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RESEARCH REPORT

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Changes in axonal and clinical function during intravenous and subcutaneous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy

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Abstract

Background and Aims: Intravenous immunoglobulin (IVIg) has a rapid clinical effect which cannot be explained by remyelination during each treatment cycle in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). This study aimed to investigate axonal membrane properties during the IVIg treatment cycle and their potential correlation with clinically relevant functional measurements.

Methods: Motor nerve excitability testing (NET) of the median nerve was performed before and 4 and 18 days after initiation of an IVIg treatment cycle in 13 treatment-naïve (early) CIDP patients and 24 CIDP patients with long term (late) IVIg treatment, 12 CIDP patients treated with subcutaneous immunoglobulin (SCIg) and 55 healthy controls. Clinical function was measured extensively using the Six Spot Step test, 10-Meter Walk test, 9-Hole Peg test, grip strength, MRC sum score, Overall Neuropathy Limitations Score and Patient Global Impression of Change.

Results: Superexcitability and S2 accommodation decreased significantly in the early treatment group from baseline to day 4 and returned to baseline levels at day 18, suggesting temporary depolarization of the axonal membrane. A similar trend was observed for the late IVIg group. Substantial clinical improvement was observed in both early and late IVIg groups during the entire treatment cycle. No statistically significant correlation was found between clinical and NET changes. No change was found in NET or clinical function in the SCIg group or controls.

Interpretation: NET suggested temporary depolarization of the axonal membrane during IVIg treatment in treatment naïve CIDP patients. The relation to clinical improvement, however, remains speculative.

KEYWORDS
axonal function, chronic inflammatory demyelinating polyneuropathy, immunoglobulin treatment, nerve excitability testing

1 | INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by progressive paresis and sensory dysfunction in the extremities causing disability.[1] The prevalence is estimated to be 1–2/100.000.[2,3] Diagnosis is based on a combination of clinical symptoms, electrophysiology and spinal fluid examination.[4]

Electrophysiological examination shows reduced nerve conduction velocity, temporal dispersion of compound motor action potentials, motor conduction block, and increased F-wave latencies.[4–6] Microscopic examination reveals segmental demyelination, remyelination, and axonal fiber loss in peripheral nerves.[4]

Immunoglobulin is considered first line treatment in CIDP[7] administrated intravenously[8–12] or subcutaneously.[13,14] The exact mechanism of action in the treatment of CIDP has not been determined, but effects on different components of the immune system, including antibodies, the complement system, macrophage activation, co-stimulatory and adhesion molecules has been demonstrated.[15–17] Upon treatment, a rapid improvement in clinical function has been found.[18] However, very sparse change was demonstrated in conventional nerve conduction studies (NCS). The clinical improvement occurring within days after treatment is too rapid to be caused alone by ongoing remyelination following the anti-inflammatory action of immunoglobulin treatment. It has previously been suggested that immediate clinical improvement following intravenous immunoglobulin (IVIg) treatment could be caused by changes in axonal ion channel function[19–24] that cannot be captured by conventional NCS.

Using nerve excitability testing (NET), prior studies evaluating patients with CIDP during IVIg treatment found that treatment modulated axonal excitability, stabilized the membrane potential, and promoted functional recovery.[23,24] However, the studies were performed in a limited number of patients and the pharmacodynamic effects responsible for these excitability changes are still not fully understood at a cellular level.[25] Further, although a previous study found no correlation between changes in NET and muscle strength,[23] the potential correlation with clinically relevant motor function has not been examined. The demonstration of such a correlation could pave the way for future pharmacological treatment specifically modulating axonal function.

We aimed to evaluate changes in axonal properties in CIDP patients treated with IVIg using NET. Second, we aimed to search for correlations between NET changes and functional changes measured by comprehensive clinical testing. We examined patients treated with subcutaneous immunoglobulin (SCIg) and controls for comparison.

2 | METHODS

2.1 | Study design

This prospective study was conducted at two sites, Odense University Hospital (OUH) and Aarhus University Hospital. All patients were recruited as out-patients. Subjects were divided into four groups: (1) Naïve (early) CIDP patients examined during the first ever IVIg treatment, (2) CIDP patients (late) treated with IVIg for more than 3 months, (3) CIDP patients treated with SCIg, and (4) controls. For CIDP patients treated with IVIg, examination was performed before treatment (0–4 h prior), 0–4 h after the last treatment of the cycle (day 4) and 14 days after the last treatment of the cycle (day 18; Figure 1). CIDP patients treated with SCIg and controls were examined at corresponding time points.

2.2 | Study population

All patients previously diagnosed with CIDP treated with either IVIg or SCIg were invited to participate in the study. The diagnosis was confirmed according to European Federation of Neurological Societies/Peripheral Nerve Society criteria.[7] Patients treated with IVIg could either be newly diagnosed (early) or on long-term treatment (late). Patients in the early group were treatment naïve while patients in the late group had at least three cycles of immunoglobulin. Patients in the SCIg group had all previously been treated with IVIg for at least three cycles while duration of SCIg treatment varied. However, additional treatment with corticosteroids at any dose was allowed. Patients were excluded if they were younger than 18 or older than 80 years old. Severe systemic disease, pathology affecting the spinal roots or spinal cord and other diseases affecting the ability to walk were also exclusion criteria. Age-matched control subjects were recruited through ads at the OUH website and Facebook page.

2.3 | Study procedures

NET, conventional NCS, functional tests and questionnaires grading everyday functioning were performed at each examination.

NCS were performed on median and peroneal nerves on the right side following standard protocols using surface electrodes. KeyPoint.net (Natus Medical Inc., Middleton, WI) was used for NCS.

NET with threshold tracking was performed on the right median nerve. Using surface electrodes, the compound muscle action potential was recorded from the abductor pollicis brevis muscle. Standard TRONDNF protocol was used.[26] This method examines the excitability of axons, assessing the passive and active properties of the axolemma reflecting the properties of ion channel function.[27] Recording and data analysis was performed using the QTRAC software (Prof Hugh Bostock, UCL). Threshold electrotonus, the current-threshold relationship, strength duration time constant, rheobase and recovery cycle variables were determined a previously described.[28] Temperature was maintained at 32–34°C.

Clinical testing was conducted using standard instruments. For the upper extremities, strength and coordination was examined by measuring grip strength using a hand-held dynamometer (JAMAR, Lafayette Instrument, Inc., Lafayette, IN) and the nine-hole-peg test.[29] For the lower extremities, function and coordination was examined using the timed-10-meter-walk test and the six-spot-step test.[30] The overall strength was scored using MRC sum score[31] and the sensory

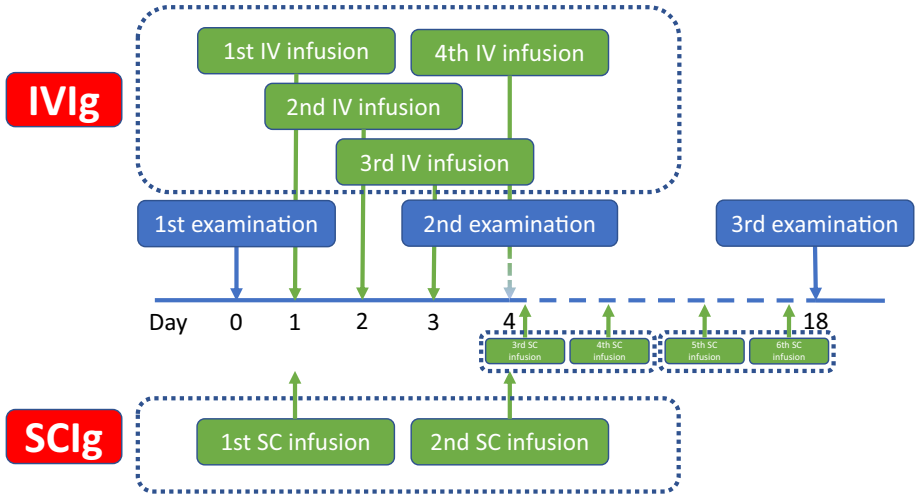

FIGURE 1 Study design. IV, intravenous; IVIg, intravenous immunoglobulin; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

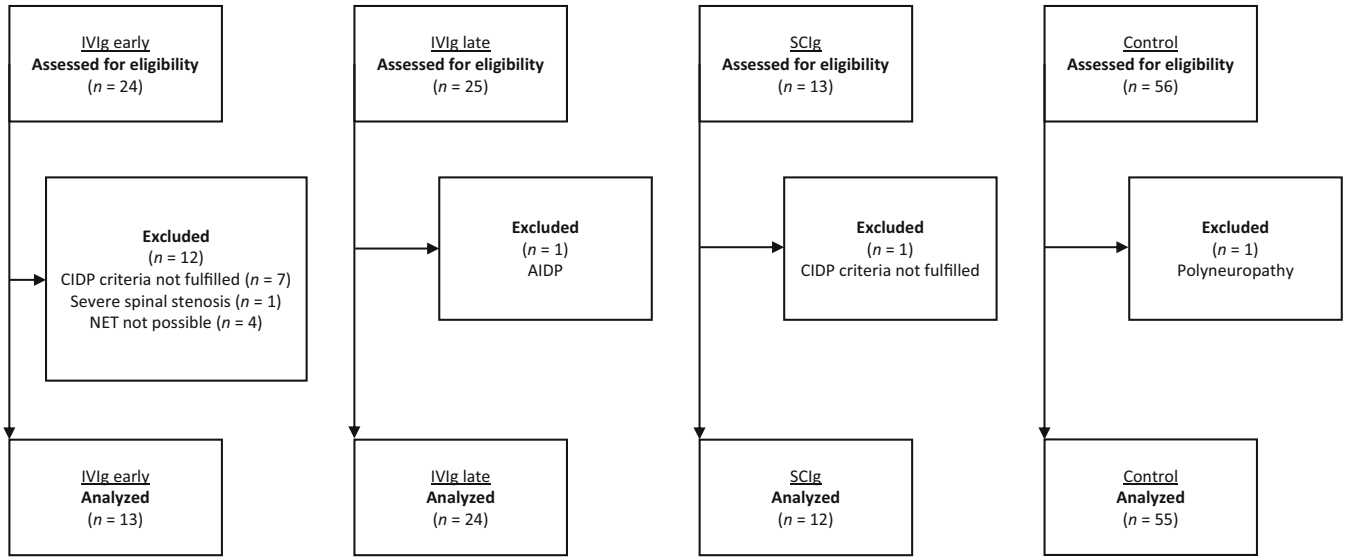

FIGURE 2 Study flow chart. AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; IVIg, intravenous immunoglobulin; NET, nerve excitability testing; SCIg, subcutaneous immunoglobulin.

function was scored using INCAT sensory sum score.[32] Everyday function was scored using the Overall Neuropathy Limitations Scale (ONLS),[33] and the Rasch-built Overall Disability scale.[34] At study entry, neuropathic pain symptoms were assessed with the Neuropathic Pain Symptom Inventory.[35] Overall change was scored using Patient Global Impression of Change (PGIC) (much improved, moderately improved, slightly improved, no change, slightly worse, moderately worse, much worse was converted to numerical scores +3 to −3).

2.4 | Data analysis

For each of the study groups, mean values at each visit were compared using ANOVA followed by Tukey's multiple comparisons test. The correlation between NET changes and clinical measures was assessed using Spearmans *r*, as data were not normally distributed. Analyses were performed using Stata BE 17.

3 | RESULTS

3.1 | Patients

Thirteen patients in the early phase of IVIg treatment, 24 in the late phase of IVIg treatment, 12 SCIg treated patients and 55 control subjects completed the study (Figure 2). Clinical characteristics are presented in Table 1. Nineteen of twenty-four patients in the IVIg late group fulfilled criteria for definite CIDP. One patient had probable CIDP. The initial NCS data was not available for validation for the last four patients. In these patients, the diagnosis of CIDP was based on detailed descriptions of NCS in medical records. All patients in the early IVIg and SCIg groups fulfilled the criteria for definite CIDP. Results of NCS at the time of CIDP diagnosis are presented in Table 2. Data are presented as the deviation from reference values (standard deviations). As expected, F-wave latency was the most affected variable.

TABLE 1 Clinical characteristics.

	Patient groups			
	IVIg early ($n = 13$)	IVIg late ($n = 24$)	SCIg ($n = 12$)	Control ($n = 55$)
Age, years, median (range)	58 (45–69)	65 (47.5–70.5)	66 (49–71)	57 (45–68)
Sex (M/F)	5/8	15/9	6/6	23/32
Smoking (pt)	3	4	1	3
Alcohol consumption more than 5 units per day (pt)	0	0	0	0
Diabetes (pt)	0	0	1	0
Onset of symptoms to diagnosis (months), median (range)	6 (1–24)	22 (11.5–60)	24 (6–48)	
Diagnosis to inclusion (months), median (range)	2 (1–2)	28 (6–42)	22 (15–67)	
Fulfill criteria for demyelinating polyneuropathy (pt)	13	22[a]	11[a]	
Cerebrospinal fluid protein level (mg/mL) at diagnosis, median (range)	0.56 (0.46–0.78)	0.60 (0.50–0.75)	0.50 (0.40–0.56)	
MGUS (pt)	3	5	0	
Immunoglobulin at inclusion (g/kg/week), median (range)	0.31 (0.30–0.32)	0.33 (0.30–0.39)	0.33 (0.30–0.39)	
Neuropathy scores at diagnoses				
MRC, median (range)	164 (158–168)	163 (150–167)	158 (150–166)	
10-MWT (s), median (range)	6.9 (5.3–6.9)	6.2 (5.2–6.9)	6.7 (5.3–9.9)	
ODSS, arms, median (range)	1 (1–2.5)	2 (1–2)	2 (1.5–2.5)	
ODSS, legs, median (range)	1 (1–1)	2 (1–2)	1.5 (1–2)	
ODSS, total, median (range)	2 (2–3.5)	3 (2–4)	3 (2.5–4.5)	
Neuropathy scores after 1 year of treatment				
MRC, median (range)	168 (166–170)	168 (166–170)	166 (164–168)	
10-MWT (s), median (range)	5.9 (5.6–6.4)	6 (5.6–7.0)	5.6 (5.2–7.4)	
ODSS, arms, median (range)	1 (1–2)	1 (1–2)	1 (1–2)	
ODSS, legs, median (range)	1 (0–1)	1 (1–1)	1 (0–1)	
ODSS, total, median (range)	2 (1–3)	2 (1–3)	2 (1–3)	
Doctors' global impression of change, median (range)	2 (2–3)	2 (2–3)	3 (2–3)	
CIDP diagnosis according to criteria of European Federation of Neurological Societies				
Definite	13	19	11	
Probable	0	1	0	
Possible	0	0	0	
Neuropathic pain symptom inventory				
Burning (superficial) spontaneous pain, mean (SD)	1.77 (2.86)	1.63 (2.94)	1.08 (2.15)	0.44 (1.42)
Pressing (deep) spontaneous pain, mean (SD)	3.23 (4.92)	1.92 (3.83)	2.16 (4.02)	0.24 (1.40)
Paroxysmal pain, mean (SD)	4.62 (6.99)	2.25 (3.43)	1 (1.68)	0.44 (2.49)
Evoked pain, mean (SD)	7.62 (9.28)	3.29 (6.11)	3 (4.82)	0.65 (2.27)
Paresthesia/dysesthesia, mean (SD)	7 (5.60)	4.21 (3.87)	3.25 (3.33)	3.09 (3.45)
Total pain score, mean (SD)	24.23 (18.68)	13.0 (13.39)	10.5 (11.37)	1.93 (6.66)

[a]One patient from the SCIg group had both axonal and demyelinating pathology. Two patients of the IVIg late group had severe muscle atrophy and primarily motor nerve pathology, respectively. However, all fulfilled European Federation of Neurological Societies/Peripheral Nerve Society criteria for CIDP.

3.2 | Nerve excitability testing

The results of NET are presented in Figure 3, Figure 4 and Figures S1 and S2. There was a significant decrease in superexcitability from baseline to day 4 after treatment initiation ($p = .0083$) and a similar increase from day 4 to day 18 in the early IVIg group (Figure 3). Further, S2 accommodation decreased significantly between baseline and day 4 ($p = .0348$; Figure 4).

In the late IVIg group, a borderline significant decrease in the relative refractory period was found comparing day 4 to day 18 ($p = .0493$; Figure 3), while there was a borderline significant increase in threshold reduction 10–20 ms after a hyperpolarizing current during threshold

TABLE 2 Diagnostic nerve conduction studies—deviation from reference values.

	Patient groups		
	IVIg early ($n = 13$)	IVIg late ($n = 24$)	SCIg ($n = 11$)
Median nerve			
Distal motor latency, standard deviations, mean (range)	4.16 (2.32–5.43)	2.76 (0.59–6.73)	2.76 (2.00–6.33)
Conduction velocity, standard deviations, mean (range)	−5.39 (−9.78–[−2.57])	−3.79 (−9.37–[−2.47])	−6.70 (−9.44–[−3.95])
Compound muscle action potential, distal, standard deviations, mean (range)	−0.44 (−1.83–0.01)	−1.37 (−3.24–0.56)	−0.45 (−1.13–0.06))
Compound muscle action potential, proximal, standard deviations, mean (range)	−1.34 (−3.50–[−0.68])	−3.00 (−4.24–[−0.59])	−1.22 (−3.40–[−0.06])
F–wave latency, standard deviations, mean (range)	7.62 (2.46–11.99)	6.23 (1.92–12.38)	9.00 (6.23–15.59)
Peroneal nerve			
Distal motor latency, standard deviations, mean (range)	1.47 (−0.13–2.28)	0.16 (−0.41–1.61)	2.35 (0.17–4.08)
Conduction velocity, distal, standard deviations, mean (range)	−2.62 (−4.61–[−0.89])	−2.62 (−4.75–[−1.24])	−4.80 (−5.37–[−1.19])
Conduction velocity, proximal, standard deviations, mean (range)	−1.20 (−2.47–[−0.95])	−1.94 (−2.48–[−0.90])	−1.18 (−2.47–[−0.86])
Compound muscle action potential, distal, standard deviations, mean (range)	−2.20 (−3.51–[−0.77])	−2.18 (−3.91–[−1.12])	−2.31 (−3.27–[−0.39])
Compound muscle action potential, proximal, standard deviations, mean (range)	−3.06 (−4.12–[−2.03])	−3.25 (−5.75–[−1.76])	−2.92 (−4.56–[−2.15])
F–wave latency, standard deviations, mean (range)	6.10 (5.56–10.31)	5.75 (3.25–10.33)	8.38 (5.72–12.45)
Tibial nerve			
F–wave latency, standard deviations, mean (range)	7.47 (4.02–15.15)	7.08 (4.35–12.45)	11.94 (5.16–18.32)

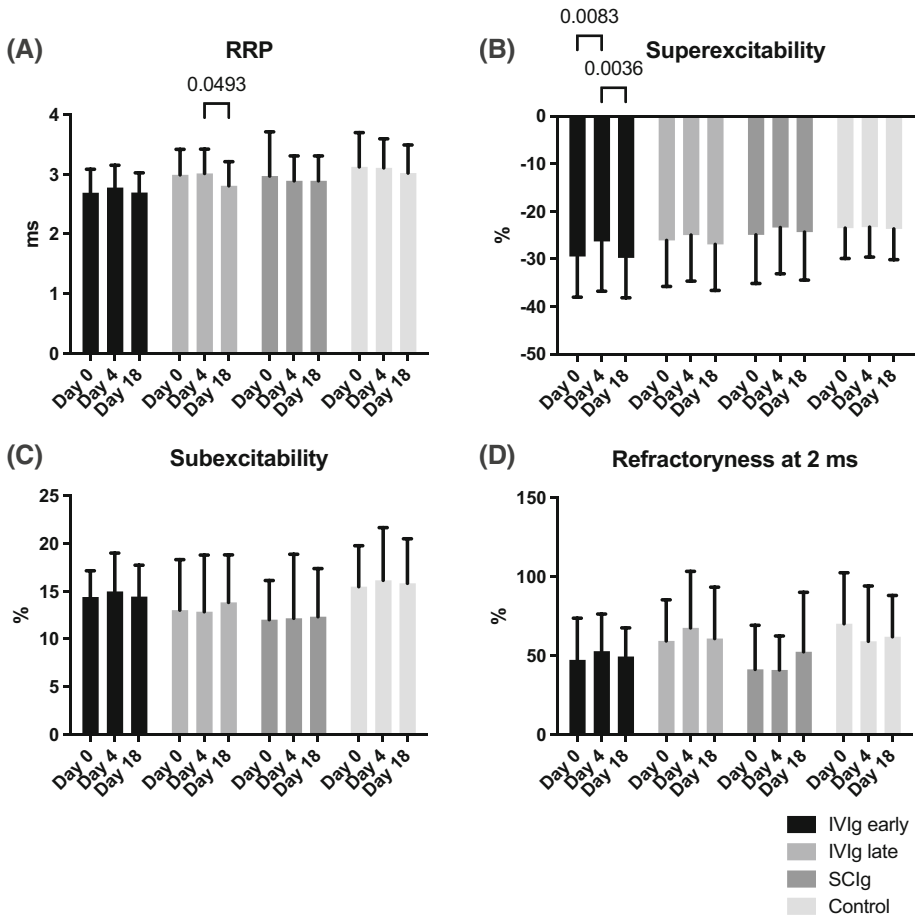

FIGURE 3 Nerve excitability testing—recovery cycle. The relative refractory period (A), superexcitability (B), subexcitability (C) and refrectoryness at 2 ms (D) before (day 0) and 4 and 18 days after initiation of intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) during early (IVIg early) and late (IVIg late) treatment phases and in CIDP patients treated with subcutaneous immunoglobulin (SCIg) and healthy controls. Mean and standard deviation.

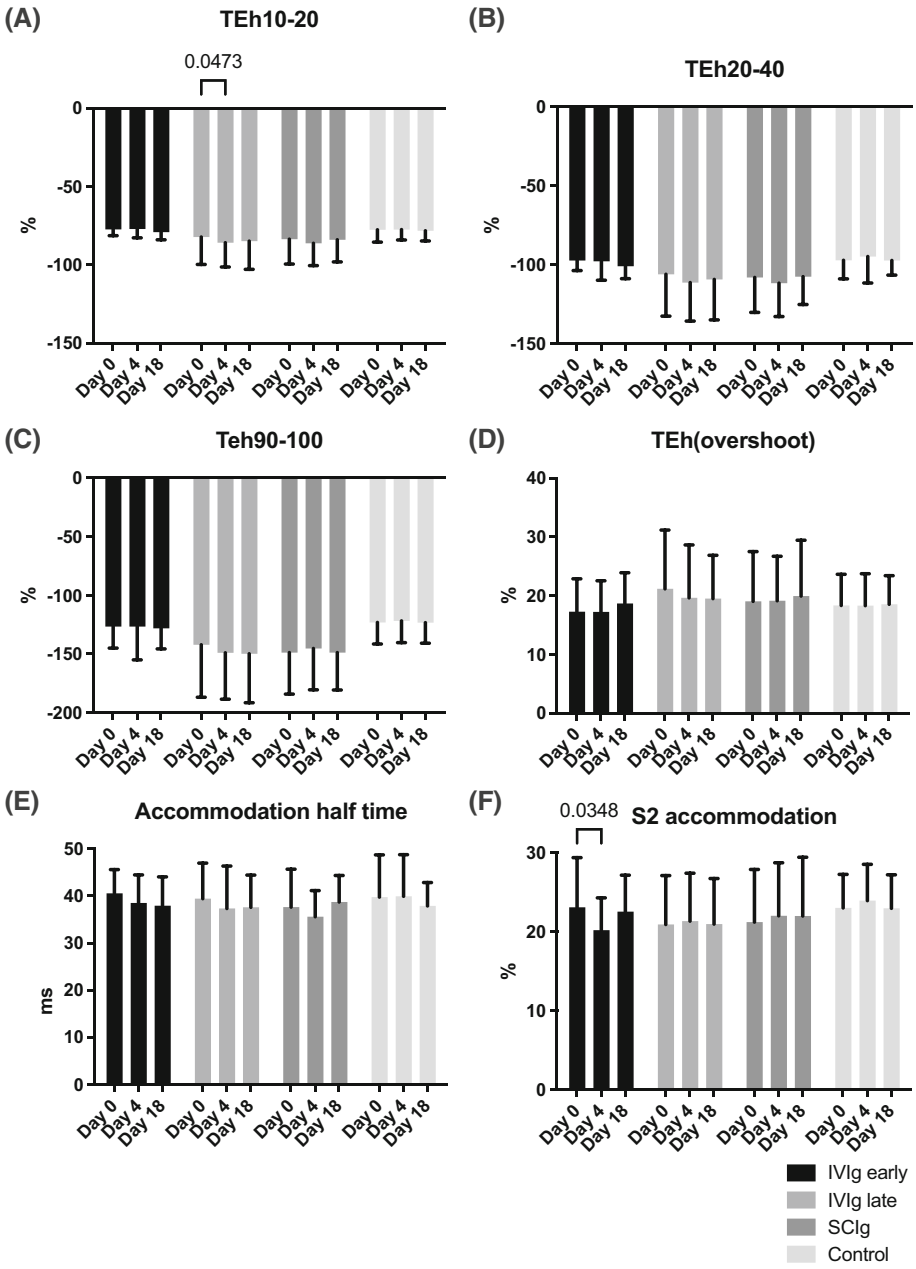

FIGURE 4 Nerve excitability testing—threshold electrotonus. Threshold reduction after 10–20 ms (TEh10–20) (A), 40 ms (TEh20–40) (B), 90–100 ms (TEh90–100) (C) delay and during overshoot (TEh(overshoot)) (D) following hyperpolarization and accommodation half time (E) and S2 accommodation (F) before (day 0) and 4 and 18 days after initiation of intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) during early (IVIg early) and late (IVIg late) treatment phases and in CIDP patients treated with subcutaneous immunoglobulin (SCIg) and healthy controls. Mean and standard deviation.

electrotonus from baseline with day 4 ($p = .0473$; Figure 4). Regarding superexcitability, a nonsignificant trend toward changes similar to those found in the early IVIg group was observed (Figure 3).

In both groups, there was a nonsignificant trend toward increased relative refractory period and refractoriness at 2 ms. There were no significant changes for any measurements in the SCIg and control groups.

NET findings are summarized in Figure 5.

3.3 | Clinical function, neuropathy limitations, muscle strength, and patient global impression of change

Regarding clinical tests, neuropathy limitations and muscle strength (Figures 6 and 7), highly significant reductions in SSST, 10-MWT, and 9-HPT duration and ONLS and highly significant increases in grip strength and MRC sum score were observed in the early IVIg group from baseline to day 18. Further, there was a highly significant reduction in SSST duration and increase in grips strength and MRC sum score from baseline to day 4 in the early IVIg group. 9-HPT duration and ONLS were significantly reduced, while the MRC sum score increased significantly between days 4 and 18.

In the late IVIg late group, significant decreases were also observed in SSST and 9-HPT duration and the INCAT sensory sum score along with increased grip strength and MRC sum score from baseline to day 18. From baseline to day 4, a significant decrease was found in SSST duration and the INCAT sensory sum score, while there was a significant increase in MRC sum score. Between days 4 and 18, grip strength increased.

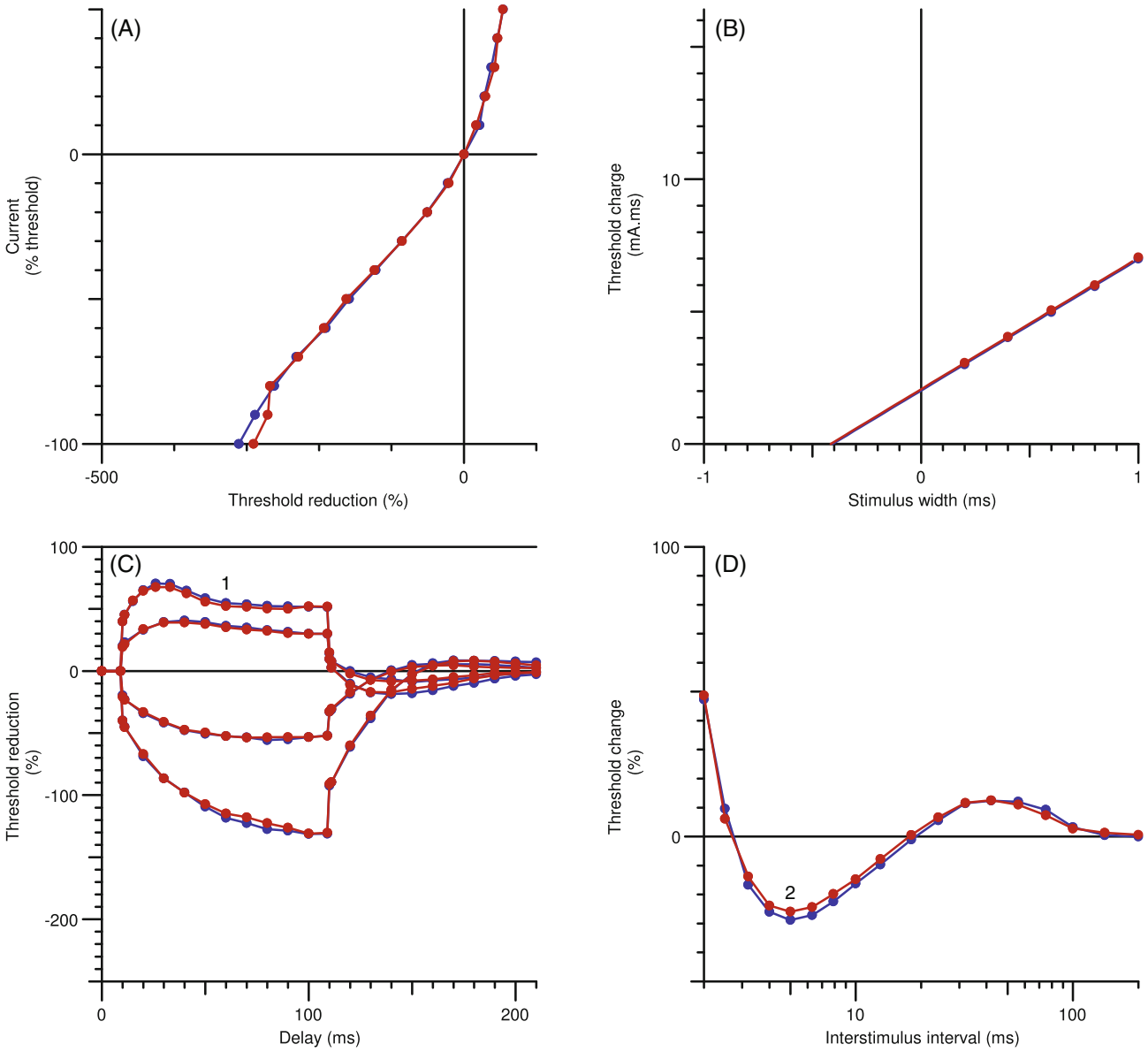

FIGURE 5 Summary of nerve excitability testing. Current-threshold relationship (A), strength-duration properties (B), threshold electrotonus (C) and recovery cycle (D) in patients with chronic inflammatory demyelinating polyneuropathy during early phase intravenous immunoglobulin treatment at day 0 (before treatment) (blue) and day 4 after initiation of immunoglobulin treatment (red). 1: accommodation following depolarizing current during threshold electrotonus. 2: superexcitability.

Patients reported a significant increase in global function measured by PGIC in both the IVIg early and IVIg late groups (Figure 7).

3.4 | Correlation between NET and clinical tests

The results of correlation analyses between superexcitability and S2 accommodation and clinical variables are presented in Table 3. Although there were trends toward a reduction in duration of both SSST and 10-MTW and an increase in PGIC with increase in superexcitability and correspondingly trends toward increased duration of both SSST and 10-MTW with increase in S2 accommodation, no statistically significant correlation was observed.

4 | DISCUSSION

Significant changes in nerve excitability were observed from baseline to day 4 in treatment naïve patients and nerve excitability returned to baseline levels at day 18 of the IVIg treatment cycle. On the other hand, we found substantial improvement in functional tests, neuropathy limitations, muscle strength and patient impression in both treatment naïve and late IVIg treated patients. Improvement was significant at day 4 after initiation of treatment and further improvement was observed at day 18. We found no correlation between changes in NET and clinical measures between baseline and day 4. The findings do not directly support the hypothesis that clinical improvement is a result of changes in axonal excitability. As expected,

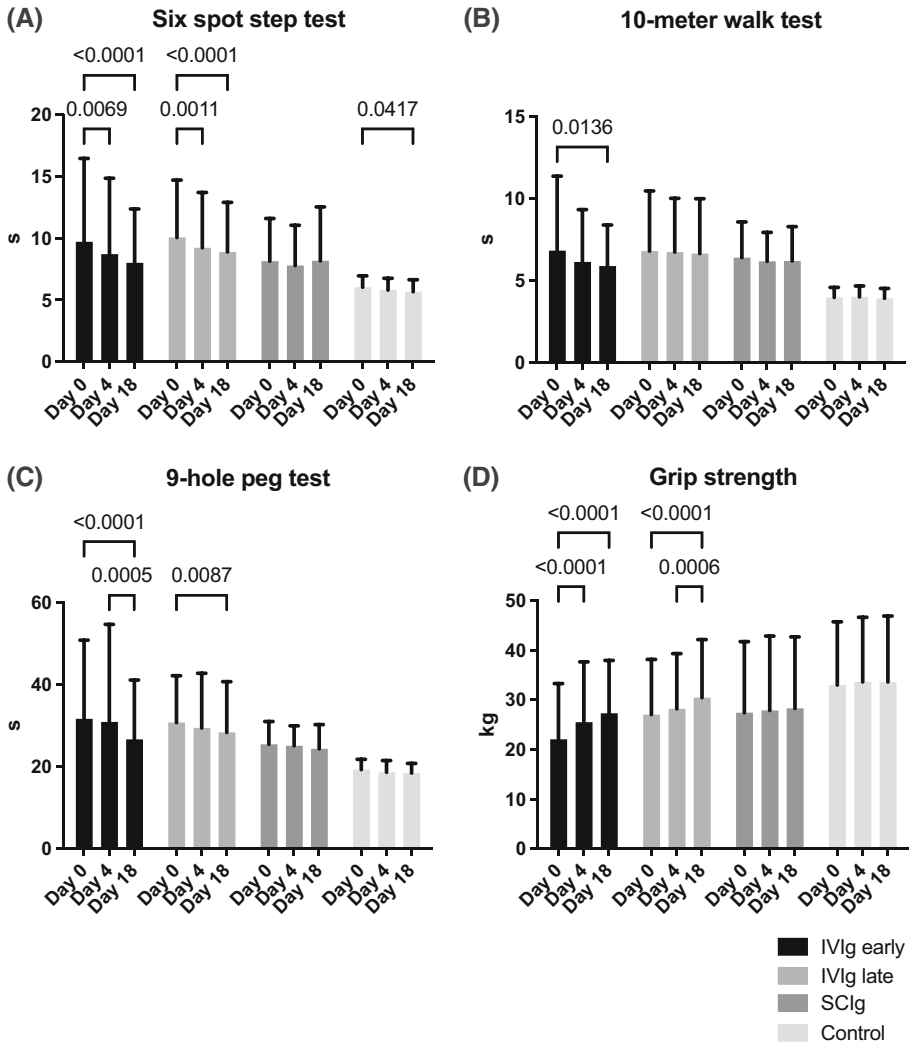

FIGURE 6 Clinical testing. The six spot step test (A), 10-meter walk test (B), 9-hole peg test (C) and grip strength (D) before (day 0) and 4 and 18 days after initiation of intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) during early (IVIg early) and late (IVIg late) treatment phases and in CIDP patients treated with subcutaneous immunoglobulin (SCIg) and healthy controls. Mean and standard deviation.

no significant change was found in neither SCIg treated CIDP patients nor healthy controls.

Superexcitability and S2 accommodation were significantly reduced from baseline to day 4 in the early IVIg group. These findings, and the nonsignificant tendency toward increased refractoriness at 2 ms and increased relative refractory period, suggest that IVIg has a depolarizing effect on the membrane potential. The changes reflect that refractoriness is increased while there is a "fanning in" of the threshold electrotonus waveform. The decrease in superexcitability could reflect changes in the transient potassium channel properties, while the decrease in S2 accommodation could reflect activation of hyperpolarizing conductance with slow kinetics.[36,37] Although no statistically significant changes in nerve excitability were observed, trends toward similar changes were found during IVIg treatment in the late group.

No significant correlation was found between these changes in superexcitability and S2 accommodation and clinical function, although there were trends toward better performance on SSST, 10-MWT, 9-HPT and PGIC with the change in superexcitability and a better performance on SST and 10-MWT with the change in S2 accommodation. The lack of significant correlation indicates that other factors than nerve excitability are involved in the clinical improvement observed from baseline to days four and 18 of the IVIg treatment cycle. Immunoglobulins affect various components of the immune system including antibody degradation, complement, and macrophage activation as well as co-stimulatory and adhesion molecules.[15] It is possible that clinical improvement following IVIg does not depend on structural recovery of damaged nerves, but rather the removal of factors involved in CIDP pathophysiology, such as autoantibodies binding to the node of Ranvier, which can occur much faster.

Although other studies have shown long-term clinical improvement in CIDP patients during treatment with IVIg, only a few studies have investigated the clinical changes during a treatment cycle.[5,18] Harbo et al.[18] demonstrated that after brief withdrawal of IVIg treatment in eight CIDP patients, there was a rapid increase in isokinetic muscle strength and decrease in duration of the 9-HPT and 40-m walk test by day 5, 10, and 15 after re-establishment of IVIg treatment, consistent with our findings. A significant change in F-wave latencies was demonstrated in median, ulnar, peroneal, and tibial nerves, suggesting improved nerve conduction properties as the reason for the clinical improvement. No other changes were found in motor or sensory nerve conduction variables.

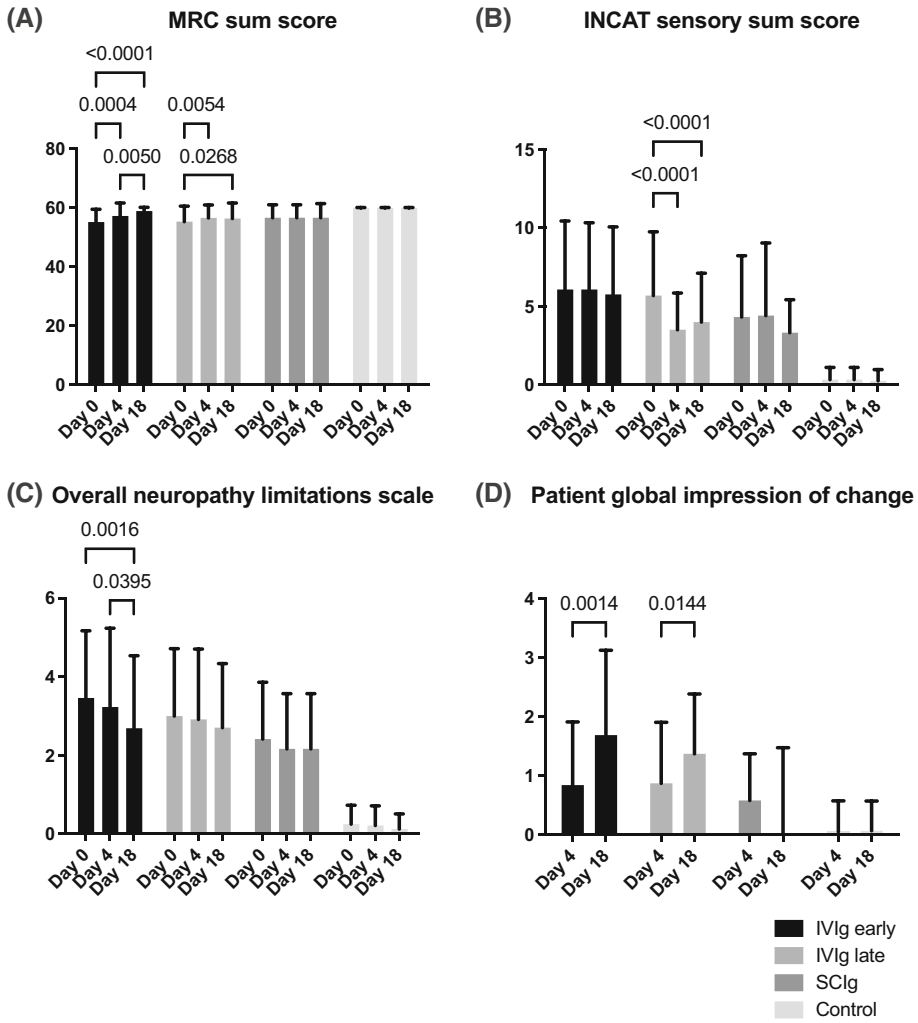

FIGURE 7 Clinical testing. The medical research council (MRC) sum score (A), inflammatory neuropathy cause and treatment (INCAT) sensory sum score (B), overall neuropathy limitations scale (C) and patient global impression of change (D) before (day 0) and 4 and 18 days after initiation of intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) during early (IVIg early) and late (IVIg late) treatment phases and in CIDP patients treated with subcutaneous immunoglobulin (SCIg) and healthy controls. Mean and standard deviation.

TABLE 3 Correlation between changes in nerve excitability variables superexcitability and S2 accommodation and clinical variables from baseline to day 3.

	Superexcitability			S2 accommodation		
	Spearmans *r*	95% CI	*p*	Spearmans *r*	95% CI	*p*
Six spot step test	−0.489	−0.825–0.103	.093	0.137	−0.462–0.651	.651
10-meter walk test	−0.351	−0.764–0.264	.239	0.017	−0.552–0.575	.964
9-hole peg test	−0.143	−0.654–0.457	.639	−0.256	−0.716–0.360	.396
Grip strength	0.025	−0.547–0.580	.939	0.512	−0.073–0.835	.076
MRC sum score	−0.129	−0.646–0.469	.674	−0.123	−0.473–0.642	.687
INCAT sensory sum score	0.281	−0.335–0.729	.350	0.020	−0.550–0.577	.952
Overall neuropathy limitations score	−0.211	−0.692–0.401	.500	−0.239	−0.708–0.375	.438
Patient global impression of change	0.584	−0.004–0.872	.050	0.038	−0.561–0.611	.910

Abbreviations: INCAT, inflammatory neuropathy cause and treatment; MRC, medical research council.

4.1 | Comparison with previous nerve excitability studies

Two studies have investigated the axonal excitability changes in patients with CIDP during immunoglobulin treatment. Boërio et al.[23] compared 10 CIDP patients treated with IVIg to controls before and 3–5 days after treatment. They found reduced strength-duration time constant and increased rheobase and concluded that excitability changes may precede clinical changes observed in the days following IVIg infusion. However, similar to our results, no correlation

could be found between changes in MRC score of the ulnar muscle and excitability measures. Lin et al.[24] studied 20 CIDP patients during IVIg treatment after several prior treatment cycles and a clinical response. NET examination was performed preinfusion, 1 week, and 2 weeks after infusion. Within a treatment cycle, the study found reduction in strength-duration time constant, in accommodation to depolarization and in threshold change during hyperpolarization as well as a decrease in superexcitability and subexcitability. Looking at longitudinal data, these excitability changes were consistent within multiple treatment cycles and a correlation to improvement in MRC score was found. The conclusion of the study was that IVIg has a modulatory effect on axonal function in CIDP with stabilization of axonal membrane potential and promotion of axonal recovery. Interestingly, we were not able to reproduce the excitability changes found by Lin et al. within a treatment cycle in our IVIg late group of 24 CIDP patients. However, comparison of the studies is difficult due to differences in examination time points. A possible explanation for the differences could be that our late IVIg group started treatment on average 22 months after onset of symptoms. No data regarding time from disease onset to treatment initiation was reported by neither Lin et al. nor Boërio et al. It is possible that patients in the current study had more severe neuropathy due to a longer delay from symptom onset to treatment. However, clinical characteristics revealed no difference in axonal damage in our late IVIg group compared with the data reported by Boërio et al. and Lin et al.[23,24] Another difference in the cohorts is that the time point of investigation of our late IVIg group was at a median of 28 months after the diagnosis, which was longer compared to Boërio et al. reporting a median disease duration of 1 year, and arguably longer than Lin et al., testing at the time of disease stability on IVIg.

This is the first study to examine axonal changes in both treatment naïve CIDP patients and patients with long term IVIg treatment. Interestingly, axonal excitability changes were predominately found during early IVIg treatment. A possible explanation is that the potential for reversibility of axonal dysfunction is more preserved during the early phase of treatment when secondary axonal loss is still limited. Alternatively, the axonal membrane could be more exposed to drugs affecting axonal function in treatment naïve patients due to a higher degree of demyelination.

4.2 | Strengths and limitations

A major strength of the study is that the diagnosis in all CIDP patients was validated according to European Federation of Neurological Societies/Peripheral Nerve Society criteria. Although prior studies[23,24] have performed NET in patients with CIDP, our study is the first to examine both treatment naïve and long term IVIg treated patients. Further, compared to previous studies, we added an examination at day 18 to investigate changes during the later part of the treatment cycle. We performed extensive clinical examinations of arms and legs involving motor and sensory function combined with functional tests and neuropathy scores during each visit. Prior studies have not been able to compare the changes in nerve excitability to clinically relevant function.[23,24] Including 24 CIDP patients in the late group, our sample size is the largest yet in CIDP NET studies.

Our study has some limitations. First, patients were examined at baseline, after last IVIg dosage (day 4), and 14 days after last dosage (day 18). A study has shown that the optimal clinical function occurred 10 days after IVIg treatment in CIDP patients.[18] However, the study also found the change to persist at day 14. Second, the sample size of our early IVIg group is fairly small and we may have overlooked important changes and correlations due to low statistical power. Third, there was no blinding of neither patients nor examiners, which may have biased clinical examinations and neuropathy scores.

In conclusion, we found that patients treated with intravenously administrated immunoglobulin have significant changes in superexcitability and S2 accommodation from baseline to day 4 suggesting depolarization of the axonal membrane. Statistically significant changes were neither observed during late IVIg treatment nor during SCIg. The findings confirm that immunoglobulins induce axonal changes, but their relation to clinical improvement remains speculative.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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