Council.

^Typical CIDP vs. DADS.
^Typical CIDP vs. MADSAM.
^DADS vs. MADSAM.
of the ulnar and tibial nerves correlated to INCAT-ODSS \((r = -0.559, \ p = 0.0004; r = -0.447, \ p = 0.004)\). The results of the correlation of distal CMAP amplitude to modified MRC sum score were similar to the results of the correlation of distal CMAP amplitude to INCAT-ODS (Table 2).

**Electrophysiological profile of the CIDP subtypes**

Comparing the different NCS variables, each subgroup revealed further distinct differences (Table S1). F-wave persistence was significantly lower in the ulnar nerve in MADSAM patients compared to DADS patients \((p = 0.013)\), while F-wave latency was lower in the tibial nerve in MADSAM patients compared to typical CIDP \((p = 0.013)\) and DADS \((p = 0.035)\) patients. Moreover, MADSAM patients had a higher motor NCV in the tibial nerve compared to typical CIDP \((p < 0.001)\) and DADS patients \((p = 0.003)\). Besides the markers of axonal damage, further electrophysiological characteristics of the motor nerves of the upper limbs did not differ between MADSAM and typical CIDP.

**DISCUSSION**

We were able to demonstrate that, in contrast to demyelination markers, markers of axonal damage represented by reduced distal CMAP and SNAP amplitudes are the key determinants of clinical disability.

**TABLE 2** Correlation of clinical disability to the electrophysiological parameters of axonal damage separated by the different variants of chronic inflammatory demyelinating polyradiculoneuropathy

| Distal CMAP amplitude | Typical CIDP | DADS | MADSAM |
|-----------------------|--------------|------|--------|
| **INCAT-ODSS**        |              |      |        |
| Median nerve          |              |      |        |
| \(p = 0.102\)         | \(p = 0.018\) |      | \(p = 0.201\) |
| \(r = -0.321\)        |              |      |        |
| Ulnar nerve           |              |      |        |
| \(p < 0.001\)         | \(p = 0.583\) |      | \(p = 0.004\) |
| \(r = -0.421\)        |              |      |        |
| Tibial nerve          |              |      |        |
| \(p = 0.036\)         | \(p = 0.453\) |      | \(p = 0.029\) |
| \(r = -0.225\)        |              |      |        |
| Peroneal nerve        |              |      |        |
| \(p = 0.001\)         | \(p = 0.312\) |      | \(p = 0.259\) |
| \(r = -0.348\)        |              |      |        |
| **Modified MRC sum score** |          |      |        |
| Median nerve          |              |      |        |
| \(p = 0.205\)         | \(p = 0.007\) |      | \(p = 0.645\) |
| \(r = 0.365\)         |              |      |        |
| Ulnar nerve           |              |      |        |
| \(p < 0.001\)         | \(p = 0.492\) |      | \(p = 0.046\) |
| \(r = 0.401\)         |              |      |        |
| Tibial nerve          |              |      |        |
| \(p = 0.004\)         | \(p = 0.338\) |      | \(p = 0.188\) |
| \(r = 0.302\)         |              |      |        |
| Peroneal nerve        |              |      |        |
| \(p = 0.002\)         | \(p = 0.147\) |      | \(p = 0.372\) |
| \(r = 0.332\)         |              |      |        |
| **SNAP amplitude**    |              |      |        |
| **INCAT sensory score** |          |      |        |
| Median nerve          |              |      |        |
| \(p = 0.039\)         | \(p = 0.102\) |      | \(p = 0.271\) |
| \(r = -0.220\)        |              |      |        |
| Ulnar nerve           |              |      |        |
| \(p = 0.124\)         | \(p = 0.006\) |      | \(p = 0.097\) |
| \(r = -0.372\)        |              |      |        |
| Radial nerve          |              |      |        |
| \(p = 0.003\)         | \(p = 0.077\) |      | \(p = 0.258\) |
| \(r = -0.318\)        |              |      |        |
| Sural nerve           |              |      |        |
| \(p = 0.070\)         | \(p = 0.460\) |      | \(p = 0.066\) |
| \(r = -0.350\)        |              |      |        |
| Peroneal nerve        |              |      |        |
| \(p = 0.634\)         | \(p = 0.012\) |      | \(p = 0.473\) |
| \(r = -0.350\)        |              |      |        |

Note: Distal CMAP and SNAP amplitudes of all measured nerves were correlated to the INCAT-ODSS (A), modified MRC sum score (B), and INCAT sensory score. Weak associations are illustrated in grey. The distal CMAP amplitudes of the typical CIDP correlated more frequently to the disability markers compared to DADS or MADSAM. The bold values are the values of significance (p-values).

Abbreviations: CMAP, compound muscle action potential; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DADS, distal acquired demyelinating symmetric neuropathy; INCAT-ODSS, inflammatory neuropathy cause and treatment overall disability score; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; SNAP, sensory nerve action potential.
Previous studies have implied that CMAP amplitude [16,17] and histopathological axonal loss [18] correlate with muscle strength; however, this association was questioned, especially in late stages [4]. In the present study, we showed a high correlation between NCS and INCAT-ODSS, modified MRS sum score, and INCAT-ISS at initial diagnosis and in advanced disease stages. Evidence of axonal damage provided by correlation of distal CMAP amplitudes with creatine kinase levels and an association of PSA with distal CMAP amplitude heights is in line with the correlation of distal CMAP amplitude to muscle atrophy shown in previous studies [3]. Since axonal loss determined disability also in longitudinal analysis, it is suitable for use in monitoring CIDP patients.

The correlation of distal CMAP amplitudes of the upper limbs to disability scores was even stronger than that found for the lower limbs. This is probably attributable to extensive axonal damage and the resulting amplitude reduction in the tibial and peroneal nerves in our cohort at both initial diagnosis and during the disease course. Our results point to the importance of NCS of the upper limbs at initial diagnosis and during the disease course even if patients are asymptomatic in that area. Detection of axonal damage in asymptomatic limbs might identify patients at risk of further disease progression. Our results support the inclusion of the upper limbs in ultrasound protocols for therapy monitoring [19,20]. In the present study, the ulnar nerve had the strongest correlation to INCAT-ODSS, modified MRC sum score, and INCAT-ISS.

Our results underline the impact of axonal damage for the entire disease course. Previously, Iijima et al. [21] demonstrated an association between reduced CMAP amplitudes and insufficient response to intravenous immunoglobulin treatment, and there is histopathological evidence of a reduced number of spinal motor neurons in CIDP patients as a possible sign of dying-back axonopathy [22]. Nevertheless, distal CMAP amplitudes improve after first-line therapy in some cases [23]; therefore, probably only chronic CMAP amplitude reduction, and not a reduction due to a conduction block or temporal dispersion as often seen in MADSAM patients, should be taken as a relevant prediction factor for clinical outcome based on our cohort [24]. Even though in MADSAM patients a severe conduction block is commonly associated with concurrent paresis [25], the overall demyelination of the patients was not associated with the degree of disability.

Neurofilament light chain (NfL), electromyography and muscle ultrasonography studies support the association of axonal loss with clinical disability in several ways. First, NfL levels in pre-treated CIDP patients were significantly increased compared to healthy controls and patients after immunotherapy induction [26,27] and NfL level was able to predict 1-year disease progression [28]. Second, evidence of PSA on electromyography in CIDP has been associated with a worse long-term outcome [11]. Third, increased muscle echointensity, reflecting fibrosis and fatty infiltration due to secondary axonal damage, correlated with muscular strength and disability in CIDP patients [29].

Further studies should therefore consider axonal damage as a primary outcome marker in multivariate fashion (creatine kinase, electrophysiology, NfL, and muscle ultrasonography).

Severe axonal loss at first diagnosis might indicate an aggressive disease course from the time of onset. This implies that destruction of axonal integrity, and not only of myelinating Schwann cells, might be an intrinsic part of the pathogenesis instead of being only a side effect [18,30]. Therefore, highly effective immunotherapy with neuroprotective potential should be considered in patients with early axonal involvement [5].

Although CIDP patients are clinically divided into different CIDP subtypes [2,9,31], they are only insufficiently characterized electrophysiologically [32–35]. The following characteristics were most apparent in our study:

a. Typical CIDP patients experienced a high degree of axonal loss, especially in the lower limbs, determining a high level of disability. In contrast, axonal loss in all measured nerves in DADS patients was lower than in typical CIDP patients. This finding was accompanied by a higher INCAT-ODSS in typical CIDP patients and more frequent correlation of distal CMAP amplitudes of single nerves to clinical disability. In this context, Feng et al. [32] showed that 25% of DADS patients transitioned to typical CIDP over time, which might imply similar but more benign mechanisms in DADS pathophysiology compared to typical CIDP.

b. Corresponding to the clinical phenotype, the proximal nerve parts (F-waves) were less affected in DADS compared to typical CIDP. This is in line with the finding of a particularly pronounced swelling of the brachial and lumbosacral plexus in magnetic resonance neurography of typical CIDP patients compared to those with DADS [32].

c. MADSAM patients have a predominantly electrophysiological impairment of the upper limbs. Not only was the axonal damage more severely affected in the upper limbs, but also signs of demyelination were evident in the proximal (F-wave persistence of the ulnar nerve) and middle (motor nerve conduction velocity in the tibial nerve) nerve parts. This is also reflected in a higher INCAT-ODSS of the upper than of the lower limbs, demonstrating the multifocal character of this disease.

d. Interestingly, in our cohort, DADS patients had significant preservation of myelination of the distal nerve parts (DML in the median nerve, sensory NCV in the radial and peroneal nerves). Previously, prolonged DML has been found to be a key feature in DADS [31], more specifically, strikingly prolonged DML has been shown in patients with a clinical distal pattern and evidence of anti-MAG antibodies [36]. Our results contradict those previous findings, probably because we excluded patients with anti-MAG neuropathy from this analysis in accordance with the EFNS/PNS criteria [2]. Because patients with or without immunoglobulin M monoclonal gammapathies or anti-MAG neuropathy differ in immunotherapy response [37], they might also differ electrophysiologically.

Even though each CIDP variant has a different impact on axonal integrity, the prevention of axonal damage is as important in patients with CIDP variants as it is in those with typical CIDP.
Current available treatment options mostly target inflammatory processes, but it has already been shown by in vitro experiments with CIDP-sera-conditioned Schwann cells that axonal regeneration is impaired in CIDP patients [38]. In the light of a high economic burden above £22,000 in the United Kingdom [31], further neuroprotective agents are required. Capsaicin has [39,40] demonstrated an anti-inflammatory and anti-oxidative potential in vitro and in the experimental autoimmune neuritis rat model. Furthermore, propionic acid has shown an anti-inflammatory effect in multiple sclerosis patients [41,42] and a case report indicates a positive effect also in CIDP patients [43]. In our own unpublished data, a direct anti-inflammatory effect of propionic acid on Schwann cells and dorsal root ganglia has been demonstrated (Grüter et al., unpublished).

In conclusion, NCS markers of axonal damage were strongly associated with disability and are suitable for monitoring CIDP patients at different disease stages and with different CIDP subtypes. Axonal markers in typical CIDP patients were more strongly associated with clinical disability. Monitoring should include the upper limbs because of the greater correlation with overall clinical function.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Thomas Grüter: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Investigation (equal); Methodology (equal); Project administration (lead); Supervision (equal); Visualization (equal); Writing – original draft (lead); Writing – review and editing (equal). Jeremias Motte: Investigation (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing – review and editing (equal). Yesim Bulut: Data curation (lead); Formal analysis (equal); Methodology (lead); Visualization (equal). Anna Kordes: Data curation (equal). Diamantis Athanasopoulos: Writing – review and editing (equal). Miriam Fels: Writing – review and editing (equal). Christiane Schneider-Gold: Writing – review and editing (equal). Ralf Gold: Writing – review and editing (equal). Anna Lena Fisse: Data curation (supporting); Writing – review and editing (equal). Kalliopi Pitarokoili: Conceptualization (equal); Project administration (equal); Supervision (equal); Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed (e.g. deidentified participant data) during the present study are available from the corresponding author (thomas.grueuter@rub.de) on reasonable request.

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