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Nerve Ultrasound Predicts Treatment Response in Chronic Inflammatory Demyelinating Polyradiculoneuropathy—a Prospective Follow-Up

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Abstract

As reliable biomarkers of disease activity are lacking, monitoring of therapeutic response in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) remains a challenge. We sought to determine whether nerve ultrasound and electrophysiology scoring could close this gap. In CIDP patients (fulfilling EFNS/PNS criteria), we performed high-resolution nerve ultrasound to determine ultrasound pattern sum scores (UPSS) and predominant echotexture nerve conduction study scores (NCSS) as well as Medical Research Council sum scores (MRCSS) and inflammatory neuropathy cause and treatment disability scores (INCAT) at baseline and after 12 months of standard treatment. We retrospectively correlated ultrasound morphology with nerve histology when available. 72/80 CIDP patients featured multifocal nerve enlargement, and 35/80 were therapy-naïve. At baseline, clinical scores correlated with NCSS ($r^2 = 0.397$ and $r^2 = 0.443$, $p < 0.01$), but not or hardly with UPSS (Medical Research Council sum scores MRCSS $r^2 = 0.013$, $p = 0.332$; inflammatory neuropathy cause and treatment disability scores INCAT $r^2 = 0.053$, $p = 0.048$). Longitudinal changes in clinical scores, however, correlated significantly with changes in both UPSS and NCSS ($r^2 = 0.272$–0.414, $p < 0.0001$). Combining nerve/fascicle size with echointensity and histology at baseline, we noted 3 distinct classes: 1) hypoechoic enlargement, reflecting active inflammation and onion bulbs; 2) nerve enlargement with additional hyperechogenic fascicles/perifascicular tissue in > 50% of measured segments, possibly reflecting axonal degeneration; and 3) almost no enlargement, reflecting "burned-out" or "cured" disease without active inflammation. Clinical improvement after 12 months was best in patients with pattern 1 (up to 75% vs up to 43% in pattern 2/3, Fisher's exact test $p < 0.05$). Nerve ultrasound has additional value not only for diagnosis, but also for classification of disease state and may predict treatment response.

Keywords Nerve ultrasonography · CIDP · Polyneuropathy · Ultrasound pattern sum score · Nerve ultrasound and therapy.

Florian Härtig, Marlene Ross, Natalie Winter and Alexander Grimm contributed equally to this work.

Statistical analysis was conducted by Dr. Alexander Grimm, MD, Tübingen University

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Introduction

Diagnosis and guidance of anti-inflammatory therapy are challenging aspects of immune-mediated neuropathy, mainly because reliable biomarkers for disease activity and treatment response are lacking [1]. Currently, nerve conduction studies (NCS) (e.g., the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria) have the highest validity of any available method for diagnosis and follow-up; however, quantification of NCS results might be restricted [2]. Clinical scores may be valid tools to determine the clinical status of a patient. However, they are prone to be swayed by the patients' own interpretation of his or her well-being and do not allow for prediction of treatment response. Subsequently, even thorough neurological assessment may

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leave the clinician with significant diagnostic and therapeutic uncertainty [3].

As previously shown, high-resolution ultrasound (HRUS) of peripheral nerves represents a promising complementary diagnostic tool in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and variants [4–10]. In CIDP, HRUS typically reveals not only multifocal and inhomogeneous nerve enlargement affecting predominantly proximal nerve segments, the brachial plexus, and cervical roots [5], but also distinct echointensity patterns [8] or focal fascicle involvement [7], which may further facilitate differentiation from hereditary or noninflammatory neuropathies [9, 10].

Despite increasing evidence, knowledge about the relationship between sonographic findings and the clinical course is still very limited [11, 12]. Furthermore, the diagnostic value of ultrasonic features other than nerve enlargement (e.g., increased or decreased echosignal) is not yet clear.

Long time observations are operationalized using standardized scores, such as the ultrasound pattern sum score (UPSS)—as recently shown for multifocal motor neuropathy [7, 12, 13].

We have thus decided to evaluate the UPSS as an observational tool and prognostic biomarker for therapeutic response in treatment-naïve and long-term treated CIDP patients and to explore further ultrasonic features of CIDP and variants, particularly nerve echotexture, and their diagnostic and prognostic value. Further, we retrospectively compared histology of the sural nerve with the ultrasound morphology if available. Additionally, we operationalized nerve conduction study data in order to improve comparability with clinical and ultrasound findings.

Methods

Setting and Eligibility

Between May 2014 and May 2016, consecutive patients with CIDP and its variants, who presented to the outpatient clinic of the University Hospitals of Tübingen, Basel and Jena, were prospectively included. The study was registered in the German clinical trial registry (DRKS-ID 00005253) and approved by the local ethics committees (Tübingen 702/2015BO2, Basel 2014-230, and Jena 3663-01/13). Written informed consent to study participation was obtained from all patients.

Correct diagnosis was established according to the EFNS/PNS criteria [14]. Patients were categorized by clinical presentation and treatment status: Previously untreated patients were marked as "untreated neuritis" (UN), whereas already treated patients were marked as "treated neuritis" (TN). Patients in both groups received standard treatment during follow-up.

Neurological Examination

All patients underwent detailed clinical examination including the Medical Research Council sum score (MRCSS, ranging from 0 to 60 points), inflammatory neuropathy cause and treatment disability score (INCAT, ranging from 0 to 10) [15, 16], nerve conduction studies (NCS), and standardized HRUS examination (incl. UPSS) at baseline and after 12 months ($UPSS_{month12}$, $MRCSS_{month12}$, $INCAT_{month12}$). Clinical changes of MRCSS and INCAT score were rated as difference of score at months 12 to baseline (named $\Delta MRCSS$, $\Delta INCAT$).

NCS included the median, ulnar, tibial, and fibular nerves on their most involved side including F-waves; for median and ulnar nerve with stimulations from wrist to Erb's point if tolerated at predefined temperature. In addition, we performed sensory NCS for the sural and the ulnar nerve. NCS findings were categorized as either predominantly demyelinating or axonal. CIDP diagnosis was classified in accordance with EFNS/PNS guidelines as *definite*, *probable*, or *possible*. In patients with additional axonal damage, we added needle electromyography of corresponding muscles. To further quantify NCS data, we devised a scoring system, namely the nerve conduction study score (NCSS): Each pathologic *motor* nerve was scored with a maximum of 3 points: i) 1 point was assigned for reduced conduction velocity (CV), distal motor latency, prolonged F-wave latency, or possible conduction block, ii) 1 additional point was added if these values reached percentages proposed by EFNS/PNS guidelines, and iii) 1 further point was added for reduced amplitude of the distal compound muscle action potential. Complete lack of motor response was scored with the maximum of 3 points. Each pathologic *sensory* nerve was scored with a maximum of 2 points: i) 1 point for CV reduction and ii) 1 point for sensory nerve action potential reduction. In analogy to the motor scoring system, 2 points were assigned if no sensory nerve action potential was evocable. The sum of all points of all these nerves yields the NCSS, with a maximum total score of 16 points.

Finally, the longitudinal change of NCSS was evaluated (NCSS after 12 months—NCSS at baseline visit, $\Delta NCSS$). All patients underwent elaborated serum analysis including ganglioside antibodies, HIV serology, and immunofixation.

Ultrasound Examination

HRUS examination (performed on a Mindray 14 Mhz TE7) included measurements of nerve cross-sectional area (CSA) of the median, ulnar, tibial, and fibular nerves (summarized in the UPSA, 16 points), the diameter of the roots C5 and C6 as well as the CSA of the vagus nerve (UPSB, 3 points), and the sural nerve (UPSC, 1 point) of the most involved side at predefined locations as described before for the UPSS score [12, 13].

Homogeneity of the nerves was evaluated for the median, the ulnar, and the tibial nerve, and a maximum of 9 points was reached if all nerves were enlarged homogenously > 1.5-fold (homogeneity score, HS). The maximum score of the UPSS (UPSA + UPSB + UPSC + HS) is thus 29 points. Finally, longitudinal changes in UPSS were evaluated (UPSS after 12 months—UPSS at baseline (ΔUPSS)).

Additionally, maximum fascicle size was measured at the level of the upper arm (for median and ulnar nerve) and the knee (for fibular nerve) according to previously published boundary values (4.8 mm^2 for median, 2.5 mm^2 for ulnar, and 3.5 mm^2 for fibular nerve; [17]). Nerves were defined as mainly hypoechoic if the fascicular appearance was similar to the lumen of blood vessels (e.g., the brachial artery), as hyperechoic if the grayscale was comparable to lymph node echotexture, and as isoechoic if appearance was comparable to control nerves. Furthermore, we examined whether perifascicular tissue was hyperechoic or not. Using this information, we defined the predominant pattern of echoappearance (> 50% of measured segments) as either hyperechoic or not. Gain, probe frequency, and mechanical index were kept constant during the whole examination. With the help of these findings, we classified distinct ultrasound classes according to Padua et al. [8]. Class 1 was defined as significant nerve enlargement (UPSS ≥ 5) with predominantly hypoechoic fascicle pattern. Class 2 reveals significantly enlarged nerves (UPSS ≥ 5) and increased echointensity of the fascicles or the perifascicular tissue in at least > 50% of all measurement points. Class 3 exhibited no or only slight nerve enlargement (UPSS < 5).

Supportive CIDP Criteria

If available, we analyzed supportive diagnostic criteria stated by the EFNS/PNS guidelines (e.g., magnetic resonance imaging, MRI or histology of the sural nerve biopsy); particularly, if available, histology of the sural nerve was evaluated with regard to signs of acute inflammation (edema, infiltrative cells), chronic demyelination (e.g., onion bulbs), or axonal fiber loss. Nerve biopsies were compared to ultrasound data, when performed not more than 3 months prior to or after baseline ultrasound.

Statistical Analysis

T test with Bonferroni correction was used to evaluate differences in epidemiological data (age, gender, height and weight), clinical scores, ultrasound, and NCS data. To examine the validity of HRUS findings with respect to longitudinal disease development, we correlated ΔUPSS with ΔMRCSS, ΔINCAT, and ΔNCSS as described above (regression analysis and Pearson's correlation coefficient). Negative values of ΔUPSS, ΔNCSS,

and ΔINCAT indicate improvement, whereas a negative ΔMRCSS indicates deterioration and vice versa. Differences in all scores of at least 1 point were rated as improvement or deterioration. The correspondence of cross-sectional UPSS, NCSS, INCAT, and MRCSS as well as their Δ was evaluated by cross-table analysis and Fisher's exact test. Linear regression analysis was also used to test for a linear correlation among distinct classes, UPSS, MRCSS, INCAT, and NCSS. Predictive values for therapeutic response between all subgroups were evaluated and calculated by Fisher's exact test. For the ultrasound measurements, intrarater intraclass correlation coefficient (ICC) was measured for each center and examiner (FH and NW for Tuebingen, BD for Basel and BH and CM for Jena) by analyzing 50% of all landmarks online and offline (blinded to the first result); the interrater ICC was measured by reanalyzing every measured landmark by a second examiner (AG) blinded to the first values offline; a mean value of both measurements was used for the UPSS. The NCS scoring and the interpretation of the NCS data with regard on EFNS criteria were done by 2 examiners (AG and NW), evaluating the measurements including curve analyzing, who did not perform data acquisition. Accordingly, mean values were calculated. For all tests, a 2-sided *p* value < 0.05 was regarded as statistically significant. For statistical analysis, we used IBM SPSS Statistics, version 24 (Chicago, IL, USA).

Results

Baseline Data

80 patients were included, 35 of which presented with UN, whilst 45 were already on treatment (TN). Patients' baseline characteristics, including mean clinical, ultrasound, and NCS scores are summarized in Table 1. No significant differences were noted between the UN and TN groups, except a higher INCAT in the untreated group. Most patients exhibited classical sensorimotor symptoms.

EFNS/PNS electrophysiological diagnostic criteria led to the diagnosis of *definite* CIDP in 55, *probable* CIDP in 20, and *possible* CIDP in 5 patients. When using supportive criteria (Table 1), CIDP was considered as *definite* in 78 and as *probable* and *possible* in 1 each.

Treatment During Observation Period

Overall, therapeutic regimens after baseline did not differ significantly between both groups. During the observation period, 22/35 UN and 32/45 TN patients received intravenous immunoglobulins (IVIG) only at 6 to 12 g per kg of

Table 1 Baseline data

	Age Weight Height	UPSS 1st visit	MRCSS 1st visit	INCAT 1st visit	NCSS 1st visit	Relevant concomitant diseases	Main clinical symptoms	Supportive criteria* [15]
Untreated patients (UN) n = 35	62.1 (14.8) 80.4 (17.2) 177.3 (9.3)	12.8 (7.3)	52.3 (7.9)	4.4 (2.9)	8.8 (3.5)	DM n = 4, gammopathy n = 8, malignancy n = 4, hypothyreosis n = 2	SM n = 13; S n = 11; M n = 5; aSM n = 3; P n = 1; CN n = 2	0 n = 1; 1 n = 7; > 1 n = 27 (33 definite, 1 probable, 1 possible)
Treated patients (TN) n = 45	61.8 (15.1) 80.6 (16.1) 176.9 (8.2)	12.4 (5.5)	54.3 (4.7)	2.6 (1.6)	7.8 (3.8)	DM n = 3, gammopathy n = 4, malignancy n = 3, hepatitis C n = 1, thyroid gland dysfunction n = 3	SM n = 27; S n = 6; M n = 3; aSM n = 6; P n = 2; CN n = 1	1 n = 7; > 1 n = 38 (45 definite)

Mean values of baseline data do not differ significantly in both groups except the INCAT, which is higher in the untreated group (UN). $p = 0.001$. Standard deviations are mentioned in brackets.

INCAT = inflammatory neuropathy cause and treatment disability score, MRCSS = medical research council sum score, NCSS = nerve conduction studies score, UPSS = ultrasound pattern sum score, (a)SM = (asymmetric) sensorimotor, S = sensory, P = pain, CN = cranial nerve involvement, M = motor. DM = diabetes mellitus type 2.

*Supportive criteria according to the EFNS-guidelines: Nerve biopsy revealed inflammation or chronic demyelination in 11 of 18 cases. Cerebrospinal fluid protein was elevated (> 500 mg/l) in 69 of 80 patients. MRI of the spine was available in 27 patients, 14 of which (13 with definite, 1 with probable CIDP) showed gadolinium enhancement of the cauda equina, whereas 13 patients (7 definite, 5 probable, and 1 possible) did not. 26 of these 27 patients showed ultrasound nerve enlargement with an UPSS of ≥5 points

bodyweight over 12 months (according to clinical symptoms). 9 patients received other immunosuppressive treatment, namely rituximab (RTX), azathioprine, or steroids. Eleven patients were treated by immunosuppressants in addition to IVIG or steroids. 6 patients received no therapy due to mild symptoms during observational period.

Cross-Sectional Nerve Conduction Studies at Baseline

No significant differences in NCSS were found between UN and TN ($p > 0.05$). At baseline, the NCSS correlated significantly with the INCAT ($p < 0.001$) and inversely with the MRCSS ($p < 0.01$). In 9 of the UN and 8 of the TN patients, severe axonal damage was noted (i.e., significantly reduced compound muscle action potential amplitude and/or acute denervation in electromyography). Interrater ICC for the NCSS evaluation was 0.96.

Cross-Sectional Ultrasound Data at Baseline

In almost 90% of patients, including all patients with electrophysiologically possible CIDP, mean nerve CSA values were—as expected—significantly increased compared with normal values. UPSS was usually increased to > 8 points and therefore fulfilled the previously suggested ultrasound criteria for CIDP [12]. Eight patients had an UPSS of < 5 points. Mean UPSS did not differ significantly between UN and TN patients ($p > 0.05$). Further, 67.5% of UN and TN showed at least 2 or more enlarged fascicles at the measured sites without significant differences between both groups (mean fascicle size for all patients 5.9 ± 2.5 mm^2 in median nerve, 4.8 ± 2.2 mm^2 in ulnar nerve and 3.9 ± 1.8 mm^2 in fibular nerve).

The UPSS showed no significant correlation with the MRCSS ($p = 0.332$) and a significant but very low correlation with the INCAT overall disability ($p = 0.048$) (r^2 values are shown in Table 2 and Fig. 1). We found no correlation between the ultrasound and the NCS score ($p > 0.05$). The overall intrarater ICC for the ultrasound measurements and raters was 0.95; the mean inter-rater ICC was 0.90 for 2 raters for each measurement and UPSS.

Classification of Ultrasound Findings

Combining UPSS, echointensity, fascicle size, and perifascicular tissue increase, we defined 3 classes of nerve morphology in a posthoc analysis (compare the algorithm of Fig. 2). This data analysis and classification is in line with previously published findings of Padua et al. [8]. We found a different distribution of ultrasound patterns within UN and TN patients (Table 2; Fig. 3). Class 1 (significant nerve enlargement (UPSS ≥ 5; Fig. 2A) with predominantly hypoechoic fascicle pattern and without prominent

Table 2 Cross-sectional data for UPSS and correlation with MRCSS and INCAT and longitudinal change according to classes and groups

	ΔUPSS (12 months–baseline)	ΔMRCSS (12 months–baseline)	ΔINCAT (12 months–baseline)	ΔNCSS (12 months–baseline)	Concordant changes (correspondence in %)	Correlation (baseline)	Correlation (12 months)
All patients	− 1.6 (3.2)	+ 2.1 (7.7)	− 0.9 (1.2)	− 0.4 (0.7)	UPSS/MRCSS: 69.8 UPSS/INCAT: 73.6 NCSS/MRCSS: 63.1 NCSS/INCAT: 65.8	UPSS/MRCSS: $r^2 = 0.013$, $p = 0.332$ **UPSS/INCAT: $r^2 = 0.053$, $p = 0.048$** **NCSS/MRCSS: $r^2 = 0.397$, $p = 0.005$** **NCSS/INCAT: $r^2 = 0.443$, $p = 0.002$** NCSS/UPSS: $r^2 = 0.040$, $p = 0.168$	UPSS/MRCSS: $r^2 = 0.042$, $p = 0.216$ UPSS/INCAT: $r^2 = 0.141$, $p = 0.056$ **NCSS/MRCSS: $r^2 = 0.261$, $p = 0.005$** **NCSS/INCAT: $r^2 = 0.423$, $p = 0.043$** NCSS/UPSS: $r^2 = 0.056$, $p = 0.123$
UN all patients	− 1.8 (4.0)	+ 4.4 (8.2)	− 2.3 (1.5)	− 1.0 (2.6)	UPSS/MRCSS: 66.7 UPSS/INCAT: 66.7 NCSS/MRCSS 61.3 NCSS/INCAT: 67.1		
TN all patients	+ 0.1 (7.8)	+ 0.1 (7.8)	− 0.2 (1.7)	+ 0.1 (3.3)	UPSS/MRCSS: 75.5 UPSS/INCAT: 72.2 NCSS/MRCSS 65.6 NCSS/INCAT: 62.1		
Class 1 n = 30 (65.5% UN)	*− 2.3 (4.5)*	*+ 5.5 (9.3)*	*− 1.9 (1.5)*	*− 1.0 (2.9)*			
Class 2 n = 42 (66.6% TN)	*− 1.2 (3.7)*	*+ 0.2 (6.4)*	*− 0.4 (1.7)*	*0.1 (1.3)*			
Class 3 n = 8 (87.5% TN)	*+ 0.1 (1.2)*	*− 0.4 (1.5)*	*− 0.1 (1.8)*	*0.3 (1.1)*			
Subgroups:							
Cranial nerve involvement *n = 3*	− 8.0 (2.5)	+ 12.5 (7.6)	− 3.3 (2.5)	− 1.3 (0.1)			
Pain predominant *n = 3*	+ 1.0 (2.9)	− 2.0 (2.3)	− 1.0 (1.2)	+ 1.5 (0.7)			

Concordances were evaluated by cross-tab analysis, correlations by regression analysis. Significant correlations ($p < 0.05$) are shown in bold print. Significant differences between the distinct ultrasound classes (t test with Bonferroni $p < 0.05$) are shown in italic

INCAT = inflammatory neuropathy cause and treatment disability score, MRCSS = medical research council sum score, NCSS = nerve conduction studies score, UN = untreated neuritis, UPSS = ultrasound pattern sum score, TN = treated neuritis
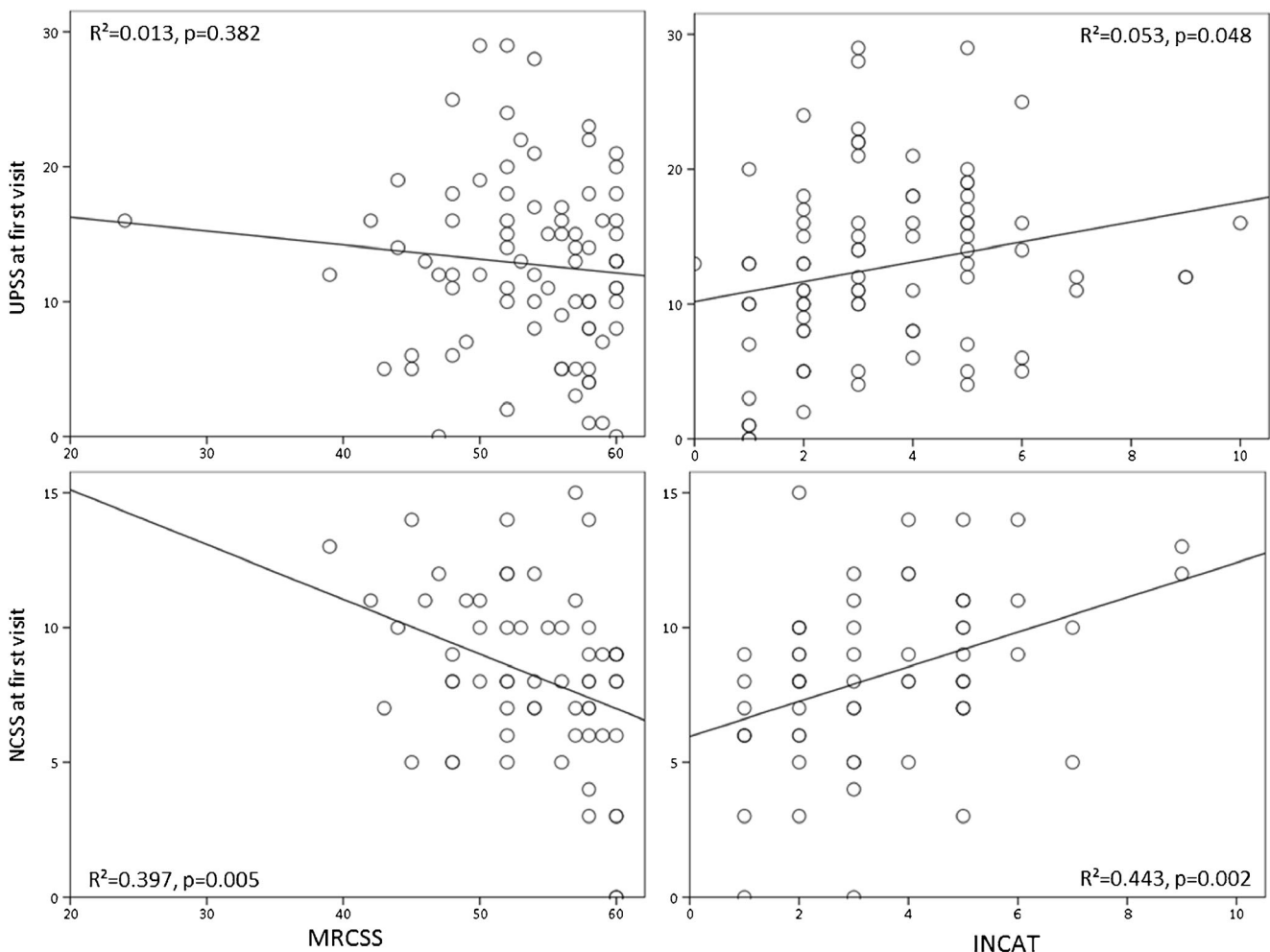
Fig. 1 Linear regression analysis between the UPSS or NCSS and the MRCSS or INCAT scores at baseline. Whereas NCSS correlates significantly with clinical impairment ($p < 0.001$), ultrasound only does insufficiently, particularly with motor impairment, MRCSS ($p = 0.332$).

INCAT = inflammatory neuropathy cause and treatment disability score, MRCSS = medical research council sum score, NCSS = nerve conduction studies score, UPSS = ultrasound pattern sum score

perifascicular tissue increase) was the predominant pattern in UN (65.5%; compared to TN with 34.5%), whereas in the TN group, class 2 (featuring significantly enlarged nerves (UPSS ≥ 5; Fig. 2B) and increased echointensity of the fascicles or the perifascicular tissue at > 50% of all measurement points) was more frequent (66.6 vs 33.4% in the UN group). Class 3 (Fig. 2C) exhibited no or only slight nerve enlargement (UPSS < 5), sometimes with increased echointensity and was mostly found in treated patients (87.5; compared to 12.5% in UN). Fascicles were significantly more often enlarged in class 1 patients (96.2%) compared with those in class 2 (48.6%) and class 3 (25%), (Fisher's exact test, $p < 0.0001$). No significant differences were found between classes for motor impairment MRCSS, concomitant diseases, therapeutic regime, or supportive diagnostics ($p > 0.05$). The mean INCAT score, however, was significantly higher in class 1 and 2 compared to class 3 patients ($p < 0.01$ for both).

Supportive Criteria, Comparison of Nerve Biopsy, and Ultrasound Morphology

Supportive criteria are summarized in Table 1. Nerve biopsy was performed in 18 patients. In 11 of these 18 biopsies, we found signs of acute inflammation (e.g., macrophages, T-lymphocytes, perineural edema) or chronic demyelination (e.g., onion bulbs). 9 of these were performed at baseline visit and therefore concurrent with baseline ultrasound data (4 patients [2 UN and 2 TN] revealed class 1 pattern, 4 [2 UN and TN each] class 2 pattern and 1 TN class 3 pattern); overall results are summarized in Fig. 2. Taken together, all patients with class 1 presentation featured signs of acute inflammation or demyelination, i.e., onion blubs (Fig. 2A), whereas in class 2 presentation, at least moderate to severe (additional or solely) axonal damage was found with only slight signs of inflammation or demyelination (Fig. 2B). In class 3 (Fig. 2C), severe
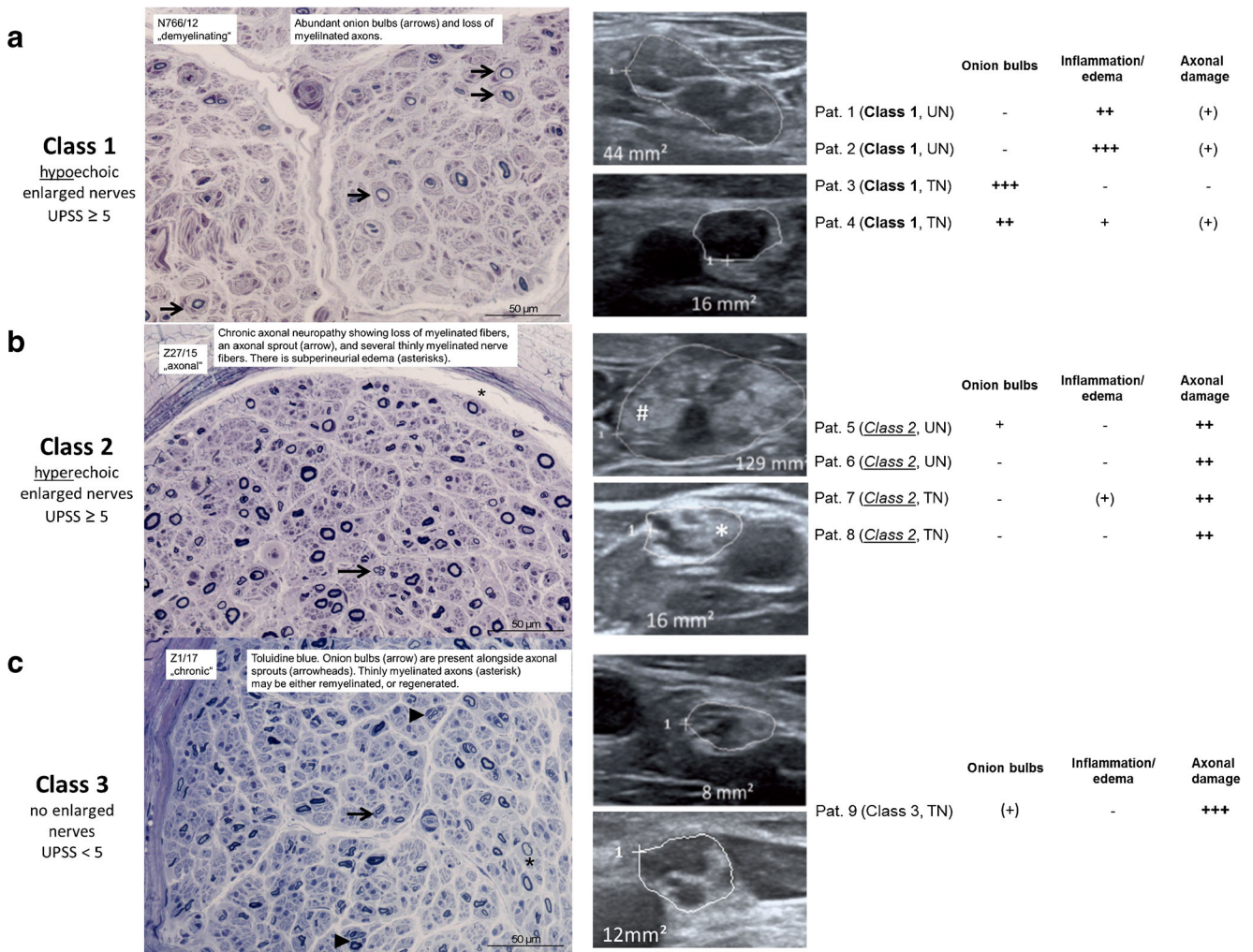
	Onion bulbs	Inflammation/edema	Axonal damage
Pat. 1 (Class 1, UN)	-	++	(+)
Pat. 2 (Class 1, UN)	-	+++	(+)
Pat. 3 (Class 1, TN)	+++	-	-
Pat. 4 (Class 1, TN)	++	+	(+)

	Onion bulbs	Inflammation/edema	Axonal damage
Pat. 5 (Class 2, UN)	+	-	++
Pat. 6 (Class 2, UN)	-	-	++
Pat. 7 (Class 2, TN)	-	(+)	++
Pat. 8 (Class 2, TN)	-	-	++

	Onion bulbs	Inflammation/edema	Axonal damage
Pat. 9 (Class 3, TN)	(+)	-	+++

Fig. 2 The distinct ultrasound pattern classes (based on previously published data from Padua et al. [8]) of immune-mediated neuropathies. If UPSS does not reach ≥ 5 points, the patient is classified class 3, whereas an UPSS ≥ 5 points with increased perifascicular tissue (single asterisk) or increased fascicle echosignal (number sign) is defined class 2 and patients with enlarged nerves without increased echosignal or tissue are defined class 1 (Fascicles can be hypo- and isoechoic). Corresponding histology images are shown for class 1 (A, with many onion bulbs, black arrows, Patient 3) and 2 (B, with signs of additional axonal damage, arrow and slight edema, asterisk, Patient 7). (C) The nerve biopsy of patient 9 with severe axonal damage and no signs of acute inflammation. The 9 patients' biopsy results are summarized concerning onion bulbs, infiltration/edema and axonal damage (− = not found, + = found with mild +, moderate ++, or high amount +++, (+) = only slight findings). Of note, in untreated class 1 neuropathy patients (UN) inflammation and edema predominated, whereas in treated ones (TN), onion bulbs were the catchiest finding. UN = untreated neuritis, UPSS = ultrasound pattern sum score, TN = treated neuritis
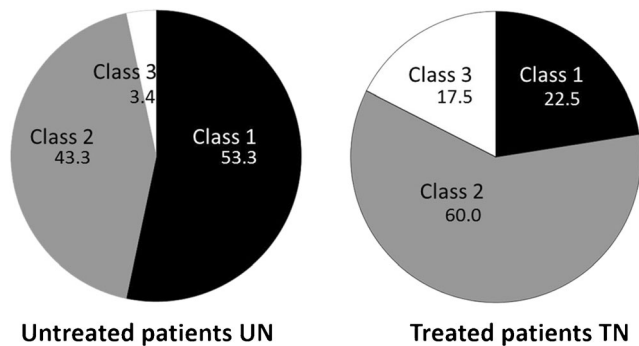

Fig. 3 The distribution of the 3 distinct classes as pie charts in the therapy naïve (untreated) and the chronic treated group in percentages

axonal damage or no inflammation was found. Histology of untreated class 1 patients predominantly exhibited infiltration and edema, whereas in treated class 1 patients, onion bulbs were the most frequent finding.

Longitudinal Ultrasound, Electrophysiological, and Clinical Data After 12 months Follow-Up

The development of clinical scores, NCSS, and ultrasound parameters is shown for all patients as dot plots with improved, deteriorated or stable conditions in Fig. 4. This overall development correlated well not only for the UPSS with MRCSS and INCAT scores (between 70 and 75%
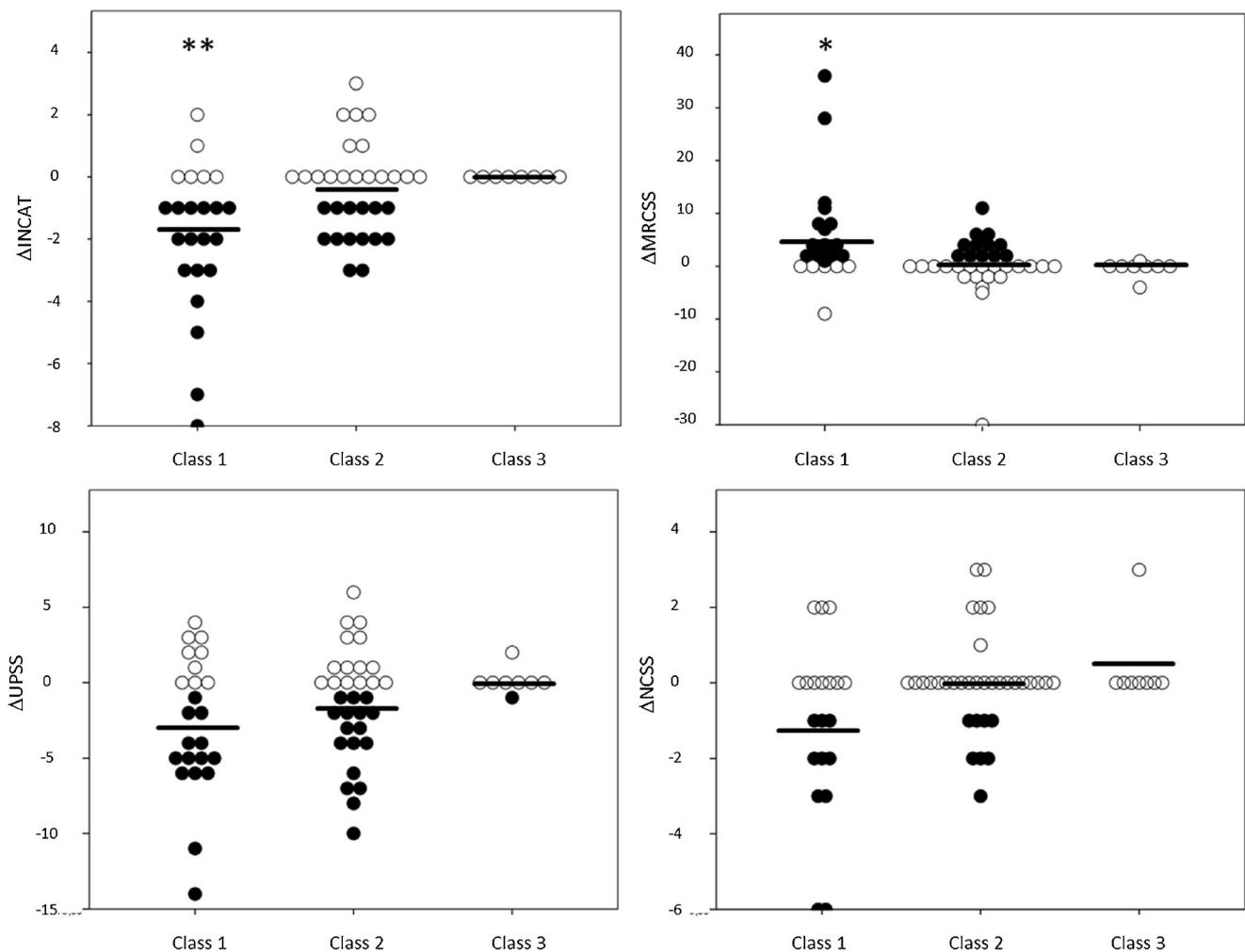
Fig. 4 Intraindividual (dots) and mean (black lines) change (Δ) of the UPSS, the MRCSS, the INCAT overall disability score, and the NCSS for all 3 classes. There is significant higher number of patients with improvement (black dots) in class 1 for MRCSS compared to class 2 (single asterisk) and for INCAT compared to classes 2 and 3 (double asterisk), although intraindividual course can be distinct, independently from morphological pattern. Patients with unchanged or deteriorated scores compared to baseline are marked with white dots. INCAT = inflammatory neuropathy cause and treatment disability score, MRCSS = medical research council sum score, NCSS = nerve conduction studies score, UPSS = ultrasound pattern sum score

concordance), but also for the NCSS with MRCSS and INCAT (63 and 65% concordance) (Table 2). The relative concordances were similar between UN and TN patients (Table 2). In contrast to the overall findings, 3 UN and 2 TN patients developed progressive nerve enlargement (with an increase in UPSS) despite clinical improvement or at least stabilization. In these cases, therapy was either delayed (initiation > 12 months from symptom onset) or applied with an inconsistent therapeutic regime. 12 patients (6 UN and 6 TN) were lost to follow-up at 12 months.

UPSS and NCSS as Longitudinal Biomarkers

ΔUPSS correlated significantly with the ΔINCAT ($p < 0.0001$) and inversely with the ΔMRCSS ($p < 0.0001$) for both UN and TN patients (Fig. 5 including r^2 values).

Also, the ΔNCSS correlated significantly with ΔMRCSS or ΔINCAT ($p < 0.0001$ for both). Changes in UPSS and NCSS also correlated significantly ($r^2 = 0.165$, $p < 0.0001$).

Ultrasound Morphology as a Prognostic Biomarker

Both patient groups with nerve enlargement (hypoechoic class 1 and hyperechoic class 2) did not show any significant differences concerning mean baseline UPSS ($p = 0.188$), NCSS ($p = 0.213$), or baseline clinical scores ($p = 0.842$ and $p = 0.986$), indicating that patients in both groups were evenly clinically affected. None of the patients showed essential morphological switch from 1 to another class within the 12-month period. However, as shown in Fig. 4, class 1 patients showed a significantly better improvement of MRCSS and INCAT
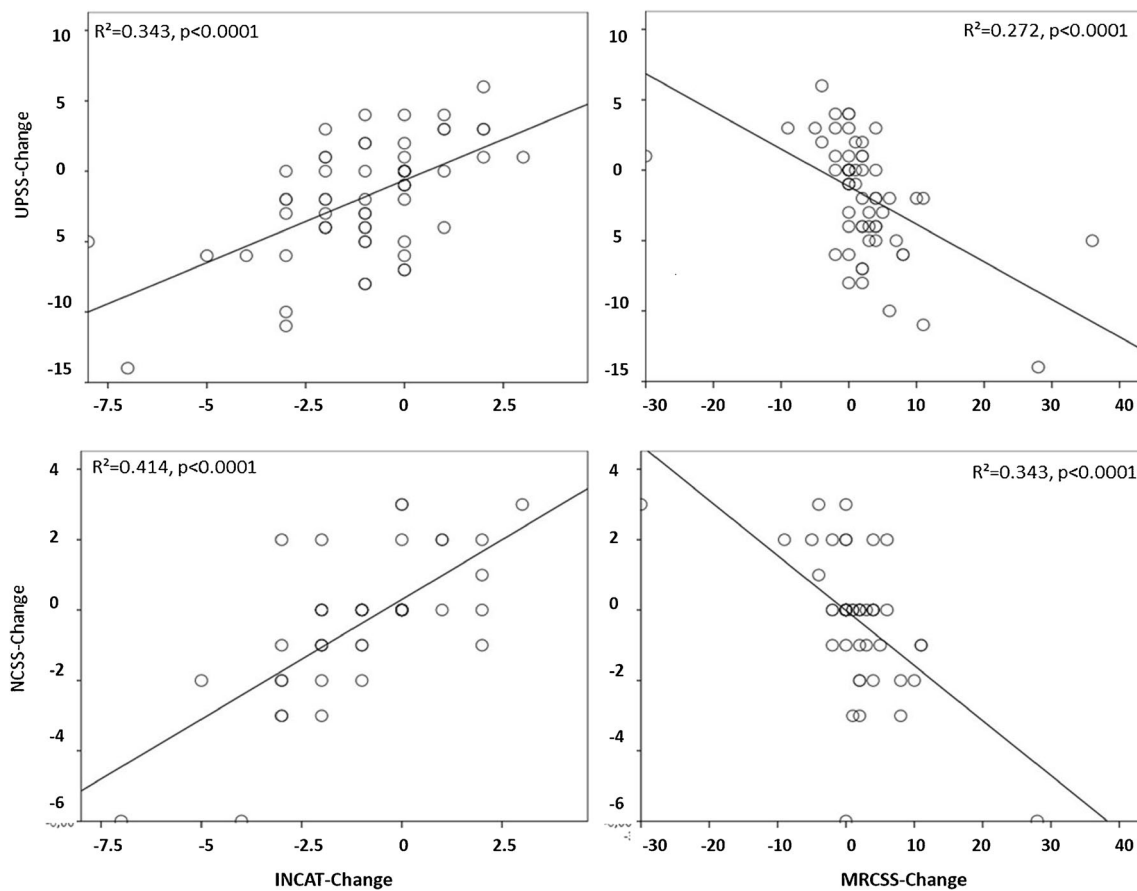
Fig. 5 The linear regression between the changes of the ultrasound pattern sum score (UPSS) and nerve conduction study score (NCSS) and MRC sum score or INCAT disability score in all patients. MRC = Medical Research Council, INCAT = inflammatory neuropathy cause and treatment disability score

compared to those in class 2 (*t* test $p < 0.03$ for MRCSS and $p < 0.01$ for INCAT) and class 3 ($p < 0.05$ for INCAT).

Cross-table analyses indicated that presence of class 1 had a positive predictive value (PPV) for good therapeutic response of 0.69 for MRCSS improvement and 0.75 for INCAT improvement, whereas class 2 presence only revealed a PPV for therapeutic response of 0.40 for MRCSS and 0.43 for INCAT improvement, and class 3 pattern a PPV of 0 for both scores. Fisher's exact revealed significance in favor of class 1 for PPVs of MRCSS (9.354, $p = 0.008$) and INCAT improvement (11.100, $p < 0.001$). Consequently, mean NCSS and UPSS improvement was significantly higher in class 1 compared to classes 2 and 3 (*t* test with Bonferroni correction $p < 0.01$). Figure 6 shows an example of regression of nerve enlargement in a patient with class 1 pattern and clinical improvement.

Particular Clinical Features and Therapeutic Regimes

Patients with cranial nerve involvement experienced better improvement when compared to other patients, whereas patients with pain showed a higher risk for deterioration, which

was also shown for UPSS and NCSS change (*t* test with Bonferroni correction $p < 0.05$; Table 2). Other CIDP variants did not show significant differences ($p > 0.05$).

We could not find any significant differences concerning the development of MRCSS, INCAT, NCSS, and UPSS or the effect of morphology classes with regard to different therapeutic regimens (*t* test with Bonferroni correction $p > 0.05$ for Δs between patients with IVIG, patients with steroids/immunosuppressants, patients with a mixture of several therapies, and patients without treatment). Therapeutic response was not different between patients with definite, probable or possible UN or TN.

Cross-Sectional Ultrasound and NCS Data at 12 months

Just like at baseline, the cross-sectional $UPSS_{month12}$ did not show any significant correlation with the $MRCSS_{month12}$ and $INCAT_{month12}$, neither in UN nor in TN, whilst the $NCSS_{month12}$ did (with $MRCSS_{month12}$ $p < 0.01$ and with $INCAT_{month12}$ $p < 0.05$, r^2 values in Table 2). $NCSS_{month12}$ and $UPSS_{month12}$ did not correlate ($p > 0.05$).
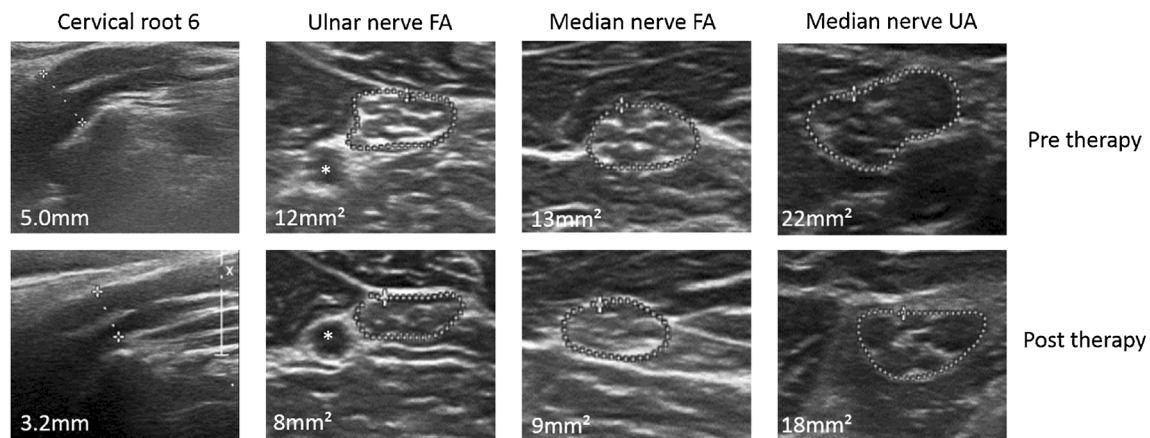
Fig. 6 Example of ultrasound results (class 1) of a patient with CIDP before and 12 months after treatment. Significant reduction of the cross-section areas in ulnar and median nerve (FA = forearm, UA = upper arm) and of the diameter of the cervical root 6 (C6) is shown. CIDP = chronic inflammatory demyelinating polyradiculoneuropathy

Discussion

Multifocal nerve and fascicle enlargement, quantified by the ultrasound pattern sum score (UPSS), is notable in about 90% of untreated and treated CIDP variants, but the amount of nerve enlargement does not consistently correlate with clinical impairment. Over a 12-month follow-up period, however, UPSS changes correlate significantly with clinical development under treatment, showing a decrease of nerve enlargement in case of improvement and vice versa. Similarly, a quantification of nerve conduction studies, as realized by the nerve conduction study score (NCSS), facilitated the interpretation of the electrophysiology data. This score correlated significantly with the clinical development, the ultrasound behavior, and the current clinical status according to clinical scores.

Additionally, ultrasound provided important information about nerve morphology. Our data suggest that therapeutic response is better in patients with hypoechoic nerve enlargement (PPV up to 0.75), which might reflect acute inflammation, than in those with hyperechoic fascicles or perifascicular tissue proliferation and those without nerve enlargement (PPV up to 0.43), which may correspond to predominantly axonal damage or non inflammatory stages. This assumption was confirmed in a small retrospective comparison with sural nerve biopsy results. We therefore conclude that ultrasound studies may significantly enrich nerve conduction data and that the findings of both of these noninvasive techniques could—if summarized in scores and classes—represent promising biomarkers for therapy response.

Cross-Sectional Baseline Data

In our cohort, all patients fulfilled the criteria of definite, probable, or possible CIDP or its variants. Accordingly, most of them featured proximal and predominantly multifocal nerve enlargement. Both treatment-naïve and treated patients featured nerve enlargement to a similar amount—as described in the literature—however, with different intraindividual variability (Fig. 1).

Correlation between nerve enlargement, as seen in HRUS, and clinical disability has been discussed controversially [8, 12, 18]. In our study, there were no consistent direct correlations of nerve enlargement (UPSS) and clinical scores or the NCSS, neither at baseline nor at follow-up and neither in the therapy-naïve nor in the treated group. Our NCS score, however, significantly reflected clinical impairment at first baseline and follow-up (Table 2; Fig. 1).

Ultrasound Morphology

Differences concerning echointensity depending on disease duration have been previously described [8, 12, 19]. We summarized findings and classified 3 distinct classes of ultrasound morphology. The 3 HRUS morphology classes are in line with previous data from Padua et al. [8] and are consistent with the finding of several histopathological CIDP types. In our cohort with 9 chronologically comparable nerve biopsies, we found infiltration of inflammatory cells, edema, or onion bulbs in all patients with class 1, whereas in patients with classes 2 and 3 (additive or solely), axonal damage without significant inflammation or prominent onion bulbs was seen. In conclusion, our classification likely reflects histopathophysiological features which may represent the major advantage of ultrasound over NCS data.

Until now, different clinical aspects and distinct therapeutic responses have been described [20, 21]. Ultrasound might help closing this gap of diagnostic uncertainty.

Longitudinal Data over 12 months

Impact of anti-inflammatory therapy on ultrasonic nerve structure remains unclear, although decrease of nerve enlargement

with successful treatment has been discussed [18, 22]. In our cohort, therapeutic response was significantly better in patients with enlarged nerves and hypoechoic signal (class 1) compared to those with predominant hyperechoic fascicles or perifascicular tissue ($p < 0.03$; Fig. 4). Patients without nerve enlargement revealed almost unchanged ultrasonic presentation at follow-up, regardless of treatment. There was no switch from one to another class during the observation period. As shown in our comparison with nerve histopathology, this emphasizes the suggestion that hypoechoic nerve enlargement corresponds to reversible inflammatory changes like edema or infiltration, whereas hyperechoic changes might indicate chronic irreversible changes with predominantly axonal damage, increased connective/scar tissue or fibrosis (Fig. 2A, B). This consideration, however, must be interpreted with caution as nerve biopsy was only performed in few patients of our cohort. Nevertheless, this is, to the best of our knowledge, the first comparison of ultrasound morphology and nerve histology in CIDP as prognostic and therapeutic marker.

In case of clinical improvement, decrease of nerve enlargement was notable in most patients, regardless of onset morphology. In contrast, when clinical disability increased, nerve enlargement usually progressed, in both UN and in TN. Significant correlations were found between ΔUPSS, ΔNCSS, and ΔMRCSS as well as ΔINCAT overall disability scores ($p < 0.0001$) (Table 2; Fig. 5). Even changes of electrophysiological and ultrasonic findings correlated significantly ($p < 0.0001$), in contrast to the cross-sectional data at baseline and at 12 months. The implementation of a quantitative NCS score facilitated the comparison of the follow-up and the baseline data.

HRUS in general and the UPSS in particular, together with the NCSS, could represent promising therapeutic response markers in therapy-naïve as well as in chronic/treated CIDP and could improve the guidance of immunomodulatory regimens. The changes of clinical, ultrasonic, and electrophysiological scores are useful to document patients' development. Distinct ultrasound morphologies in CIDP reflecting distinct histopathology and distinct therapeutic susceptibility emphasize the additive role of ultrasound in immune-mediated neuropathies in addition to NCS. As an advantage, ultrasound might even be of diagnostic value in case of marked axonal damage, in which NCS validity may be limited. In analogy to disease surveillance concepts in multiple sclerosis (MS), imaging modalities might enrich the future in CIDP therapy, comparable to the "no evidence of disease activity" (NEDA) in MS [23].

Limitations

Some nerves in CIDP patients can progressively enlarge despite improving symptoms [19], as it was the case in 3 UN patients as well as 2 TN patients of our cohort despite clinical improvement (or at least stability). An explanation for this may be a delay in treatment initiation or an inconsistent therapeutic regime due to lack of patient compliance, as it was the case in these patients. It must be kept in mind, that some patients show hypertrophic nerve enlargement progression independent from clinical development. Obviously, prolonged longitudinal data from larger cohorts will be necessary to understand ultrasound pathomorphology in CIDP. Our small group of comparable histology and ultrasound data must be interpreted with caution, e.g., missing nerve enlargement (class 3) could be a sign of curation (no evidence of disease activity) as well as "burned-out" disease stage. Further, additional testing—e.g., paranodal antibodies—must be bared in mind for further sonomorphology studies.

The NCSS, which was developed by our group in order to facilitate follow-up interpretation of electrophysiological findings, represents a new tool to operationalize NCS data. This score currently lacks validation in large prospective multicenter studies; however, it helped in this study to accurately compare UPSS and NCS data.

Of note, the screening examination of all patients by UPSS and NCSS might take more than 1 h depending on examiner's experience, which might be difficult to realize in daily routine, although the follow-up exams are easier to perform and NCSS validation only enriches the daily NCS routine and does not waste much time. Trainee programs would be helpful to facilitate examination. Furthermore, the UPSS could be shortened in the future by defining the most sensitive measurement points as Goedee and colleagues already tried to do [5]. More multicenter data or meta-analyses will be necessary to find out the most sensitive landmarks for diagnosis and standardization of ultrasound in CIDP.

With regard on distinct therapeutic procedures, we could not evaluate significant differences, which might be surprising with regard on the anti-edematous effect of steroids. However, we must consider that i) our study population had no predefined therapeutic regime and therefore many of them had combination of distinct substances or at least other medication during observation period than before. ii) In some patients, switch of medication was necessary during observation period and therefore the distinct subgroups were too small for reliable data analysis. Clearly, further studies with homogenous patient groups and prospectively defined therapies are warranted. The results of our study can help to design such studies. Nevertheless, this therapeutic heterogeneity reflects the daily routine in our centers.

Conclusion

The severity of NCS pathologies as evaluated by a scoring system correlates well with clinical disability in cross-sectional observation of both treatment-naïve and treated

CIDP patients and operates as an accurate longitudinal biomarker of disease severity. Similarly, the ultrasound pattern sum score (UPSS) was found to be a suitable longitudinal observation marker with changes in ultrasonic parameters correlating significantly with the change in clinical disability, independently of disease stage or therapeutic protocol.

Additionally and most importantly, ultrasound morphology may represent a marker for therapeutic susceptibility: patients with hypoechoic fascicles and enlarged nerves (representing inflammation and onion bulbs) experienced a significantly improved clinical course during treatment than those with increased fascicular or perifascicular echointensity (associated with axonal damage). Patients without nerve enlargement remain almost unchanged in ultrasound, electrophysiological, and clinical scores. Those patients might be candidates for therapeutic release.

Compliance with Ethical Standards

Abbreviations Anti-MAG, myelin-associated glycopeptide antibodies; C5 and 6, cervical roots 5 and 6; CIDP, chronic inflammatory demyelinating polyradiculoneuritis; TN, treated chronic neuritis; CSA, cross-sectional area; DADS, distal acquired demyelinating sensory neuropathy; EFNS, European Federation of Neurological Societies; HRUS, high-resolution ultrasound; INCAT, inflammatory neuropathy cause and treatment disability score; IVIG, intravenous immunoglobulin; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MGUS, monoclonal gammopathy of unknown significance; MRCSS, medical research council sum score; NCS, nerve conduction studies; ON, onset neuritis; PPV, positive predictive value; RTX, rituximab; UPSS, ultrasound pattern sum score

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