Nerve ultrasound improves detection of treatment-responsive chronic inflammatory neuropathies

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Abstract

Objective
To examine the diagnostic accuracy of nerve ultrasound in a prospective cohort of consecutive patients with a clinical suspicion of chronic inflammatory neuropathies, including chronic inflammatory demyelinating polyneuropathy, Lewis-Sumner syndrome, and multifocal motor neuropathy, and to determine the added value in the detection of treatment-responsive patients.

Methods
Between February 2015 and July 2018, we included 100 consecutive incident patients with a clinical suspicion of chronic inflammatory neuropathy. All patients underwent nerve ultrasound, extensive standardized nerve conduction studies (NCS), and other relevant diagnostic investigations. We evaluated treatment response using predefined criteria. A diagnosis of chronic inflammatory neuropathy was established when NCS were abnormal (fulfilling criteria of demyelination of the European Federation of Neurological Societies/Peripheral Nerve Society) or when the degree of nerve enlargement detected by sonography was compatible with chronic inflammatory neuropathy and there was response to treatment.

Results
A diagnosis of chronic inflammatory neuropathy was established in 38 patients. Sensitivity and specificity of nerve ultrasound and NCS were 97.4% and 69.4% and 78.9% and 93.5%, respectively. The added value of nerve ultrasound in detection of treatment-responsive chronic inflammatory neuropathy was 21.1% compared to NCS alone.

Conclusions
Nerve ultrasound and NCS are complementary techniques with superior sensitivity in the former and specificity in the latter. Addition of nerve ultrasound significantly improves the detection of chronic inflammatory neuropathies. Therefore, it deserves a prominent place in the diagnostic workup of chronic inflammatory neuropathies.

Classification of evidence
This study provides Class IV evidence that nerve ultrasound is an accurate diagnostic tool to detect chronic inflammatory neuropathies.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Polyneuropathy is one of the most common disorders in neurologic practice. Chronic inflammatory neuropathies, including chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis-Sumner syndrome (LSS), and multifocal motor neuropathy (MMN), need to be distinguished from the more common causes, since proper treatment improves strength, function, and outcome. Nerve ultrasound is an emerging tool for the diagnostic workup of polyneuropathies. We showed in a cross-sectional study that sonographic nerve enlargement of the brachial plexus and median nerve reliably distinguishes patients with chronic inflammatory neuropathies from those with the more common axonal neuropathies and motor neuron disease.

Current diagnostic criteria of chronic inflammatory neuropathies depend primarily on results from extensive and time-consuming nerve conduction studies (NCS) that are often necessary to detect features of demyelination. Although they have high specificity, they lack sensitivity, and therefore cannot be used to exclude a diagnosis of treatment-responsive neuropathy. Nerve ultrasound is a reliable and reproducible diagnostic tool. The use of nerve ultrasound could shorten the time to diagnosis and could possibly improve identification of chronic inflammatory neuropathies.

The diagnostic performance of nerve ultrasound has not been studied in an unbiased approach, i.e., among consecutive patients whose differential diagnosis includes chronic inflammatory neuropathy. In this study, we aimed to establish the clinical value of a previously published sonographic protocol in an incident cohort of consecutive patients with a clinical suspicion of chronic inflammatory neuropathy. In addition, we assessed whether nerve ultrasound could improve the identification of treatment-responsive patients compared to NCS.

### Methods

#### Study design and patients

This prospective cohort study was performed between February 2015 and July 2018 in the UMC Utrecht, a large tertiary referral center for neuromuscular disorders in the Netherlands. We included consecutive patients at our outpatient clinic with a clinical suspicion of a chronic inflammatory neuropathy. We defined clinical suspicion as a subacute or chronic sensorimotor
polyneuropathy (complaints ≥6 weeks) and ≥2 of the following criteria: (1) asymmetric involvement, (2) proximal weakness, (3) generalized areflexia, (4) sensory ataxia, (5) rapid progression of complaints, (6) postural tremor, and (7) pain in a symmetric or multifocal distribution; or a subacute or chronic pure motor or pure sensory neuropathy with ≥1 of the above-mentioned criteria. This definition covers asymmetric variants (i.e., MMN and LSS) as well as classical, pure motor, and pure sensory variants of CIDP. Exclusion criteria for this study were (1) previous diagnosis (and treatment) of polyneuropathy, (2) age <18 or >80 years, or (3) physical inability to undergo nerve ultrasound investigation.

Routine diagnostic workup
Diagnostic workup of all patients consisted of a standardized interview using questionnaires, clinical examination, appropriate laboratory investigations, and NCS. In addition, treating physicians could request any additional tests (e.g., MRI...
brachial plexus, lumbar puncture) they deemed necessary to establish a diagnosis. Questionnaires included the INCAT Overall Disability Sum Score (ODSS) and Rasch-built Overall Disability Scale (RODS; for CIDP or MMN depending on the clinical phenotype). Standardized clinical examination consisted of bilateral grading of motor function of 14 muscle groups in arms and legs using the Medical Research Council (MRC) scale, bilateral measurement of grip strength in Kilopascals (kPa) with the Martin Vigorimeter (Martin Medizintechnik, Tuttingen, Germany), and testing of sensory function with the modified INCAT Sensory Sum Score (ISS).

NCS were performed according to a previously described protocol, which takes approximately 90 minutes (excluding time to properly warm limbs), by experienced clinical neurophysiologists who were blinded for nerve ultrasound results and additional diagnostic investigations. Limbs were warmed in water at 37°C (hot tub) for 45 minutes prior to examination with a Nicolet VIKING IV EMG machine (CareFusion Japan, Bunkyo-ku). All NCS were graded following the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP (definite, probable, or possible) or MMN (definite conduction block, probable conduction block, no conduction block).

For the purpose of this study, we categorized NCS that met definite/probable/possible criteria for CIDP or the presence of at least one definite or probable conduction block for MMN as abnormal and other outcomes as normal.

### Nerve ultrasound

Central to this study was nerve ultrasound following a protocol described previously, which takes approximately 20 minutes. Nerve ultrasound was performed by an experienced ultrasonographer, blinded for the results of NCS and additional diagnostic investigations. Investigations were performed on a Philips Epiq 7 (Philips Medical Instruments, Best, the Netherlands) with a 5–18 MHz linear array transducer. In short, we assessed nerve size (cross-sectional area) at standardized sites bilaterally: the median nerve at 1/3 of the forearm, at 1/2 of the upper arm, and the C5, C6, and C7 nerve roots, as this combination had previously high diagnostic accuracy to detect patients with a confirmed diagnosis of chronic inflammatory neuropathy. Nerve ultrasound was regarded as abnormal if unilateral or bilateral nerve enlargement was found at ≥1 of the measured sites.

### Diagnosis and treatment protocol

We used previously published diagnostic criteria for CIDP, LSS, and MMN with the amendment of nerve ultrasound abnormalities that were relevant in the context of this study. In short, we considered a diagnosis of chronic inflammatory neuropathy when patients had (1) a clinical phenotype fitting the EFNS/PNS clinical criteria for CIDP/MMN in combination with (2) a clinical course fitting CIDP/MMN during a 1-year follow-up period and either (3a) NCS abnormalities in

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**Table 1** Baseline characteristics of 100 patients in whom there was a clinical suspicion of a chronic inflammatory neuropathy

| Inclusions (n = 100) |  |
|---------------------|--|
| **Age, y, median (IQR)** | 58.9 (19.5) |
| **Sex** |  |
| Male | 78 |
| Female | 22 |
| **Duration of symptoms, mo, median (IQR)** | 24.0 (36.5) |
| **Clinical criteria set A** |  |
| Sensorimotor | 31 |
| Motor > sensory | 6 |
| Pure motor | 46 |
| Pure sensory | 17 |
| **Clinical criteria set B** |  |
| Asymmetrical complaints | 54 |
| Proximal weakness | 33 |
| Areflexia | 36 |
| Sensory ataxia | 14 |
| Rapid progression | 13 |
| Postural tremor | 9 |
| Pain (symmetric/multifocal) | 24 |
| **Clinical suspicion of** |  |
| CIDP |  |
| Classical | 30 |
| Pure motor | 8 |
| Pure sensory | 17 |
| LSS | 8 |
| MMN | 37 |
| **Definite diagnosis** |  |
| CIDP |  |
| Classical | 14 |
| Pure motor | 2 |
| Pure sensory | 4 |
| LSS | 4 |
| MMN | 14 |
| **Other diagnosis** | 62 |

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; IQR = interquartile range; LSS = Lewis-Sumner syndrome; MMN = multifocal motor neuropathy.

Data are shown as number of patients unless stated otherwise.
For the purpose of this study, we stratified patients into 4 groups. Patients with both NCS and nerve ultrasound results compatible with chronic inflammatory neuropathy (group 1) and patients with abnormal NCS but normal nerve ultrasound results (group 2) were treated with IV immunoglobulin (IVIg) or corticosteroids, or both (figure 1). Patients with normal results for both NCS and nerve ultrasound (group 3) did not receive treatment, and were excluded from further follow-up. Patients with normal NCS but abnormal nerve ultrasound results (group 4) in whom no other diagnosis could be established were either directly offered trial treatment with IVIg and/or corticosteroids, or both, by their treating physician, or, in case there was uncertainty about the initial diagnosis, were invited for a second evaluation at the outpatient clinic. If this did not result in another diagnosis, patients were also offered trial treatment with IVIg.

**Evaluation of treatment response**

We assessed improvement after treatment as follows: (1) MRC sum score: increase of ≥1 point; (2) hand-held dynamometry: an increase in strength of ≥10% in 2 muscle groups in the same region (proximal arm, distal arm, proximal leg, distal leg) or an increase in strength of ≥25% in one muscle group; (3) vigorimetry: an increase of ≥8 kPa in one or both hands; (4) RODS: a minimal clinically important difference (MCID) score (calculated for each patient using individually obtained standard errors) >1.96 for CIDP and >1.00 for MMN; (5) ODSS: a decrease of ≥1 point; and (6) ISS: a decrease of ≥1 point. We defined treatment response as an improvement in MRC sum score (modality 1) in combination with improvement in ≥1 of the other modalities (2–6). Clinical course and treatment response were evaluated during a 1-year follow-up period.

**Statistical analysis**

All data were summarized as mean (SD) for normally distributed variables, median (interquartile range) for non-normally distributed variables, and n (%) for categorical variables. Depending on the distribution of the variable, we compared results of groups of patients using the independent *t* test (continuous, normal), Wilcoxon test (continuous, non-normal), or *χ*² test (categorical). Results were considered significant when *α* was below 0.05. Both NCS and nerve ultrasound were scored as abnormal (1) or normal (0); we used a similar approach towards a diagnosis of chronic inflammatory neuropathy (1) or not (0). We calculated the sensitivity, specificity, positive predictive value, and negative predictive value from 2 × 2 tables. All analyses were conducted in SPSS 22 (SPSS Inc., Chicago, IL).

**Table 2** Treatment response of the 8 patients with normal nerve conduction studies and abnormal nerve ultrasound with a diagnosis of chronic inflammatory neuropathy

| Patient | Diagnosis | Follow-up duration, mo | MRC sum score | RODS MCID | Vig right | Vig left | ODSS | ISS | HHD |
|---------|-----------|------------------------|---------------|-----------|-----------|---------|------|-----|-----|
| 1       | CIDP      | 12                     | +1            | +         | +5        | +7      | −2   | −17 | NP  |
| 2       | CIDP      | 12                     | +14           | +         | +70       | +58     | 0    | 0   | NP  |
| 3       | MMN       | 12                     | +1            | +         | −14       | −5      | −1   | NA  | +   |
| 4       | CIDP      | 16                     | +6            | −         | +3        | +30     | −3   | −4  | +   |
| 5       | MMN       | 16                     | +3            | −         | −22       | −20     | 0    | NA  | +   |
| 6       | MMN       | 16                     | +1            | −         | +13       | +10     | 0    | NA  | +   |
| 7       | MMN       | 15                     | +3            | +         | −10       | +11     | 0    | NA  | +   |
| 8       | CIDP      | 19                     | +8            | −         | +20       | +24     | 0    | NP  | +   |

Abbreviations: − = no improvement; + = improvement; CIDP = chronic inflammatory demyelinating polyneuropathy; HHD = hand-held dynamometry; ISS = INCAT Sensory Sum Score; MCID = minimal clinically important difference; MMN = multifocal motor neuropathy; MRC = Medical Research Council; NA = not applicable; NP = not performed; ODSS = Overall Disability Sum Score; RODS = Rasch-built Overall Disability Scale; Vig = vigorimetry.

The score per modality shown in the figure was calculated as the difference between pretreatment and posttreatment.

accordance with the respective EFNS/PNS criteria or (3b) nerve ultrasound abnormalities as defined previously in combination with treatment response.⁸

This prospective cohort study provides Class IV evidence that nerve ultrasound accurately detects 8/38 additional patients (21.1%) with treatment-responsive chronic inflammatory neuropathy in a cohort of 100 patients with a clinical suspicion of chronic inflammatory neuropathy (sensitivity and specificity 97.4% and 69.4%, respectively).
Data availability
The data that support the findings of this study will be available on request from the corresponding author.

Results
Baseline characteristics
Baseline characteristics of the 100 patients initially suspected of having a chronic inflammatory neuropathy are shown in table 1. All final diagnoses are shown in table e-1 (doi.org/10.5061/dryad.7sqv9s4nx).

Diagnosis of chronic inflammatory neuropathy
A diagnosis of chronic inflammatory neuropathy was established in 38 of 100 patients (CIDP [n = 20], LSS [n = 4], and MMN [n = 14]) (tables e-2 and e-3, doi.org/10.5061/dryad.7sqv9s4nx). Distribution of the patients among groups is shown in figure 1. Group 4 consisted of 25 patients, of whom 15 were treated despite normal NCS results. Of the 15 treated patients, 8 had treatment response, and, therefore, the defined diagnostic criteria of chronic inflammatory neuropathy, as used in this study, were fulfilled (CIDP [n = 4], MMN [n = 4]; table 2). There were no significant differences in clinical characteristics between patients with normal NCS and abnormal NCS (table 3).

In addition to the 8 patients with a final diagnosis of CIDP and MMN based on the combination of normal NCS, abnormal nerve ultrasound, and response to treatment, 3 patients in group 4 improved on treatment but did not meet the predefined criteria for treatment response (improvement of MRC sum score with 10 points and improvement of the RODS score but without MCID [n = 2]; improvement of MRC sum score could not be reached because of maximum baseline score but improvement in ≥1 of the other modalities was fulfilled [n = 1]) (table e-3, doi.org/10.5061/dryad.7sqv9s4nx). Although there was no alternative diagnosis than chronic inflammatory neuropathy, we regarded nerve ultrasound data of these patients as false-positive in the analyses, as these patients did not fulfill the predefined criteria for treatment response.

The distribution of the diagnoses of chronic inflammatory neuropathy established with abnormal NCS, abnormal nerve ultrasound, or both is shown in figure 2. The added value of nerve ultrasound in the detection of treatment-responsive patients was 21.1%.

Diagnostic accuracy of nerve ultrasound and NCS
Sensitivity and specificity for the diagnosis of chronic inflammatory neuropathy were 97.4% and 69.4%, respectively, for nerve ultrasound and 76.9% and 93.5% for NCS (table 4). Based on the results of this study, we devised 2 potential strategies to diagnose treatment-responsive chronic inflammatory neuropathy (figure 3).

Supportive criteria
Results from ancillary investigations are provided in table e-2 (doi.org/10.5061/dryad.7sqv9s4nx).

Discussion
In this study, we found that nerve ultrasound is a useful tool for the diagnosis of chronic inflammatory neuropathy. It showed high sensitivity and acceptable specificity in a cohort of consecutive patients with a clinical suspicion of CIDP, LSS, and MMN, thereby improving identification of patients...
who may respond to treatment. Nerve ultrasound and NCS test characteristics differ, with superior sensitivity in the former and specificity in the latter. These investigations are therefore complementary rather than comparable techniques in the diagnostic workup of chronic inflammatory neuropathy.

In contrast to previous studies, we aimed to obtain our results by using an unbiased approach. Previous studies suggested both high sensitivity (61%–90%) and specificity (72%–100%) of nerve ultrasound for the identification of patients with chronic inflammatory neuropathy, but the inclusion of patients with a diagnosis according to the EFNS/PNS or American Academy of Neurology consensus criteria was a source of potential bias. Although we found comparable high levels of sensitivity, specificity of nerve ultrasound may be slightly lower than previously reported. The lower specificity was caused by the higher number of false-positive sonographic test results. This was the result of several factors, including the design of the study, in which patients with a clinical suspicion rather than a confirmed diagnosis were included. The use of nerve ultrasound allows detection of additional patients who will respond to treatment at the expense of some false-positives. This implies that nerve ultrasound and NCS can best be used as complementary techniques. Moreover, future modifications of nerve ultrasound and NCS protocols may further improve the accuracy of detecting treatable forms of chronic inflammatory neuropathies.

In the group of patients with normal NCS and abnormal ultrasound results, we identified 8 patients with treatment response based on the predefined criteria. Baseline characteristics were not different from patients with a diagnosis of CIDP or MMN according to diagnostic consensus criteria, and extensive diagnostic evaluation revealed no other cause of complaints. We therefore assumed that these patients also had CIDP or MMN. However, in this group we also identified patients with the clinical phenotype of chronic inflammatory neuropathy, but the inclusion of patients with a diagnosis according to the EFNS/PNS or American Academy of Neurology consensus criteria was a source of potential bias. Although we found comparable high levels of sensitivity, specificity of nerve ultrasound may be slightly lower than previously reported. The lower specificity was caused by the higher number of false-positive sonographic test results. This was the result of several factors, including the design of the study, in which patients with a clinical suspicion rather than a confirmed diagnosis were included. The use of nerve ultrasound allows detection of additional patients who will respond to treatment at the expense of some false-positives. This implies that nerve ultrasound and NCS can best be used as complementary techniques. Moreover, future modifications of nerve ultrasound and NCS protocols may further improve the accuracy of detecting treatable forms of chronic inflammatory neuropathies.
neuropathy according to the EFNS/PNS criteria who probably responded to treatment but not according to the predefined criteria (n = 3) or did not improve after treatment (n = 4).21,22 In CIDP, response rates of first-line treatment (IVIg, corticosteroids, and plasma exchange) up to 80% have been described, which suggests that we could have missed patients with a diagnosis of chronic inflammatory neuropathy due to our predefined criteria.31,32 Our estimate of the added value of nerve ultrasound in identifying treatment-responsive patients with chronic inflammatory neuropathy and therewith diagnostic accuracy of nerve ultrasound may therefore be relatively conservative.

Nerve ultrasound study results are as yet not incorporated in the diagnostic consensus criteria for CIDP and MMN.21,22,33 These criteria currently rely mostly on NCS study results, although a diagnosis of possible MMN can be made in the absence of conduction block or other demyelinating features.21,22 However, the rate of treatment response may be disappointing.19,34 The finding of treatment response rates higher than 50% in patients with normal NCS but abnormal nerve ultrasound suggests that nerve ultrasound abnormalities have a higher predictive value than other accepted ancillary investigations for CIDP and MMN (e.g., abnormal brachial plexus MRI, abnormal protein content of the CSF, presence of anti-GM1 immunoglobulin M antibodies) and are similar to the rate of treatment response in patients with NCS abnormalities. Our sonographic protocol has low interrater and interhospital variability and has fewer disadvantages including burden to the patient, cost, duration, and limitations in availability.16 Therefore, nerve ultrasound deserves inclusion as diagnostic tool in future sets of diagnostic criteria. The high sensitivity of nerve ultrasound allows its use as a primary screening tool (figure 3: strategy B) for patients suspected to have chronic inflammatory neuropathy. In this scenario, NCS could be used to confirm the diagnosis of chronic inflammatory neuropathy in patients with abnormal nerve ultrasound results, to detect CIDP, LSS, and MMN in cases with normal nerve ultrasound but with strong clinical suspicion, or to further predict response to treatment with immunoglobulins. This approach could decrease both the demand for labor-intensive NCS and the burden to patients and may thus improve cost-effectiveness.

Our study has some limitations. Not all 100 patients with suspected chronic inflammatory neuropathy received treatment. In theory, treatment-responsive patients without NCS and nerve ultrasound abnormalities could have been missed and diagnostic accuracy of both NCS and nerve ultrasound

Figure 3 Possible diagnostic strategies of chronic inflammatory neuropathy

Possible diagnostic strategies based on a subset of patients with documented treatment response. (A) NCS as primary investigation strategy. (B) Nerve ultrasound as primary investigation. Total treatment: total number of patients who were treated per strategy. − = normal, + = abnormal. CIN = chronic inflammatory neuropathy; NCS = nerve conduction studies; ultrasound = nerve ultrasound.
could thus be overestimated. However, immunoglobulin treatment carries the risk of potentially severe adverse events and treatment of all 100 patients with a clinical suspicion of chronic inflammatory neuropathy would not have been ethical. Moreover, the physicians who assessed treatment response were not blinded for the results of both nerve ultrasound and NCS, due to the study design, in which only patients with abnormal nerve ultrasound, abnormal NCS, or a combination of both were treated. Another limitation was the difference in follow-up duration. Nevertheless, we followed all patients for at least 1 year. Finally, the treating physician was free in his or her treatment decisions and therefore small differences in treatment protocol between patients were present, but all patients received immunoglobulins (and in case of CIDP also corticosteroids) if necessary.

Our sonographic protocol has high diagnostic accuracy in patients with a clinical suspicion of chronic inflammatory neuropathy. Nerve ultrasound and NCS show complementary test characteristics and nerve ultrasound improves identification of treatment-responsive patients by 21%.

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