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ORIGINAL ARTICLE

Serum neurofilament light chain does not detect self-reported treatment-related fluctuations in chronic inflammatory demyelinating polyneuropathy

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Abstract

Introduction: Serum neurofilament light chain (sNfL) is a marker for axonal degeneration. Patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) often report a fluctuation of symptoms throughout one treatment cycle with intravenous immunoglobulins (IVIG). The aim of this study was to determine whether sNfL is suitable to quantify patient-reported symptom fluctuations.

Methods: Twenty-nine patients with the diagnosis of CIDP or a CIDP-variant under treatment with IVIG were recruited in this study and underwent examination before IVIG infusion, in the middle of the treatment interval, and before their next IVIG infusion. Patients were surveyed regarding symptom fluctuations at the last visit and divided into two groups: those with and without fluctuations of symptoms. At the first visit, sociodemographic and disease-specific data were collected. Clinical scores were assessed at every examination. sNfL values were compared between both groups at the different time points after conversion into Z-scores—adjusted for age and body mass index.

Results: Patients with CIDP show elevated sNfL Z-scores (median at baseline: 2.14, IQR: 1.0). There was no significant change in sNfL Z-scores or questionnaire scores within the treatment cycle in either group. There was no significant difference in sNfL levels between the patients with and without symptom fluctuations.

Conclusions: CIDP patients show elevated sNfL levels. However, sNfL is not suitable to reflect patient-reported fluctuations of symptoms. This indicates that symptom fluctuations during treatment with IVIG in patients with CIDP are not caused by a neuroaxonal injury. Furthermore, repeated sNfL measurements within one treatment cycle with IVIG seem to have no benefit for symptom monitoring.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, cohort study, serum neurofilament light chain

INTRODUCTION/OBJECTIVES

Monitoring of treatment and disease activity in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is challenging, hence there is an urgent need of biomarkers in CIDP [1]. The measurement of neurofilament light chain in cerebrospinal fluid (CSF), serum (sNfL), or plasma (pNfL) is a well-established biomarker for the detection of neuroaxonal damage in various neuroimmunological and neurodegenerative diseases [2]. In CIDP and other imflammatory neuropathies, sNfL and pNfL have previously been shown to correlate with the disease severity and treatment response [3–5].

CIDP represents the most common chronic, immune-mediated inflammatory neuropathy. It is characterized by peripheral nerve demyelination, leading to weakness or loss of sensory functions of the extremities [1, 6, 7]. The most important first-line treatment is the cyclic administration of intravenous immunoglobulins (IVIG). Patients undergoing cyclic immunotherapy with IVIG frequently report fluctuating clinical symptoms between infusions, described as treatment-related fluctuations (TRFs) [8]. These manifest as initial improvement after infusion of IVIG followed by worsening of clinical symptoms like sensory deficits in the next few weeks.

Evaluating these TRFs remains difficult, since worsening of disease symptoms are reported subjectively as, in most cases, there is no regular patient–physician contact between two IVIG infusions. Their objective assessment is possible by measuring daily grip strength [8], which is not practical outside of clinical trials. Furthermore, the relationship between TRFs and progressing neuronal damage is unclear and it is not yet known what significance TRFs have for patients regarding long-term disease stability or whether neuronal damage is responsible for the fluctuations.

In this study, we first aimed to investigate whether sNfL is a suitable biomarker to monitor TRFs between two IVIG infusions in patients with CIDP to identify patients who are at risk of developing future disease progression. Second, we evaluated whether sNfL is an appropriate surrogate marker for disability in CIDP and if sNfL levels are elevated in treated CIDP patients.

METHODS

Study design

Patients were examined prior to IVIG infusion (T_0), in the middle of the IVIG treatment cycle (T_1), and immediately before the next IVIG infusion (T_2) (Figure 1a). Serum samples and clinical data were collected at all visits.

Patients

Patients with the diagnosis of CIDP or a CIDP variant, already receiving treatment with IVIG, were enrolled in a single-center, prospective, observational study (St. Josef-Hospital, University Hospital Bochum,
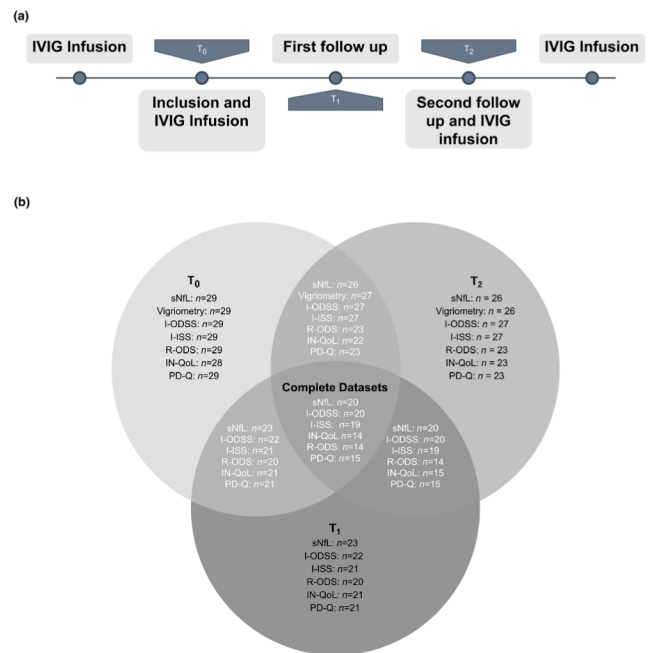

FIGURE 1 Study characteristics. (a) Study design and visits. (b) Completeness of datasets for each time point and overlapping completeness of datasets. I-ISS, Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score; IN-QoL, Quality of Life Questionnaire in Inflammatory Neuropathies; I-ODSS, Inflammatory Neuropathy Cause and Treatment (INCAT) Overall Disability Sum Score; IVIG, intravenous immunoglobulins; PD-Q, painDETECT Questionnaire; R-ODS, Rasch-built Overall Disability Scale; sNfL, serum neurofilament light chain.

Bochum, Germany). Patients were diagnosed in accordance with the diagnostic criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) [7, 9]. No patient had a change in therapy in the previous 12 months. The study was conducted between July 2021 and October 2021. Twenty-nine patients were enrolled, and two patients were lost to follow-up.

Standard protocol approvals, registrations, and patient consents

The ethics committee of the Ruhr-University Bochum approved our study (Immunmediated Neuropathies Biobank INHIBIT; vote-no. 18-6534-BR). Written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendment or comparable ethical standards.

Outcome analyses

Clinical disability was evaluated using Inflammatory Neuropathy Cause and Treatment Overall Disability Score (INCAT-ODSS) [10],

Inflammatory Neuropathy Cause and Treatment Sensory Sum Score (INCAT-ISS) [11], Rasch-built Overall Disability Scale (R-ODS) [12], Quality of Life Questionnaire in Inflammatory Neuropathies (IN-QoL) [13], as well as the painDETECT Questionnaire (PD-Q) [14] at all three time points. Grip strength was evaluated using a vigorimeter [15] with a rubber ball adjusted according to the hand size at the first and last time point. Questionnaires with more than 10% missing answers were excluded from the analysis. Sum scores were calculated for the INCAT-ODSS, INCAT-ISS, R-ODS, and PD-Q. Centiles were also calculated for the R-ODS sum scores. Statistical analysis of the R-ODS and PD-Q was conducted after estimation of missing values by a clinical practitioner according to the patient's constitution (in $n = 6$ cases for R-ODS out of 72 questionnaires and $n = 15$ for PD-Q out of 73 questionnaires). INCAT-ODSS and INCAT-ISS had no missing values. The estimation did not lead to different results compared with the exclusion of these cases. All other tests were performed without estimation of missing values. The IN-QoL questionnaire score was evaluated by calculating a mean score and transforming it to a centile metric scale ranging from 0 (worst measurable health status) to 100 (best measurable health status). The IN-QoL questionnaire is divided into the subscales 'mental' and 'functional'.

Treatment-related fluctuations were defined as patient-reported typical fluctuations in symptoms (e.g., sensomotoric symptoms) between the two IVIG infusions and were assessed retrospectively at the last visit (time point T_2) by a clinical practitioner through personal interview of the patients. Patients were asked whether they had experienced fluctuating symptoms such as an increase or decrease in sensory disturbances or muscle weakness in the period after the last infusion of IVIG.

Peripheral blood sampling and isolation of serum were performed according to a standardized protocol. Samples were stored at −80°C. sNfL levels were measured at the Department of Biophysics, Center for Protein Diagnostics (PRODI), Ruhr-University Bochum, Bochum, Germany by the commercially available Simoa NF-light Kit (Quanterix) according to the manufacturer's instructions. Samples were coded randomly and were analyzed blinded for the patient's group and outcome. To adjust sNfL measurements for age and body mass index (BMI), Z-scores were calculated for further analysis using the Serum Neurofilament Light Chain Reference App provided by the Department of Clinical Research, University Hospital Basel, Basel, Switzerland. These Z-scores describe the distance an sNfL value deviates from the mean of the control group without central nervous system diseases—corrected for age and BMI—analyzed recently [16].

Statistics

Statistical analysis was performed using GraphPad Prism version 9.5.0 (GraphPad Software, www.graphpad.com). Parametric data are presented as mean with standard deviation (SD), and nonparametric data as median with interquartile range (IQR) if not stated otherwise. Nominal and dichotomous variables are presented as counts and percentages. Demographics and clinical characteristics were compared between groups using Student's t-test for numerical normally distributed variables, Mann–Whitney U test for numerical non-normally distributed values, or chi-squared test (χ^2-test) for nominal variables. Pairwise comparison was performed using Friedman test with post hoc Dunn's multiple comparison for non-normally distributed variables (this includes the primary analysis of sNfL changes throughout the different time points). Correlations were performed using Spearman's rank correlation for non-normally distributed variables. For all analyses, the statistically significant threshold was set at p-value <0.05. Graphs showing linear regressions are plotted with 95% confidence intervals (CIs).

RESULTS

Patient characteristics

Blood samples were collected from 20 patients at all three time points. Of the clinical data, the INCAT-ODSS was collected in 20 patients at all three time points, the INCAT-ISS in 19 patients, the R-ODS and the IN-QoL in 14 patients, and the PD-Q in 15 patients. Vigorimeter data were collected at the first and last visit in 27 patients (Figure 1b).

Twenty-one patients (72.4%) were male and the mean age at inclusion was 64.1 years (SD: 11.18). Fifteen patients were diagnosed with typical CIDP and 14 with CIDP variants (distal CIDP $n = 9$, multifocal CIDP $n = 5$). The time since disease onset was 7 years at median (IQR: 6). The cycle length of the treatment interval ranged from 28 to 86 days (median: 56, IQR: 20) and the time to first follow-up (T_1) ranged from 13 to 35 days (median: 25, IQR: 9). The median IVIG dose in the treatment cycle was 90 g (IQR: 20), which corresponds to a median dosage per kilogram bodyweight of 0.97 g/kg per IVIG cycle (IQR: 0.17). Disease severity was measured by INCAT-ODSS (median T_0: 3, IQR: 3), INCAT-ISS (median T_0: 7, IQR: 4.5), vigorimeter (mean T_0: 60.3 kPa, SD: 22.3 kPa), R-ODS sum score (median T_0: 33, IQR: 11.5) corresponding to a centile score of 57.0 (IQR:11.5), IN-QoL mental (median T_0: 74.3, IQR: 25.6), IN-QoL functional (median T_0: 73.6, IQR: 27.9), and PD-Q (median T_0: 13, IQR: 18). At the last visit, 11 of 27 patients (40.7%) reported fluctuation of symptoms (TRFs) during the treatment cycle.

There were no significant differences in patient characteristics at enrollment between patients who reported fluctuating symptoms and those who did not (Table 1).

sNfL is increased in CIDP patients

sNfL correlated significantly with age and BMI (Figure 2a,b) in patients with CIDP, so we also used Z-scores for further analysis. The median sNfL level at enrolment was 25.92 pg/mL (IQR: 25.58). The study cohort showed elevated sNfL Z-scores with a median of 2.14 (IQR: 0.995, 25th percentile: 1.395, 75th percentile:

TABLE 1 Patient characteristics.

Variable	All patients	Value fluctuation	Value no fluctuation	P-value
Patients, n	29	11	16	
Male patients, n (%)	21 (72.4)	9 (81.8)	10 (62.5)	0.405
Age of patients (years), mean (SD)	64.1 (11.2)	62.6 (14.6)	65.4 (9.0)	0.539
Patients with typical CIDP, n (%)	15 (51.7)	4 (36.4)	10 (62.5)	0.252
Years since disease onset (years), median (IQR)	7.0 (6.0)	7.0 (8.0)	7.5 (4.5)	0.778
Interval length (days), median (IQR), n	56.0 (20.0), 27	57.0 (21.0), 11	52.0 (22.5), 16	0.428
Time to first follow-up (days), median (IQR), n	25.0 (9.0), 23	24.5 (10.5), 10	25.0 (11.0), 11	>0.999
IVIG dosage (g), median (IQR)	90.0 (20.0)	100.0 (30.0)	85.0 (20.0)	0.113
IVIG dosage (g/kg bodyweight per IVIG cycle), median (IQR)	0.97 (0.17)	0.97 (0.37)	0.96 (0.12)	0.473
ODSS score, median (IQR), n	3.0 (3.0), 29	4.0 (3.0), 11	3.0 (3.0), 16	0.330
Additional therapy, n (%)	7 (24.1)	4 (26.3)	3 (18.75)	0.391
Rituximab, n (%)		3 (75.0)	1 (33.33)	
Azathioprin, n (%)		1 (25.0)		
Other, n (%)			2 (66.66)	
I-ISS sum score, median (IQR), n	7.0 (4.5), 29	8.0 (3.0), 11	6.5 (5.3), 16	0.155
Vigorimetry dominant hand (kPa), mean (SD), n	60.3 (22.3), 29	59.6 (31.2), 11	59.1 (16.0), 16	0.958
R-ODS sum score, median (IQR), n	33.0 (11.5), 29	28.0 (7.0), 11	35.0 (8.75), 16	0.081
R-ODS centile score, median (IQR), n	57.0 (11.5), 29	50.0 (10.0), 11	59.5 (13.5), 16	0.081
IN-QoL mental score, median (IQR), n	74.3 (26.1), 28	74.0 (24.4), 11	73.2 (29.1), 15	0.929
IN-QoL functional score, median (IQR), n	73.6 (27.9), 26	76.4 (29.9), 10	72.2 (31.3), 14	0.676
PD-Q score, median (IQR), n	13.0 (18.0), 29	6.0 (21.0), 11	14.5 (17.8), 16	0.951
sNfL value (pg/mL), median (IQR)	25.9 (25.6), 29	20.7 (27.5), 11	24.6 (19.5), 16	0.645
sNfL Z-score, median (IQR), n	2.1 (1.0), 29	2.1 (2.0), 11	2.0 (0.8), 16	0.903

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; I-ISS, Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score; IN-QoL, Quality of Life Questionnaire in Inflammatory Neuropathies; IQR, interquartile range; IVIG, intravenous immunoglobulins; ODSS, Overall Disability Sum Score; PD-Q, painDETECT Questionnaire; SD, standard deviation; R-ODS, Rasch-built Overall Disability Scale; sNfL, serum neurofilament light chain.
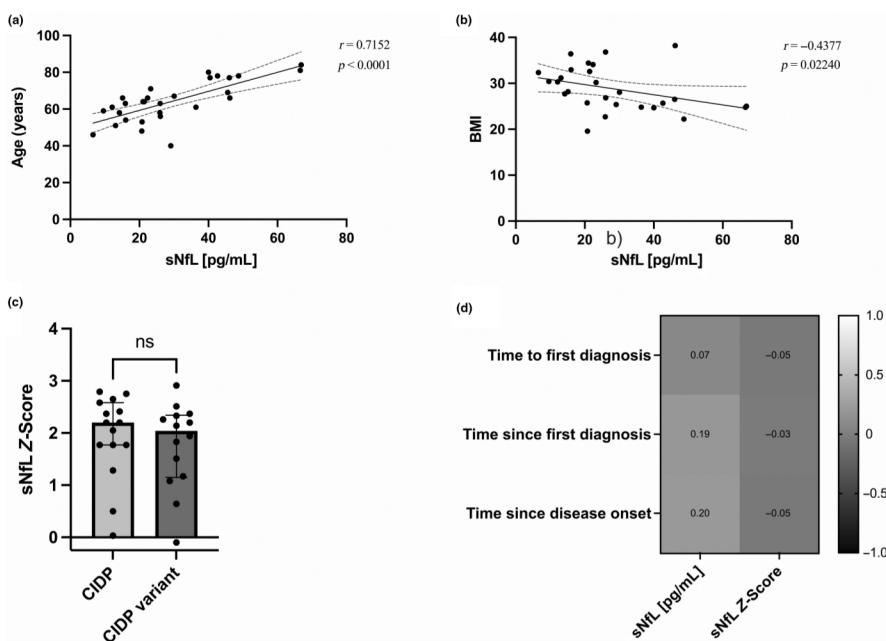

FIGURE 2 Relationship between serum neurofilament light chain (sNfL) and baseline characteristics. (a) Correlation of sNfL values and age at time of inclusion (T_0). (b) Correlation of sNfL values and body mass index (BMI) at time of inclusion (T_0). (c) Mann–Whitney U test between patients diagnosed with typical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) ($n = 15$) and CIDP variants ($n = 14$). (d) Correlation of sNfL values and Z-scores with baseline characteristics at time point T_0. Spearman's rho values are displayed inside the boxes. Correlations did not show significant results.

2.39) compared with the reference group of Benkert et al. [16], which corresponds to the 98.38th percentile. Thirteen of the 29 (44.83%) included patients had a Z-score below the 97.5th percentile at the first visit.

We found no difference in Z-scores between patients with typical CIDP and CIDP variants (Figure 2c).

In addition, we examined the association between time of disease onset and time of diagnosis and sNfL levels. Time since symptom onset, time since diagnosis, or time to diagnosis did not correlate with either raw sNfL values or adjusted Z-scores (Figure 2d).

sNfL levels do not correspond with treatment-related fluctuations

Next, we examined whether sNfL levels changed during the IVIG treatment cycle in patients with and without fluctuations. We did not find significant changes in sNfL values or Z-scores during the treatment cycle (Figure 3), either in patients who reported fluctuations or in those who did not.

Clinical characteristics stay stable throughout the treatment cycle

To further assess intra-cycle patient-reported symptom fluctuation, we examined whether clinical symptoms and patient-reported symptoms changed throughout the treatment cycle with IVIG. We found no significant change in grip strength, INCAT-ODSS, INCAT-ISS, R-ODS, IN-QoL, and PD-Q in the overall group and in both the non-fluctuating and fluctuating symptom subgroups.

Correlation of sNfL with clinical characteristics

We also examined correlations between questionnaire scores and sNfL levels. Raw sNfL levels showed a correlation with INCAT-ODSS scores at time points T_0—although it barely did not reach significance—and a correlation at T_2. Interestingly, the lower limb

FIGURE 3 Longitudinal analysis of serum neurofilament light chain (sNfL) values and sNfL Z-scores. (a) Median and interquartile range (IQR) of sNfL values for Non-Fluctuation ($n=11$) and Fluctuation ($n=9$) group at time points T_0, T_1, and T_2. (b) Median and IQR of sNfL Z-scores for Non-Fluctuation ($n=11$) and Fluctuation ($n=9$) group at time points T_0, T_1, and T_2.

subscore correlated well with raw sNfL values, in contrast to the upper limb subscore. This correlation was not statistically significant at T_1, but was at T_0 and T_2. Nevertheless, only the interrelation of the lower limb score and sNfL Z-scores at T_2 could be seen (Figures 4–6).

Other questionnaire scores did not show a consistent correlation with either raw sNfL values or Z-scores throughout the visits (Figures 4a, 5a, and 6a).

We also examined whether absolute and relative changes in questionnaire scores (INCAT-ODSS, INCAT-ISS, R-ODS sum score, R-ODS centile score, PD-Q, IN-QoL mental score, IN-QoL functional score) and clinical data (vigriometry between time points T_0 and T_2) correlated with changes in sNfL scores. Again, we could not detect any clear association between a change in clinical characteristics and the change in sNfL values and Z-scores.

DISCUSSION

First, we demonstrated that sNfL is not a suitable biomarker to monitor short-term inter-cyclic TRFs in CIDP patients between two IVIG infusions. Therefore, we conclude that the measurement of sNfL values during one IVIG cycle does not show an advantage for disease monitoring in stable CIDP patients. Moreover, well-established clinical scores such as INCAT-ODSS, INCAT-ISS, or R-ODS were also not able to detect these fluctuations. The reason for this is either that the short-term fluctuations have no pathophysiological correlate in terms of axonal damage, or that sNfL cannot dynamically depict these fluctuations due to its half-life in serum. Even in multiple sclerosis, where sNfL is much more established as a biomarker, there is still a lack of knowledge about the dynamics of sNfL [17]. Moreover, our results highlight the importance of further characterization of TRFs. The TRFs were collected by an experienced clinical practitioner and thus reflect routine clinical practice. However, we were not able to reflect the TRFs perceived by the patient with any of the tools used. Therefore, it is also important for future studies to develop validated methods to create a higher comparability between different studies.

Second, our study showed that sNfL is elevated in many CIDP patients who are on continuous IVIG treatment without any change in treatment in the previous 12 months, which means that they are not obviously progressive in their disease but are apparently stable. Even after correction for age and BMI, calculated median Z-Scores for sNfL were above the 97.5th percentile. These results are consistent with previous studies showing increased levels of sNfL in patients with CIDP [18]. In a recent study, CIDP patients achieved normal plasma NfL levels after induction of a treatment with IVIG [4]. The elevated sNfL levels in our cohort could therefore mean that the apparently stable patients may be suffering from progressive neuroaxonal damage. This is supported by the fact that 40% of the patients reported subjective inter-cyclic TRFs, which could be an expression of active disease. However, patients who do not report inter-cyclic TRFs also have elevated Z-Scores. Thus, subclinical disease activity can also be expected in these patients. Our cohort of CIDP patients was enrolled in a specialized university hospital.
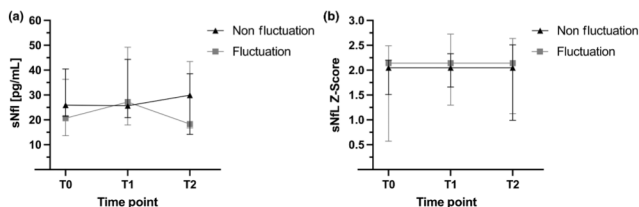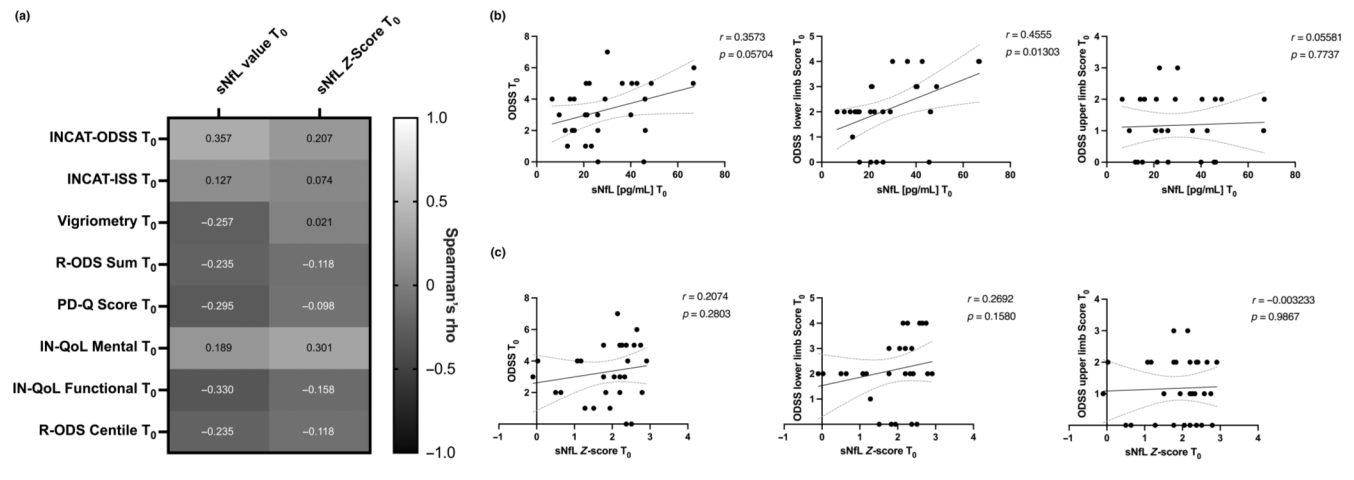
FIGURE 4 Correlation of serum neurofilament light chain (sNfL) values and Z-scores with questionnaire scores at T_0. (a) Correlation of sNfL values and Z-scores with Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) ($n = 29$), Inflammatory Neuropathy Cause and Treatment Sensory Sum Score (INCAT-ISS) ($n = 29$), vigriometry ($n = 29$), Rasch-built Overall Disability Scale (R-ODS) ($n = 29$), painDETECT Questionnaire (PD-Q) ($n = 29$), Quality of Life Questionnaire in Inflammatory Neuropathies (IN-QoL) mental ($n = 28$), IN-QoL functional ($n = 26$), and R-ODS Centile ($n = 29$) at time point T_0. Spearman's rho values are displayed inside the boxes; no correlation showed significance. (b) Correlation of sNfL values and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_0. (c) Correlation of sNfL Z-scores and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_0.
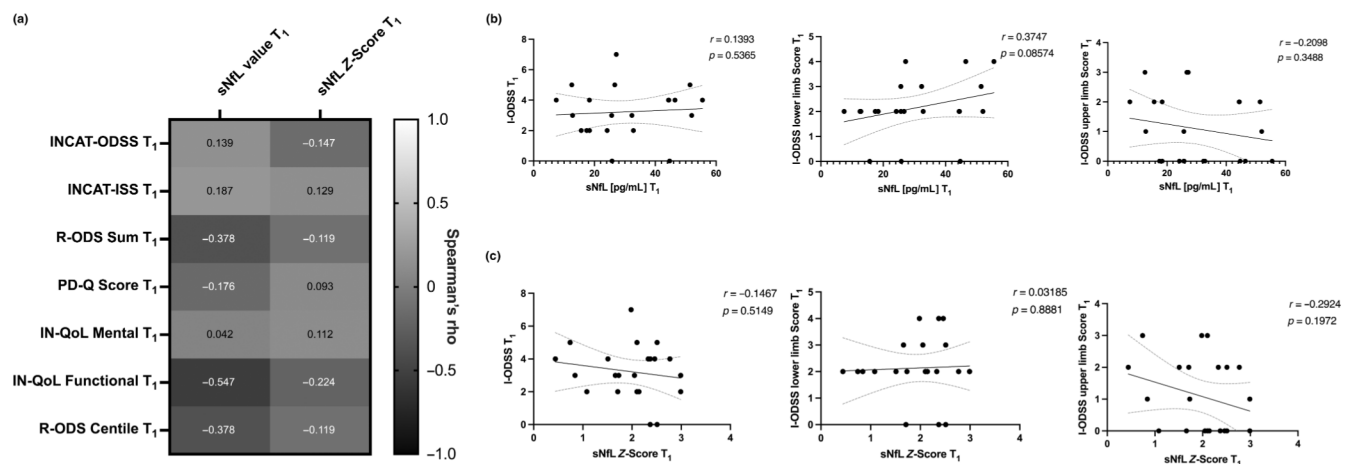

FIGURE 5 Correlation of serum neurofilament light chain (sNfL) values and Z-scores with questionnaire scores at T_1. (a) Correlation of sNfL values and Z-scores with Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) ($n = 22$), Inflammatory Neuropathy Cause and Treatment Sensory Sum Score (INCAT-ISS) ($n = 21$), Rasch-built Overall Disability Scale (R-ODS) ($n = 21$), painDETECT Questionnaire (PD-Q) ($n = 21$), Quality of Life Questionnaire in Inflammatory Neuropathies (IN-QoL) mental ($n = 21$), IN-QoL functional ($n = 16$), and R-ODS Centile ($n = 21$) at time point T_1. Spearman's rho values are displayed inside the boxes; IN-QoL functional and sNfL value showed moderate correlation ($p = 0.03$). (b) Correlation of sNfL values and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_1. (c) Correlation of sNfL Z-scores and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_1.

Patients in our INHIBIT registry undergo extensive and regular thorough follow-up examinations. This highlights the problem that the disease activity, as measured by the sNfL, is not captured by the established follow-up examinations and is not evident in physician–patient contacts. Our results suggest that more attention needs to be paid to the progression of CIDP. Also, further studies are needed to show whether these patients benefit from intensified immunotherapy or potential neuroprotective substances [19] to achieve long-term stability.

In addition, our data from the 29 included patients show a positive correlation between raw sNfL levels and the INCAT-ODSS. Interestingly the lower limb subscore of the INCAT-ODSS correlated better with sNfL than either the overall INCAT-ODSS or the upper limb score. This may indicate that the neuroaxonal damage in CIDP is highest in the nerves of the lower limbs, which is in line with electrophysiological results from the INHIBIT cohort [20, 21]. However, the correlation disappears when Z-Scores are calculated, so this suggestion should be interpreted with caution.
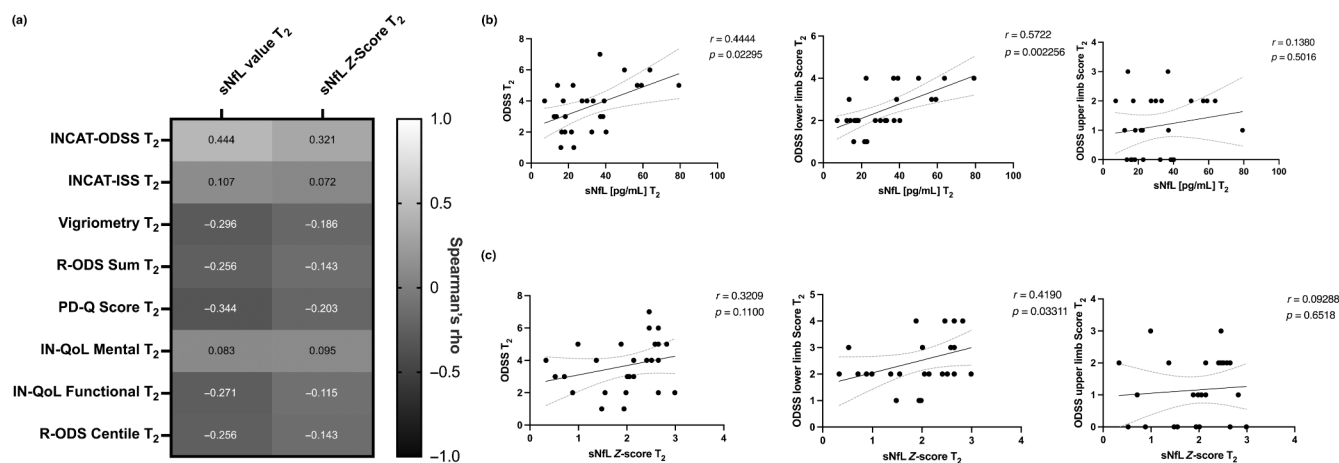
FIGURE 6 Correlation of serum neurofilament light chain (sNfL) values and Z-scores with questionnaire scores at T_2. (a) Correlation of sNfL values and Z-scores with Inflammatory Neuropathy Cause and Treatment Overall Disability Sum Score (INCAT-ODSS) ($n=26$), Inflammatory Neuropathy Cause and Treatment Sensory Sum Score (INCAT-ISS) ($n=26$), vigriometry ($n=25$), Rasch-built Overall Disability Scale (R-ODS) ($n=23$), painDETECT Questionnaire (PD-Q) ($n=23$), Quality of Life Questionnaire in Inflammatory Neuropathies (IN-QoL) mental ($n=23$), IN-QoL functional ($n=19$), and R-ODS Centile ($n=23$) at time point T_2. Spearman's rho values are displayed inside the boxes; I-ODSS and sNfL value showed significant correlation. (b) Correlation of sNfL values and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_2. (c) Correlation of sNfL Z-scores and I-ODSS Score, I-ODSS lower limb subscore, and I-ODSS upper limb subscore at time point T_2.

One reason for the lack of correlation between INCAT-ODSS and Z-Scores could be that the INCAT-ODSS does not reflect active neuronal damage, but also reflects residual damage that does not result in elevated sNfL levels. This finding is in line with a recent study showing that TRFs measured by grip strength do not seem to lead to a higher long-term disease burden [22]. This again indicates that TRFs have no pathological correlate in the sense of neuronal damage.

A strength of our study is the correction of sNfL for age and BMI since other previous studies on CIDP were performed without calculating Z-Scores for sNfL.

A limitation of our study is that the classification between patients with TRFs and without TRFs is based only on the subjectively reported outcome of the patients. Currently, no validated method is available to assess TRFs in CIDP. Although the assessment was performed by an experienced clinical practitioner, none of our screening tools used could reflect the self-reported fluctuations. We were not able to further validate our method of categorizing patients as fluctuating or non-fluctuating. However, were able to show that the sNfL is not able to reflect self-reported fluctuations. However, since sNfL is a marker for axonal degeneration, we cannot determine a more precise cause for TRFs. Another weakness of our study is that there was no gradation of TRFs, with TRFs only collected as a dichotomy variable. However, in the GRIPPER study, TRFs were reported by approximately 50% of the patients, which is comparable to our result of 40%. We did not perform vigorimeter examination at T_1, which could help to objectify TRFs according to the GRIPPER study [8]. Another limitation is that not all patients participated in the follow-up examination, resulting in different group sizes at the respective time points.

CONCLUSIONS

In conclusion, our data show elevated sNfL levels in CIDP patients despite unchanged immunotherapy and apparently stable disease. However, TRFs during an IVIG cycle cannot be detected by sNfL, demonstrating the limitations of short-term repeated measurement of sNfL in CIDP for disease monitoring. Our findings indicate that TRFs in CIDP are not caused by neuroaxonal injury. Further studies are needed to investigate whether patients with elevated sNfL levels have subclinical disease activity and benefit from intensified immunotherapy.

AUTHOR CONTRIBUTIONS

Philip Lennart Poser: Formal analysis, investigation, writing—original draft preparation. **Gulchan Shazadi Sajid**: Data curation, investigation, writing—review and editing. **Léon Beyer**: Data curation, investigation, writing—review and editing. **Alina Hieke**: Data curation, investigation, writing—review and editing. **Aurelian Schumacher**: Data curation, investigation, writing—review and editing. **Lea Horstkemper**: Formal analysis, investigation, writing—review and editing. **Anna-Sophia Karl**: Formal analysis, investigation, writing—review and editing. **Thomas Grüter**: Supervision, writing—review and editing. **Melissa Sgodzai**: Data curation, investigation, writing—review and editing. **Kalliopi Pitarokoili**: Conceptualization, supervision, writing—review and editing. **Klaus Gerwert**: Project administration, writing—review and editing. **Ralf Gold**: Conceptualization, project administration, writing—review and editing. **Anna Lena Fisse**: Conceptualization, project administration, supervision, writing—original draft preparation. **Barbara Gisevius**: Conceptualization, project administration, supervision, writing—original draft preparation.

Jeremias Motte: Conceptualization, project administration, supervision, writing—original draft preparation.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data collected from this study are available upon reasonable request from the corresponding author.

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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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