THE DIAGNOSTIC VALUE OF NERVE ULTRASOUND IN INFLAMMATORY NEUROPATHIES

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De diagnostische waarde van zenuwechografie bij inflammatoire polyneuropathieën

(met een samenvatting in het Nederlands)

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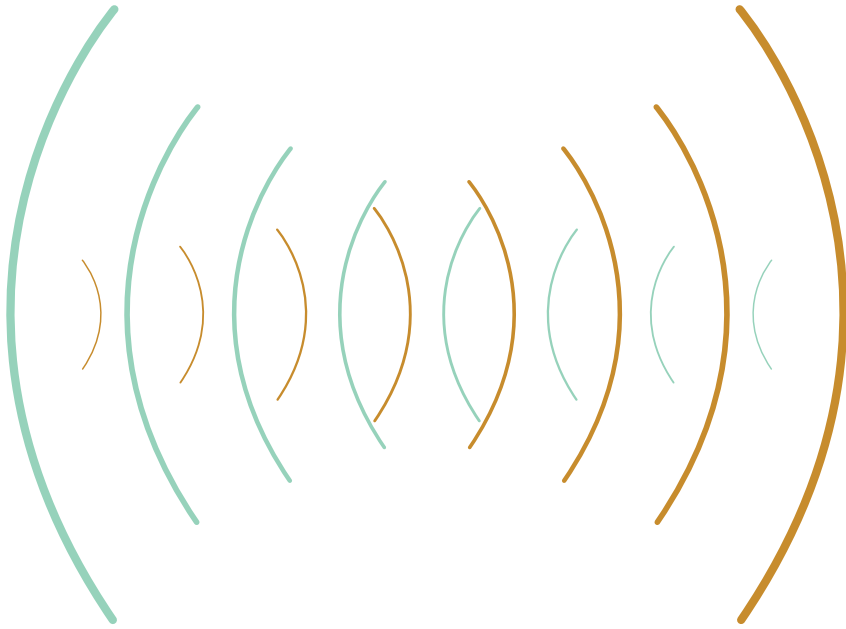Prof. dr. L.H. Visser

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CHAPTER 1

Introduction

BACKGROUND

Polyneuropathies

Polyneuropathy is a common medical condition with an estimated incidence of 7.7/100.000 persons-years in The Netherlands. These figures may increase in an aging population.[1,2] Polyneuropathy is characterized by length-dependent deficits and usually starts in the hands and feet.[3] It is a clinical diagnosis, but ancillary investigations are often needed to unravel its etiology, which is highly variable. The distinction of axonal and demyelinating variants is useful for clinical practice and is based on results from nerve conduction studies. The most common causes of polyneuropathy are summarized in **Table 1.1**.[1,2] Demyelinating neuropathies are much rarer and are often caused by hereditary abnormalities (i.e. Charcot-Marie-Tooth disease (CMT)) or inflammation. The inflammatory neuropathies encompass various disease entities including chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and Lewis Sumner syndrome (LSS). They often respond to immunomodulatory treatment such as intravenous or subcutaneous immunoglobulins (IVIg, SCIg).[4-8]

Table 1.1 Causes of polyneuropathy

Subtype	Causes
Metabolic	Diabetes mellitus, chronic kidney failure, hypothyroidism
Idiopathic	Chronic idiopathic axonal polyneuropathy
Toxic	Alcoholic or due to neurotoxin medication/substance use
Inflammatory	Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy, Lewis Sumner syndrome
Paraproteinemic	IgM-monoclonal gammopathy of unknown significance (MGUS), anti-MAG associated polyneuropathy, polyneuropathy organomegaly endocrinopathy M-protein and skin changes (POEMS), Waldenström
Vascultic	Polyarteriitis nodosa, non-systemic vasculitis neuropathy, microscopic polyangiitis
Systemic diseases	Amyloidosis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Infectious	HIV, lyme's disease, leprosy
Carcinoma/paraneoplastic	Small cell lung cancer, lymphoma
Hereditary	Charcot-Marie-Tooth disease, neurofibromatosis, hereditary neuropathy with liability to pressure palsies

An overview of the causes of polyneuropathy. Only some examples are shown per subtype of origin.

Nerve ultrasound

Nerve ultrasound uses high frequency sound waves, which can be reflected, deflected or absorbed in the body. The degree of reflection determines how the tissue is imaged, with more reflection the tissue is more hyperechogenic (i.e. 'whiter') and with less reflection more hypoechogenic (i.e. 'darker'). Transducers consist of piezoelectric crystals, which are able to convert electrical energy in sound waves and vice versa. The use of ultrasound as a medical diagnostic technique began in the late 1940's with the first assessments of cardiac and fetal anatomy.[9] Dramatic improvements of ultrasound technology and resolution not only allowed more detailed visualization of larger structures, but also of peripheral nerves. In the transversal plane a normal nerve consists of a characteristic echotexture in which hypo-echoic fascicles are surrounded by a hyperechoic rim (honeycomb structure). In the longitudinal plane a normal nerve consists of a mixture of parallel hypoechoic and hyperechoic lines.[10,11]

The first study of nerve ultrasound as diagnostic tool was published in 1987. It described a mass developed from a peripheral nerve, e.g. benign tumor, in 11 patients and reference data from healthy controls.[12] After this groundbreaking study, nerve ultrasound has gradually become part of the neurologist's diagnostic repertoire and has been implemented in the diagnostic guidelines for several mononeuropathies, including carpal tunnel syndrome and ulnaropathy.[13-15] It can also be used to detect the abnormalities associated with nerve tumors (neurofibromas and schwannomas), traumatic nerve damage (axonotmesis versus neurotmesis) and leprosy.[16-22]

In more recent years the use of nerve ultrasound in polyneuropathies has been explored. Implicit or explicit aims of the first studies were to assess whether nerve ultrasound is an additional tool to distinguish axonal from demyelinating forms or whether ultrasound patterns are associated with specific forms of polyneuropathy.[23-25] A more systematic and quantitative approach showed that nerve ultrasound studies do not need to be extensive in order to be informative.[26] A protocol that consists of bilateral examination of the median nerve and the brachial plexus was shown sufficient to distinguish inflammatory neuropathies from disease mimics.

NERVE ULTRASOUND PARAMETERS

Ultrasound allows the distinction of five main parameters; (1) nerve enlargement, (2) fascicle size, (3) echogenicity, (4) vascularization and (5) thickness of epineurium (**Figure 1.1**). Nerve enlargement is probably the most useful feature, but not all parameters have been studies in equal detail.
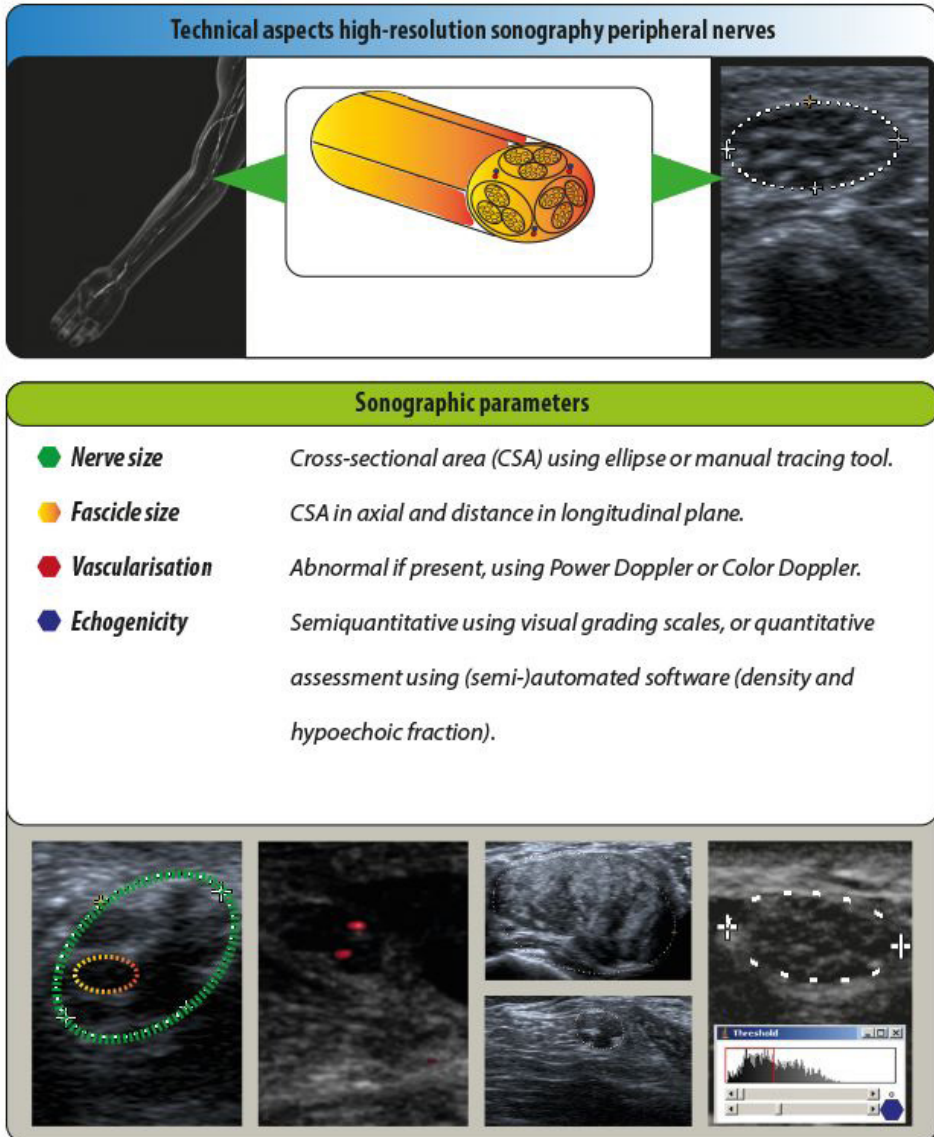
Figure 1.1 Main sonographic parameters

The different parameters which can be assessed with nerve ultrasound. Nerve size is most often measured by tracing the nerve within the epineurium (bottom row, first panel, green tracing). Fascicle size is similarly measured (bottom row, first panel, yellow tracing). Nerve vascularity is most often qualitatively assessed using power Doppler (bottom row, second panel). Nerve echogenicity can be assessed qualitatively (bottom row, third panel) or quantitatively (lower right panel).

1. Nerve enlargement

Correct assessment of nerve size is essential. The most common approach is measurement of the cross sectional area within the hyperechoic rim of the nerve in the transversal plane. Measurement of the diameter can be performed between the internal borders of the hyperechoic epineurium in longitudinal plane.

Nerve enlargement can be used for the diagnosis of mononeuropathies and probably also polyneuropathies. In mononeuropathies enlargement at a solitary entrapment site is the key feature.[13-15,27] In polyneuropathies, the pattern of nerve enlargement is more complex and differs between etiologies. Severe diffuse enlargement has been described in the hereditary demyelinating polyneuropathy Charcot-Marie Tooth type 1a (CMT type 1-a) caused by duplication of the PMP22 gene. Enlargement of proximal nerve segments is common in chronic inflammatory neuropathies including CIDP, MMN and LSS. In axonal neuropathies, nerve enlargement is limited often to entrapment sites or even absent (**Figure 1.2**).[11,26,28] An example of a severe enlarged median nerve in transversal and longitudinal plane in a patient with LSS is shown in **Figure 1.3**.

2. Fascicle size

Hypo-echoic areas within the nerve correspond with fascicles and their size can be measured in the transversal plane. Enlarged fascicles have been described in patients with CIDP and CMT.[29-31]

3. Echogenicity

Both qualitative (visually graded by sonographers) and quantitative (using computerized grey-scale analysis) assessment of echogenicity can be performed in the transversal plane. Hypo-echoic areas have been documented in diabetic neuropathy, carpal tunnel syndrome and ulnar neuropathy.[32-34]

4. Vascularization

Nerve vascularization can be evaluated using Doppler imaging. In a normal nerve, no or only limited epineural or endoneural blood flow is visible. An increased blood flow has been described in patients with, amongst others, leprosy, carpal tunnel syndrome and ulnar neuropathy.[35-37]

5. Thickness of epineurium

The thickness of the epineurium can be assessed in transversal plane. An enlarged epineurium has been described in leprosy.[22]
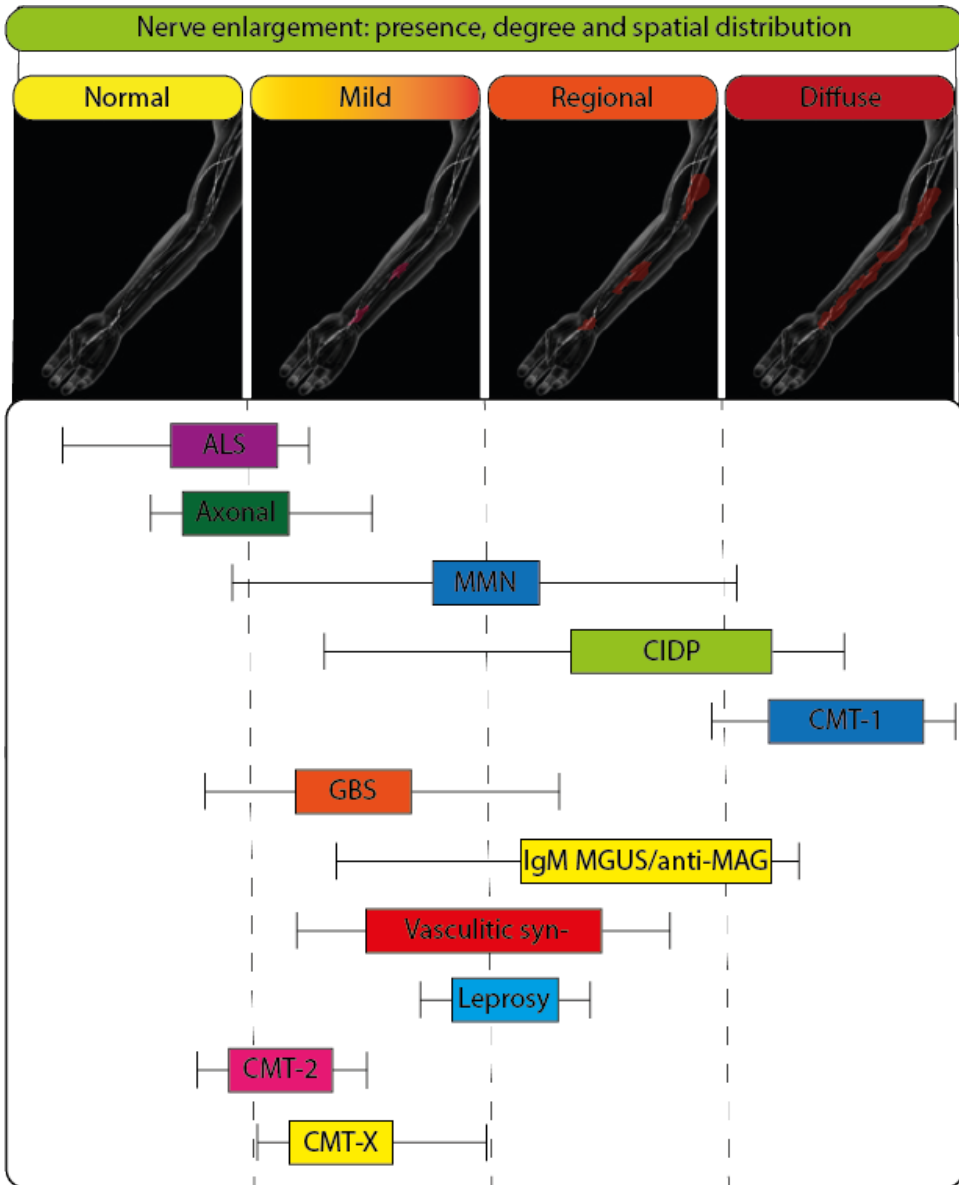
Figure 1.2 Patterns of sonographic nerve enlargement

The different patterns of nerve enlargement in various polyneuropathies and amyotrophic lateral sclerosis (ALS).
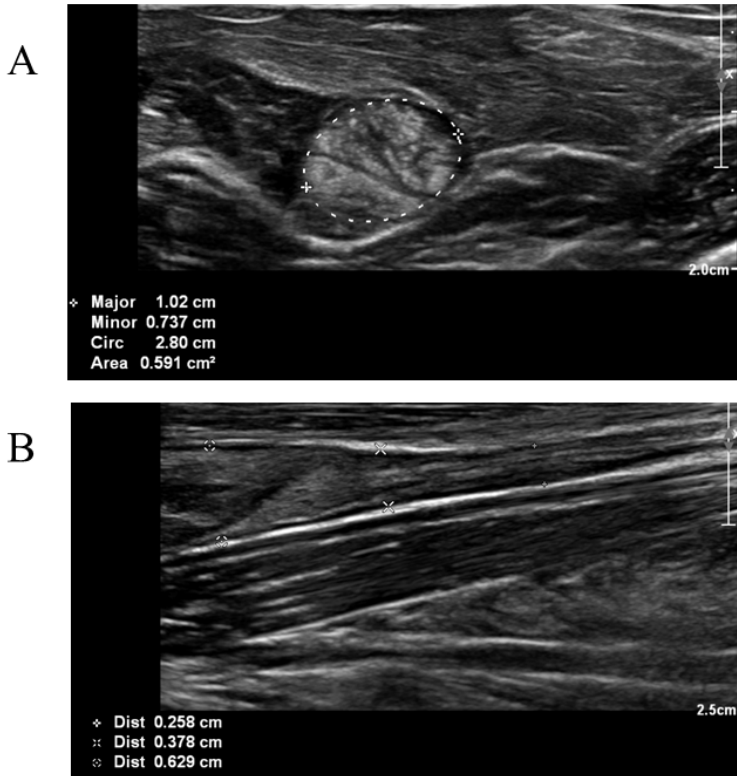
Figure 1.3 Abnormalities identified with nerve ultrasound in a patient with Lewis Sumner syndrome

Severe enlarged median nerve at the forearm in transversal plane (white tracing) and an increased diameter in longitudinal plane (distance between the white marks) in a patient with Lewis Sumner syndrome. In transversal plane the measured cross-sectional area (CSA) is 59.1 mm^2. The upper limit of normal nerve CSA of the median nerve at the forearm is 9 mm^2.

RESEARCH QUESTIONS

Nerve ultrasound and the detection of inflammatory neuropathies

It is generally acknowledged that distinction of treatable chronic inflammatory neuropathies from the more common axonal neuropathies or motor neuron disease is important since treatment can improve strength, function and outcome.[4-8] To ensure a systematic diagnostic approach diagnostic consensus criteria for CIDP (and its variants) and MMN have been developed, of which the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria are probably the most widely used.[38,39] These criteria use combinations of clinical characteristics, results from nerve conduction studies (NCS) and select supportive criteria including treatment response, raised protein in CSF, anti-GM1 IgM antibodies and results from magnetic resonance imaging of the brachial plexus, to define a rough estimate of diagnostic

certainty (i.e. definite, probable or possible CIDP or MMN). In **Table 1.2** these criteria are summarized for CIPD and MMN. For all sets of criteria, NCS results are a key element. However, NCS are not a flawless technique that allows identification of all patients who would respond to treatment. Even extensive NCS of both arms and legs cannot exclude a diagnosis of chronic inflammatory neuropathy and patients with a treatable disorder could therefore be missed.[40-43] Moreover, NCS are time and labour intensive and its execution requires specific expertise.[44-46] The alternative approach of treating all patients with a clinical phenotype of chronic inflammatory neuropathy is limited by costs, burden to patients including risk of adverse events and the lack of a clear definition of treatment response. New and better diagnostic tools for the identification of inflammatory neuropathies are therefore required and nerve ultrasound is a promising candidate, because of relatively low-cost, time-efficient imaging of multiple nerves and the lack of burden for patients. Although we previously showed that a systematic assessment of the median nerve and brachial plexus is very sensitive, this protocol has not been investigated in an unbiased multicenter setting, i.e. in patients with a clinical suspicion of chronic inflammatory neuropathy rather than an established diagnosis. We also know little of interobserver variability of nerve ultrasound and the added value of nerve ultrasound to the current approach (NCS and ancillary investigations) has not been evaluated.

Some neuropathies are associated with specific patterns of nerve enlargement, such as the striking lack of brachial plexus involvement in vasculitic neuropathy.[20] However, nerve ultrasound abnormalities of many rare neuropathies still need to be explored in detail, including those in sensory-dominant neuropathies such as Wartenberg's migrant sensory neuritis.

Natural history of inflammatory neuropathies

The disease course in chronic inflammatory neuropathies is variable, as significant disability but also remarkable improvement can occur over time. Natural history data of rare disorders can help to evaluate treatment efficacy in the longer run. For example, in Guillain-Barré syndrome longitudinal studies have helped to develop prognostic models that have been used in clinical trials that sought to determine if patients with a poor prognosis might benefit from higher IVIg dosing.[47-49] There are relatively few natural history data of chronic inflammatory neuropathies, in particular of MMN. Previous cross-sectional cohort studies of patients with MMN showed that early treatment is a predictor of better outcome.[5,50] Longitudinal studies of the natural history of MMN with reasonable sample size have not been performed. The role of nerve ultrasound as a biomarker of response to treatment or longer term outcome in chronic inflammatory neuropathies has only been investigated in single center studies with relatively small sample sizes and therefore the prognostic value of nerve ultrasound should be further addressed.[51-55]

Table **1.2** Summary of diagnostic criteria of CIDP and MMN according to the EFNS/PNS criteria

CIDP

	Clinical criteria	NCS	Supportive criteria				
			MRI brachial plexus	**CSF protein**	**Treatment**	**NCS**	**Biopsy**
	Key symptoms - Chronic (progressive, stepwise, recurrent) - Symmetric - proximal & distal - Arms & legs - Absence or reduced reflexes Supportive symptoms - Tremor - Ataxia - Cranial nerve involvement	Definite ≥ 1 features of demyelination in ≥ 2 nerves - DML ↑ - MCV ↓ - F-waves ↑ - Absence of F-wave - Temporal dispersion ↑ - Conduction block (area >50% ↓) - Distal CMAP duration ↑ Probable - Conduction block (area >30% ↓) Possible Features of demyelination as in definite but only in 1 nerve	Brachial/lumbo-sacral plexus or spinal roots Hypertrophy or gadolinium enhancement	↑	Objective response	Abnormal sensory electrophysiology in ≥ 1 nerve	Demyelination and/or remyelination
Definite	+	Definite	Not necessary				
Probable	+	Probable	≥ 1 supportive criteria				
Possible	+	Possible	≥ 2 supportive criteria				

MMN

	Clinical criteria	NCS	Supportive criteria			
			MRI brachial plexus	**CSF protein**	**Treatment**	**Lab**
	Key symptoms - Chronic progressive - Focal asymmetric - Weakness ≥ 2 nerve - No sensory symptoms Supportive symptoms -Predominant upper limb - Decrease or absent reflexes - No cranial nerve involvement - Cramps - Fasciculations	Definite - Conduction block (area >50% ↓) - Increase negative peak CMAP duration ≤ 30 % - Normal sensory nerve conduction upper limbs with conduction block Probable - Conduction block (area >30% ↓) - Increase negative peak CMAP duration ≤ 30 % or - Conduction block (area >50% ↓) - Increase negative peak CMAP duration >30% and - Normal sensory nerve conduction upper limbs with conduction block	Brachial roots Increased signal intensity on T2-weighted imaging	↑	Objective response	Anti-GM1 IgM antibodies ↑
Definite	+	Definite	Not necessary			
Probable	+ +	Probable ≥ 2 nerves Probable ≥ 1 nerve	Not necessary ≥ 2 supportive criteria			
Possible	+ Only 1 nerve weakness Only 1 nerve weakness	Not necessary Definite or probable ≥ 2 nerves Probable ≥ 1 nerves	Treatment response Not necessary ≥ 2 supportive criteria			

Clinical characteristics, nerve conduction studies criteria and supportive criteria of CIDP and MMN included in the EFNS/PNS diagnostic criteria.[38, 39]

CIDP = chronic inflammatory demyelinating polyneuropathy, CMAP = compound muscle action potential, CSF = cerebrospinal fluid, DML = distal motor latency, MCV = motor conduction velocity, MMN = multifocal motor neuropathy, NCS = nerve conduction studies

1

Treatment

The beneficial effects of intravenous immunoglobulins (IVIg) and conventional subcutaneous immunoglobulins (SCIg) in chronic inflammatory neuropathies have been shown in clinical trials.[8,56-58] Immunoglobulins are first-line treatment for CIDP and LSS, which also respond to corticosteroids and plasmapheresis, and represent the only available treatment for MMN. Disadvantages of IVIg include systemic adverse events (e.g. headache, malaise, thrombotic complications, anaphylaxis or skin reactions), which are the main reason why treatment is largely confined to hospital. Home treatment is possible in The Netherlands, but infusion needs to be performed by a specialized nurse. Although conventional subcutaneous immunoglobulin treatment is considered a good alternative as it can be self-administered and has fewer systemic adverse events, it requires injections at multiple sites due to subcutaneous volume restrictions and an increase of dosage in half of the patients.[56] Loading doses of IVIg may be necessary in a subgroup of patients who use SCIg. Ideally, administration of immunoglobulins should be possible without the disadvantages of both IVIg and SCIg. The recently introduced formulation of Human Immune Globuline 10% combined with Recombinant Human Hyaluronidase (fSCIg; HyQvia) may allow higher dosages of SCIg at one site, resulting in higher bioavailability without the systemic side effects associated with intravenous administration.[59-61] This treatment has been approved by the Food and Drug administration for primary immunodeficiency, but has not been tested in patients with chronic inflammatory neuropathies.

AIMS OF THIS THESIS

1. To assess the interobserver variability of nerve ultrasound in polyneuropathies (**chapter 2**).
2. To examine nerve enlargement patterns of previously neglected rare sensory neuropathies, i.e. Wartenberg's migrant sensory neuritis (**chapter 3**)
3. To explore the relationship between electrophysiological and sonographic abnormalities in chronic inflammatory neuropathies (**chapter 4**) and to further unravel the patterns of nerve enlargement (**chapter 5)** in these diseases and in Charcot-Marie-Tooth type 1a.
4. To determine the diagnostic and additional value of nerve ultrasound compared to NCS in chronic inflammatory neuropathies in both single and multicenter settings (**chapter 6, 7, 8**).
5. To assess the natural history of MMN in a longitudinal study to detect determinants of outcome (**chapter 9**) and to explore a possible prognostic value of nerve ultrasound of outcome and treatment response in chronic inflammatory neuropathies (**chapter 10**).
6. To explore the safety and treatment satisfaction of a new treatment; Human Immune Globuline 10% with Recombinant Human Hyaluronidase in patients with MMN (**chapter 11**).

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CHAPTER 2

Nerve ultrasound: a reproducible diagnostic tool in peripheral neuropathy

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ABSTRACT

Objective

To determine interobserver variability of nerve ultrasound in peripheral neuropathy in a prospective, systematic, multicenter study.

Methods

We enrolled 20 patients with an acquired chronic demyelinating or axonal polyneuropathy and 10 healthy controls in 3 different centers. All participants underwent an extensive nerve ultrasound protocol, including cross-sectional area measurements of median, ulnar, fibular, tibial, and sural nerves, and brachial plexus. Real-time image acquisition was performed blind by a local and a visiting investigator (reference). Five patients were investigated using different types of sonographic devices. Intraclass correlation coefficients were calculated, and a random effects model was fitted to identify factors with significant effect on interobserver variability.

Results

Systematic differences between measurements made by different investigators were small (mean difference 0.11 mm^2 (95%-CI 0.00 – 0.23 mm^2)). Intraclass correlation coefficients were generally higher in arm nerves (0.48 – 0.96) than leg nerves (0.46 – 0.61). The hospital site and sonographic device did not contribute significantly to interobserver variability in the random effects model.

Conclusions

Interobserver variability of nerve ultrasound in peripheral neuropathy is generally limited, especially in arm nerves. Different devices and a multicenter setting have no effect on interobserver variability. Therefore, nerve ultrasound is a reproducible tool for diagnostics in routine clinical practice and (multicenter) research.

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INTRODUCTION

Nerve ultrasound is a valuable and increasingly used diagnostic tool for entrapment neuropathies, traumatic neuropathies, and more recently inflammatory polyneuropathies.[1-8] Interobserver variability of nerve ultrasound has not been studied in detail in patients with mono- or polyneuropathy. This hampers the applicability of ultrasound for diagnostic work-up of peripheral neuropathy in routine clinical practice.

Previous studies that addressed interobserver variability of nerve ultrasound generally found high intraclass correlation coefficients (ICCs) but had important limitations, including data acquisition in healthy controls only, the use of still images rather than real-time image acquisition, and the assessment of a limited number of nerves and nerve sites.[9-17] Furthermore, few studies addressed the possibility of variation introduced by differences between sonographic devices, and none looked at interobserver variability in a multicenter setting.[10]

The main objective of this study was to determine reproducibility of nerve ultrasound in the assessment of peripheral neuropathy. We therefore performed a prospective, multicenter cohort study in patients and controls. We used a standardized extensive sonographic protocol to analyze interobserver variability and its determinants systematically.

METHODS

Standard protocol approvals, registrations, and patient consents

This prospective multicenter cohort study was performed between May 2016 and May 2017 at the Neurology outpatient clinics of the Elisabeth-Tweesteden Hospital Tilburg, a large general teaching hospital, and two tertiary referral centers for neuromuscular disorders, i.e. the University Medical Center Utrecht and Academic Medical Center Amsterdam. Thirty participants were included in this study: 10 healthy controls and 20 patients. Patients with chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and chronic idiopathic axonal polyneuropathy (CIAP), known at the outpatient clinics of the participating hospitals, were eligible for inclusion. Controls were recruited from the hospital staff. Inclusion criteria for patients were 1) age older than 18 years and 2a) a diagnosis of possible, probable, or definite CIDP or MMN according to the international consensus criteria, or 2b) a diagnosis of CIAP based on the criteria of clinical examination, nerve conduction studies and laboratory testing included in the Dutch guideline of polyneuropathies.[18,19] Inclusion criteria for controls were 1) age older than 18 years and 2) absence of symptoms compatible with neuropathy. Exclusion criteria for this study were 1) history of polyneuropathy other than CIDP, MMN, or CIAP and 2) physical inability to undergo the nerve ultrasound protocol. The Brabant Regional Ethics Committee (NL50375.028.14) and the boards of all participating hospitals approved this study. All participants gave written informed consent.

Study design

Nerve ultrasound protocol

We used a previously described sonography protocol that includes brachial plexus, median, ulnar, fibular, tibial, and sural nerves (**Figure 2.1**).[20] We investigated arm nerves bilaterally and leg nerves unilaterally, because we have shown previously that investigation of both legs has limited added diagnostic value.[2,5] Measurement of nerve size (cross-sectional area (CSA in mm^2)) was performed perpendicular to the nerve and within the hyperechoic rim.

Multicenter protocol and ultrasound equipment

Participants were investigated on the same day by a local investigator from one of the three participating hospitals (JT (Elisabeth-Tweesteden Hospital), SG (UMC Utrecht), CV (AMC Amsterdam)) and a visiting investigator (reference) (IH).

In the Elisabeth-Tweesteden Hospital, 10 participants (5 healthy controls, 3 patients with CIDP, and 2 with MMN) underwent nerve ultrasound on a Toshiba Xario XG (Toshiba, Tokyo, Japan) with a 7- to 18-MHz linear-array transducer (PLT-1204BT). To determine variability introduced by the use of sonographic devices of different brands, two investigators (IH and JT) evaluated another 5 participants (2 patients with CIDP, 1 with MMN, and 2 with CIAP) using both the Toshiba machine and an Esaote MyLab Class C (Esaote Benelux BV, Maastricht, The Netherlands; 6- to 18-MHz linear-array transducer (LA435)). They changed devices at random.

In the UMC Utrecht, 10 participants (5 healthy controls, 3 patients with CIDP, and 2 with MMN) underwent nerve ultrasound on a Philips EPIQ7 (Philips Medical Instruments, Bothell, WA) with a 5- to 18-MHz linear-array transducer (L18-5).

In the AMC Amsterdam an additional 5 participants (4 patients with CIDP, 1 with MMN) underwent nerve ultrasound on an Esaote MyLabTwice (Esaote, Genoa, Italy) with a 6- to 18-MHz linear-array transducer (LA435, for upper and lower extremity nerves) and a 3- to 13-MHz linear-array transducer (LA533, for brachial plexus).

Investigators (all of whom had at least one year's experience of performing nerve ultrasound measurements) were free to position participants in line with their own routine practice, and were allowed to apply their preferred window of depth and measurement tools (all investigators used the ellipse tool except for the local investigator of the AMC who used the tracked trace tool) to determine nerve CSA. This ensured that investigators performed their examination under circumstances that closely resembled their normal routine, and studies to date have not shown that depth and measurement tools increase interobserver variability.[21] However, investigators were not allowed to use a zoom function, as a previous study has already shown that this may increase interobserver variability.[22] All investigators were blinded to results of clinical examination, as well to all previously performed and one another's nerve ultrasound investigations.
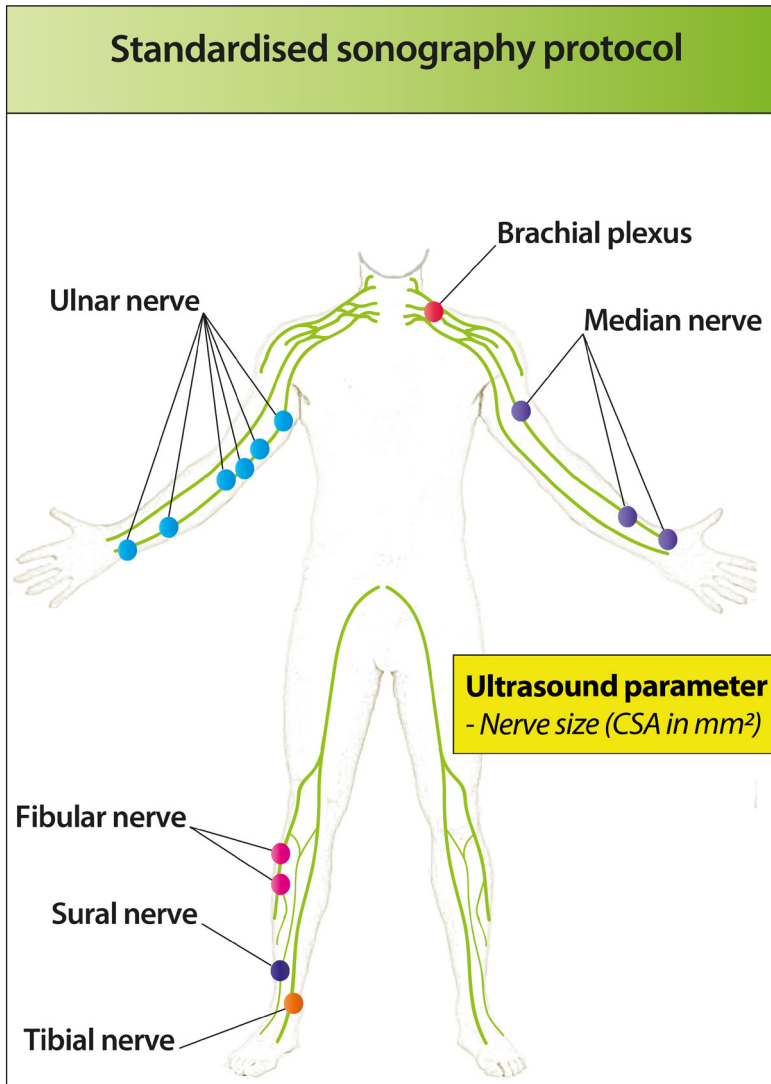
Figure 2.1 Sonographic protocol

Arm nerves were investigated bilaterally, leg nerves unilaterally. Standardized sites of measurement were applied. The median nerve was measured at the wrist, forearm (at 1/3 of the distance between wrist and elbow crease) and arm (at 1/2 of the distance between elbow crease and anterior axillary fold). The ulnar nerve was measured at the wrist, forearm (at 1/3 of the distance between wrist and medial epicondyle), 2.5 cm distal to the medial epicondyle, at the ulnar sulcus (at the level of the medial epicondyle), 2.5 cm proximal to the medial epicondyle, and at the arm (at 1/2 of the distance between medial epicondyle and anterior axillary fold). At the brachial plexus, nerve roots C5, C6, and C7 were measured at the inter-scalene level. The fibular nerve was measured at the fibular head and popliteal fossa, the posterior tibial nerve at the medial malleolus, and the sural nerve 14 cm proximal to the lateral malleolus.

Statistics

Statistical analyses were performed with IBM SPSS 22 (IBM Corp., Armonk, NY) and MLwiN 2.36 (CMM, Bristol, UK). We focused on nerve CSA, as this is the most relevant parameter in distinguishing neuropathies.[2] To determine the reliability of nerve ultrasound, several aspects were investigated.

1. Presence of systematic differences: systematic differences between measurements made by different investigators may affect the reliability of sonography for establishing a diagnosis. Bland-Altman Plot analysis was performed and the mean difference between investigators and 95%-confidence interval (CI) were calculated to determine if there were systematic differences in nerve size.

2. Variability of differences: if there are no systematic differences, a higher variability of the difference between investigators may still cause a lower reliability of sonography because diagnosis in the individual patient is often based on a single measurement and a fixed cut-off value. SD of the difference between investigators was calculated per nerve site to determine if the variability of the difference at those sites was comparable. SDs were also calculated for the different hospitals, sonographic devices, patients and controls, and for groups of nerves with different amounts of mean nerve size.

3. Correlation of nerve size measurements: to determine the correlation of CSA measurements of 2 investigators, ICCs were calculated per nerve site. One-way analysis of variance (ANOVA) with patient as factor was applied to determine the variability between groups and within groups. ICCs were calculated with the following formula: (variability between groups - variability within groups) / (variability between groups + variability within groups).

4. Correlation of the classification of measurements as abnormal: previously published reference values were used to classify measurements as 'not enlarged' or 'enlarged'.[20] To determine the level of agreement between the 2 investigators in the classification of 'not enlarged' or 'enlarged' with a single cut-off value, Fleiss' kappa values were calculated.

5. Mixed model analysis: a random effects model with the mean difference in CSA between investigators as outcome measure was fitted to quantify the effect of multiple determinants (that are commonly encountered in routine clinical practice) on variability in nerve size measurements. Nerve site was entered as second-, participant as third-, and hospital of investigation as fourth-level random effect (individual measurements nested in nerve sites nested in participants nested in hospitals). The use of different sonographic devices, measurement of either patients or controls, and of either right or left side were entered as fixed effects. Markov chain Monte Carlo algorithms were used to calculate the Bayesian Deviance Information Criterion (DIC) (the employed method in MLwiN for cross-classified factors such as participants and nerve sites).[23]

RESULTS

Patients and measurements

Baseline characteristics of participants are shown in **Table 2.1**. Comparison of ultrasound results from different investigators was possible in 829 out of a total of 840 (98.7%) measurements. Comparison was not possible because of storage problems (1 measurement), the presence of a porth-a-cath system in 1 patient (3 measurements), or problems with identifying the C7 nerve root (7 measurements).

Table 2.1 Baseline characteristics

	Patients	Controls
Total number of participants	20	10
Sex, male/female	15/5	5/5
Age in years, median (range)	60.5 (37-77)	27.5 (25-36)
Diagnosis CIDP (definite / probable / possible)	12 (10/1/1)	-
Diagnosis MMN (definite / probable / possible)	6 (5/0/1)	-
Diagnosis CIAP	2	-
Disease duration in months, median (range)	42 (2-264)	-
Treatment duration in months, median (range)	15 (0-121)	-

CIAP = chronic idiopathic axonal neuropathy, CIDP = chronic inflammatory demyelinating neuropathy, MMN = multifocal motor neuropathy

Mean difference, variability of the difference, and ICCs

Figure 2.2 summarizes nerve size measurements by 2 investigators. The mean difference between investigators was 0.11 mm^2 (95%-CI 0.00 – 0.23 mm^2). The mean difference between investigators and ICCs are shown per nerve site in **Table 2.2.**

Overall, the variability of the difference (SD) between investigators was 1.7 mm^2 but it varied substantially per nerve site (**Table 2.2).** SD of arm nerves varied from 1.0 – 1.7 mm^2. SD of large leg nerves and brachial plexus nerve roots was much higher (1.5 – 3.1 mm^2), while SD of the sural nerve was lowest (0.9 mm^2). SD also increased in larger nerves: SD 1.0 in nerves with a mean size <5mm^2 (n=179), 1.6 in nerves with a mean size ≥5 and <10mm^2 (n=485), 2.3 in nerves with a mean size ≥10 and <15mm^2 (n=134), and 3.3 in nerves with a mean size ≥15mm^2 (n=31).

SD ranged from 1.6 – 1.9 mm^2 in the three hospitals, indicating a relatively small influence of different hospitals on overall variability. SD was 1.8 mm^2 in participants investigated twice on the same sonographic device compared to 1.4 mm^2 in participants investigated on two different sonographic devices, indicating that different devices have no influence on overall variability.
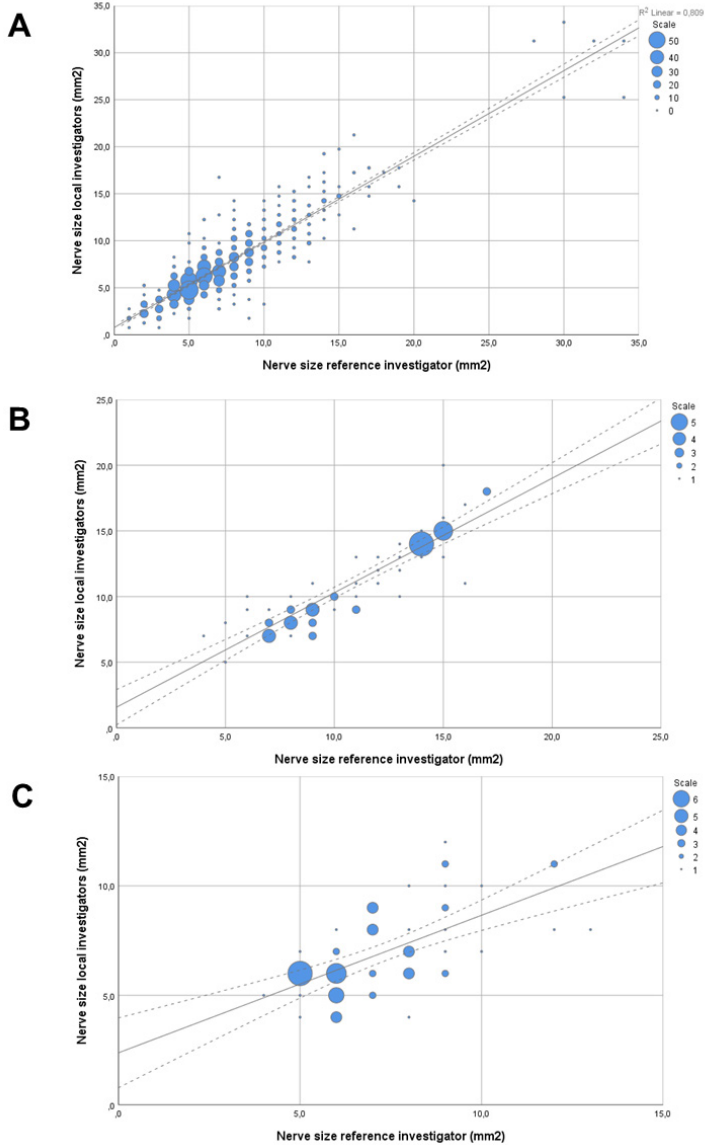
Figure 2.2 Nerve size

Figure 2.2A A comparison of the nerve size measurements of the reference investigator and the local investigators for all measurements. Sizes of circles correspond to numbers of measurements as indicated.

Figure 2.2B Nerve size measurements are shown for the median nerve in the upper arm (as example of a nerve site with a high ICC).

Figure 2.2C Nerve size measurements are shown for the median nerve in the forearm (as example of a nerve site with lower ICC).

Table 2.2 Mean, standard deviation and intra-class correlation coefficients

Nerve/site		N	Mean size (mm², SD)	Mean difference (mm²)	95%-CI of mean difference (mm²)	SD of mean difference (mm²)	Scaled mean difference	ICC
All Measurements		829	7.3 ±3.8	0.11	0.00 – 0.23	1.7	0.23	-[a]
Median	Wrist	60	10.1 ±2.6	0.22	0.00 – 0.59	1.5	0.15	0.84
	Forearm	60	7.2 ±1.8	0.28	0.00 – 0.65	1.8	0.25	0.61
	Arm	60	10.8 ±3.3	0.06	0.00 – 0.41	1.6	0.15	0.89
Ulnar	Wrist	60	5.0 ±1.1	0.14	0.00 – 0.49	1.0	0.20	0.65
	Forearm	59	5.6 ±1.4	0.18	0.00 – 0.54	1.3	0.23	0.60
	Distal to ME	60	6.1 ±1.4	0.18	0.00 – 0.53	1.2	0.20	0.67
	Sulcus (at ME)	60	7.4 ±1.6	0.46	0.04 – 0.88	1.7	0.23	0.48
	Proximalto ME	60	7.4 ±2.2	0.09	0.00 – 0.45	1.2	0.16	0.86
	Arm	60	6.9 ±2.3	0.24	0.00 – 0.61	1.3	0.19	0.85
Plexus	C5	59	7.4 ±6.0	0.08	0.00– 0.46	1.7	0.23	0.96
	C6	59	6.7 ±5.9	0.08	0.00 – 0.46	2.2	0.33	0.95
	C7	52	6.9 ±5.6	0.07	0.00 – 0.44	3.1	0.45	0.86
Fibular	Popliteal Fossa	30	6.7 ±1.7	0.41	0.00 – 0.92	1.5	0.22	0.60
	Fibular Head	30	9.1 ±1.8	0.01	0.00 – 0.42	1.9	0.21	0.61
Tibial	Medial Malleolus	30	11.9 ±2.2	0.02	0.00 – 0.42	2.7	0.23	0.46
Sural	Calf	30	2.0 ±0.5	0.05	0.00 – 0.47	0.9	0.45	0.10

The mean nerve size and mean difference between investigators with its 95%-CI for all measurements and per nerve site. Results of mean difference between investigators presented after correction by multilevel mixed modelling. In addition, SD of the difference between investigators and ICCs for measurements of nerve size are shown. A scaled mean difference was calculated for each nerve site as: (SD of mean difference/mean nerve size)

[a] not calculable due to the multilevel mixed structure of data

ICC = intra-class correlation coefficient, ME = medial epicondyle, N = number of valid measurements, SD = standard deviation, 95%-CI = 95% confidence interval

Kappa values

Kappa values for the classification of nerve enlargement are shown in **Table 2.3**. Values ranged from -0.13 – 1.00. Frequencies of discrepancies between investigators ranged from 0.0 – 28.8% of measurements, depending on the nerve site.

Kappa value for our recently published protocol to determine the presence of an acquired chronic demyelinating polyneuropathy (enlargement of the median nerve at the forearm or arm or at the C5, C6, or C7 nerve roots) was 0.72 (95%-CI 0.37 – 1.00), and with exclusion of the C6 and C7 nerve roots 0.86 (95%-CI 0.51 – 1.00).[2]

Table 2.3 Kappa values for presence of nerve enlargement

Nerve/Site		Cut-off (mm^2)	Kappa	95%-CI of Kappa	Mismatch
Overall		-	0.66	0.59 – 0.73	10.1%
Median	Wrist	≤11	0.78	0.53 – 1.00	8.3%
	Forearm	≤9	0.35	0.10 – 0.60	13.3%
	Arm	≤9	0.80	0.54 – 1.00	10.0%
Ulnar	Wrist	≤7	1.00	0.75 – 1.00	0.0%
	Forearm	≤6	0.18	-0.07 – 0.43	28.8%
	Distal to ME	≤9	0.48	0.23 – 0.74	3.3%
	Sulcus (at ME)	≤9	-0.10	-0.35 – 0.15	18.3%
	Proximal to ME	≤9	0.71	0.46 – 0.96	8.3%
	Arm	≤9	0.66	0.40 – 0.91	8.3%
Plexus	C5	≤8	0.82	0.56 – 1.00	6.8%
	C6	≤8	0.96	0.70 – 1.00	1.7%
	C7	≤8	0.65	0.38 – 0.92	13.5%
Fibular	Popliteal Fossa	≤9	0.46	0.11 – 0.82	6.7%
	Fibular Head	≤11	-0.13	-0.48 – 0.23	23.3%
Tibial	Medial Malleolus	≤14	0.26	-0.09 – 0.62	13.3%
Sural	Calf	≤3	NA		0.0%

Kappa values and 95%-confidence intervals for the correlation of classification of nerve enlargement by investigators, as well as the percentage of measurements in which there is a mismatch between the investigators in the classification 'not enlarged' or 'enlarged'.

ME = medial epicondyle, 95%-CI = 95% confidence interval

Mixed model analysis

Multilevel modeling showed that, compared to the baseline model (DIC 3264.801), a 3-level model fitted the data best (DIC 3195.163), with an estimated overall mean difference of 0.102 mm^2 and significant random effects for 'nerve site' (SD 0.30 mm^2), and 'participant' (SD 0.43 mm^2) and a residual variance (SD 1.66mm^2). Neither the addition of 'hospital' as a fourth-level random effect (DIC 3196.095) nor the addition of fixed factors 'mean nerve size', 'different devices', 'right or left side', and 'patients or controls' improved the model significantly. It should be noted that the residual variance was considerably larger than the random effects of 'nerve site' and 'participant', thus the effect of those factors on reliability seems relatively minor.

DISCUSSION

This study shows that inter-observer variability of sonographic assessment of nerve size is generally limited, and that a multicenter setting and the use of different brands of ultrasound devices do not increase this variability. For defined cut-offs for nerve enlargement, kappa values were in the range of good to excellent for most nerve sites in the arms, and poor to moderate for leg nerve sites. This indicates that nerve ultrasound is reproducible when a clearly defined protocol of arm nerves is used.

The multilevel model indicated that a large part of the observed variation remains to be explained. Significant contributing factors may be partially addressed in future multicenter studies, in particular the selection of nerves of interest (i.e. arms more than legs), but others, such as individual patient characteristics (e.g. less contrast in echogenicity between nerves and surrounding tissues due to the presence of fibrosis), can probably not be anticipated.

As most sonographic devices record nerve size in whole mm^2 or tenths of mm^2, there were no relevant systematic differences between investigators at most nerve sites. Our findings at the wrist and arm level (high ICC), and forearm and leg nerves (low ICC) were in line with previous findings.[10,11,15-17,24-27] Also, ICCs of nerve root measurements were comparable to 2 previous studies.[13 28] One other study that assessed nerve root size at intrascalene level found far lower ICCs, but this study assessed nerve size on still images, which might have hindered correct identification of the nerve roots.[29] The ICC at the ulnar sulcus was relatively low, and – comparable to a previous study – we found a systematic difference between investigators.[15] Assessing nerve diameter instead of CSA at this site may lead to less interobserver variability, but further study is required.[9] Investigators were free to position the participants during ultrasound assessment, and as a result the amount of flexion in the elbow differed to some degree. Standardized positioning of the arm when assessing the ulnar nerve at the sulcus could possibly decrease interobserver variability. For the sural nerve, we observed a low ICC, most likely due to its small size in combination with rounded measurements on whole mm^2. In future studies, therefore, measurements at this site will have to be performed at a level of precision of at least 0.1 mm^2 to prove any diagnostic value of the assessment of this nerve.

Variability of the difference between investigators varied considerably between nerve sites and increased for nerves with a higher mean nerve size (SD 1.0 for nerves <5mm^2 compared to 3.3 for nerves ≥15mm^2). SDs were highest at the brachial plexus (1.7 – 3.1 mm^2) and the tibial nerve (2.7 mm^2). The technical issues of ultrasound measurements at these sites are well known (i.e. difficulty to determine the exact site of splitting of the tibial nerve, and the considerable anatomic variation and depth of the brachial plexus and nerve roots). Although these sites may have diagnostic value in specific types of nerve pathology, the high variability makes these sites less suitable as part of diagnostic protocols or multicenter studies.

This study documented interobserver variability between physicians, hospitals, and different brands of sonographic devices; healthy controls as well as patients with CIAP, CIDP and MMN were investigated. We think that the wide range of abnormalities and the corresponding range

in CSA-values at both entrapment and non-entrapment sites support the robustness of our findings and their relevance for other mono- and polyneuropathies, including carpal tunnel syndrome, and hereditary neuropathies. In contrast to previous studies, which investigated only one parameter with regard to inter-observer variability (e.g. ICC), we investigated multiple parameters, including mean differences, SDs, kappa values, and a random effects model, thus providing very important additional information on the reproducibility of nerve ultrasound, as this is determined by a combination of multiple aspects.

A limitation of this study is the relatively small sample size of patients and the fact that not all participants were investigated by all 4 investigators. However, we found small mean differences between investigators at all nerve sites, with relatively small 95% CIs of this mean difference. It would, therefore, be unlikely that we would have found large systematic differences between investigators if we would have used a larger sample size. Another limitation is that there was some variation in experience with nerve ultrasound between investigators which may, to some degree, have affected results, but all investigators had at least 1 year of experience with sonographic investigation of the nerves included in our protocol.[11,30]

Our study shows that interobserver variability of nerve ultrasound in peripheral neuropathy is limited, especially in arm nerves. Different devices and a multicenter setting have no significant influence on this interobserver variability. Therefore, nerve ultrasound is a reproducible tool for diagnostics in peripheral neuropathy in routine clinical practice and (multicenter) research.

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CHAPTER 3

High-resolution ultrasound in patients with Wartenberg's migrant sensory neuritis, a case-control study

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ABSTRACT

Objective

Wartenberg's migrant sensory neuritis (WMSN) is a rare, patchy, pure sensory neuropathy of unknown etiology. High-resolution ultrasonography (HRUS) is an emerging diagnostic technique for neuropathies, but it has not been applied in WMSN. In this study we aimed to determine HRUS abnormalities in WMSN.

Methods

We performed a case-control study of 8 newly diagnosed patients with WMSN and 22 treatment-naive disease controls (16 patients with pure sensory axonal neuropathy and 6 with pure sensory chronic inflammatory demyelinating polyneuropathy (CIDP) or Lewis Sumner syndrome (LSS)). All patients underwent routine diagnostic evaluations and a predefined HRUS protocol.

Results

We found multifocal nerve enlargement in all 8 WMSN patients. The median nerve in the upper arm and the sural nerve were significantly larger in WMSN than in axonal controls ($p=0.01$ and $p=0.04$). In CIDP/LSS, sonographic enlargement was more extensive. Furthermore we found brachial plexus involvement in 3 of 8 (38%) WMSN patients.

Conclusions

HRUS showed enlargement of multiple nerves in all WMSN patients even if clinical testing and NCS were normal. The feature of multifocal nerve enlargement may be of additional value in establishing the diagnosis of WMSN and may support the suggestion of an auto-immune etiology.

INTRODUCTION

Wartenberg's migrant sensory neuritis (WMSN) is a rare and exclusively sensory neuropathy of unknown etiology, characterized by sudden numbness of one or multiple cutaneous nerves. Numbness may be preceded by pain in the area of distribution of the involved nerve. In some patients stretching of the affected nerve or moving the limb causes pain in the distribution of the involved nerve.[1-3] Although any cutaneous sensory nerve can be involved, deficits most commonly reported involve the sensory branches of the peroneal nerve, the digital branches in the hands, the superficial radial nerve and the sural nerve.[1,2] The disease course is generally benign, usually recurrent, and the impact on daily life being limited.[1,2] An auto-immune etiology has been suggested, although patients who received immunomodulating treatment did not improve.[1,4]

Clinical examination typically shows patchy sensory nerve involvement of limbs, trunk and face. Nerve conduction studies (NCS) may reveal a decrease of sensory nerve action potentials (SNAPs) in clinically affected nerves.[1,2,4,5] Ancillary laboratory investigations have no added value in the diagnostic work-up. However, in the absence of a conclusive diagnostic test the clinical examination still remains the gold standard.[2,4,6]

High-resolution ultrasound (HRUS) of the peripheral nerves may reveal characteristic patterns of nerve involvement suggesting a specific diagnosis, including multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis Sumner syndrome (LSS) and vasculitic neuropathies. This helps to discern them from diseases with mimicking symptoms such as motor neuron diseases in case of MMN and the more common axonal neuropathies in case of CIDP and LSS.[7-11] HRUS features could also improve the diagnostics in WMSN, but these features have not yet been investigated. We, therefore, examined the sonographic pattern of nerve involvement in WMSN and disease controls, using a standardized HRUS protocol.

METHODS

Study design

The study design was case-control. We enrolled 8 newly diagnosed patients with WMSN and, as disease controls, 16 patients with pure sensory non-inflammatory axonal neuropathies (chronic idiopathic axonal polyneuropathy (CIAP) (n=11), diabetic axonal neuropathy (n=1), drug-induced axonal polyneuropathies (n=2), axonal neuropathy due to vitamin deficiency (n=2)) and 6 treatment-naive pure sensory demyelinating neuropathies (CIDP (n=4) or LSS (n=2)). The disease controls were selected from a previous described prospective cohort.[8] The non-inflammatory axonal controls were matched for age and gender. Diagnosis of WMSN was based on the typical clinical presentation (pure sensory complaints in the distribution of one or multiple cutaneous nerves, without weakness and a benign progress of the disease course) and exclusion of other causes of polyneuropathy by NCS and laboratory investigations. Diagnosis

of non-inflammatory axonal neuropathies was based on the criteria of clinical examination, NCS and laboratory investigation included in the Dutch guideline of polyneuropathies and diagnosis of CIDP/LSS was based on the relevant diagnostic consensus criteria.[12]

Patients and routine diagnostic evaluation

Patients were enrolled between January 2013 and May 2016 at the outpatient clinic of the University Medical Center Utrecht, a large tertiary center for patients with neuromuscular diseases. All patients underwent a standardized neurological examination (IH, JT, LvP, LvB), laboratory investigations and nerve conduction studies in addition to an extensive HRUS protocol.

Sonographic protocol

All HRUS studies were performed on the Philips iU22 (Philips Medical Instruments, Bothell, WA) with a 5-17 MHz linear array transducer. We used a previously described sonographic protocol to assess nerve size and vascularisation of the median, ulnar, fibular, tibial, and sural nerves and brachial plexus at standardized anatomical sites.[8,9] We also scanned along the course of the nerves in order to detect other possible sites of enlargement. We used previously described cut-off values to determine nerve enlargement (defined as a cross sectional area (CSA) larger than + 2 SD of healthy controls) and severe enlargement (defined as a CSA larger than the CSA value encompassing 99% of the values found in axonal neuropathy and ALS disease controls in our previously published cohort).[8,9] An experienced sonographer, blinded to the results of clinical examination and NCS performed the HRUS studies (SG). We compared sonography with NCS and clinical examination in the median, ulnar and sural nerve.

Standard protocol approvals and patient consent

This study and its research protocol have been approved by the locally appointed medical ethical committee of the UMC Utrecht. All included patients gave written informed consent.

Statistical analysis

We used SPSS 22.0 software (IBM SPSS, Armonk, NY, USA) for statistical analysis. The independent T-test and the Fisher's exact test were applied to compare the different groups. We used the Benjamini–Hochberg correction to correct for multiple testing; p-value of < 0.05 after correction was considered significant.

RESULTS

Clinical findings and laboratory investigations

Patient characteristics are summarised in **Table 3.1**. All eight patients with WMSN demonstrated patchy sensory involvement, predominantly in the arms and legs. Neurological examination showed a median of 7 affected sensory nerves per patient (range 4-9), and 3 of 8 patients (38%) reported pain in the distribution of the involved nerve when stretching the arms or legs. In contrast, all non-inflammatory axonal controls and 4 of 6 CIDP/LSS controls (67%) showed distal symmetric sensory involvement (**Table 3.1**). Laboratory investigations showed no abnormalities in all WMSN patients, and excluded kidney disease, thyroid disease, diabetes mellitus and vitamin deficiency as causes of the pure sensory complaints.

Table 3.1 Patient characteristics

	WMSN (n=8)	Axonal (n=16)	CIDP/LSS (n=6)
Age (years)	40 (33-54)	51 (46-57)	54 (37-65)
Gender (male(n)/female(n))	4 / 4	8 / 8	5 / 1
Disease duration (months)	13 (9-30)	17 (11-45)	32 (13-111)
Pattern sensory involvement			
(multi)focal (n(%))	8 (100%)	0 (0%)	2 (33%)
distal symmetric (n(%))	0 (0%)	16 (100%)	4 (67%)

Data are shown as number of patients (%) or median (interquartile range).

Axonal = axonal neuropathies, CIDP = chronic inflammatory demyelinating polyneuropathy, LSS = Lewis Sumner syndrome

Sonographic studies

We found focal nerve enlargement of multiple nerves in all patients with WMSN (**Table 3.2 and Figure 3.1**). Enlargement of the median nerve at the upper arm and/or the forearm, was seen in all 8 patients (100%) with WMSN, but was not found in any of the 16 axonal controls (**Table 3.2**). Severe nerve enlargement was found in 1 patient (13%) with WMSN and in 5 patients (83%) with CIDP/LSS. Nerve enlargement was symmetric in 5 of 8 patients (63%) with WMSN and 4 of 6 patients (66%) with CIDP/LSS. The CSA values of the median nerve in the upper arm and the sural nerve were significantly higher in WMSN than in axonal controls (p=0.01 and p=0.04). We also detected nerve enlargement at multiple common sites of entrapment (i.e. the ulnar sulcus, carpal tunnel and fibular head) in patients with WMSN and disease controls. Enlargement of the brachial plexus was seen in 3 of 8 patients (38%) with WMSN and 5 of 6 patients (83%) with CIDP/LSS, yet in none of the axonal controls (**Table 3.2**). We did not find hypervascularization in any of the nerves in patients with WMSN or disease controls.

Table 3.2 Nerve ultrasound measurement in WMSN and disease controls

	Mfa	Mup	Uup	Ps	Pm	Pi	Su
Cut-off value enlargement	>9	>9	>9	>8	>8	>8	>3
Cut-off value severe enlargement	>10	>13	>11				>5
WMSN							
1	8/9	<u>**15**</u>/**11**	8/6	3/3	6/2	3/3	2/2
2	7/5	9/**11**	8/7	5/6	4/4	8/4	**4/4**
3	**10**/9	<u>**17**</u>/**13**	9/-	**11**/8	**11**/4	7/5	3/3
4	**10/10**	**10**/**11**	8/8	7/8	5/4	5/4	**4/4**
5	9/8	**11/11**	**11/11**	4/4	4/3	4/3	**4**/3
6	6/8	9/**10**	5/5	7/5	7/5	**20/12**	2/2
7	8/7	**10**/**11**	7/8	4/5	4/4	3/3	3/**4**
8	8/5	9/**10**	4/4	6/7	8/**9**	**10**/5	**4/4**
Axonal							
1	4/6	7/8	5/4	3/4	3/3	3/4	**4**/3
2	8/7	8/9	5/8	6/7	4/4	3/4	3/3
3	6/7	7/9	8/8	8/5	3/4	4/3	3/3
4	7/9	8/9	8/8	7/5	8/8	8/6	2/3
5	8/8	9/9	7/7	5/5	4/5	3/3	3/2
6	8/5	9/7	8/**11**	5/5	5/7	4/4	3/2
7	8/9	9/9	6/7	7/5	4/3	5/3	3/2
8	6/9	9/8	5/8	7/7	4/5	5/6	3/3
9	6/6	6/8	8/9	8/8	7/8	7/6	3/3
10	8/8	9/8	6/9	6/5	5/5	5/4	**5/5**
11	8/8	9/9	8/9	4/7	5/7	5/6	3/2
12	9/9	9/9	8/7	4/4	3/5	3/5	3/2
13	8/8	9/9	9/9	4/5	2/4	3/5	3/3
14	8/9	9/6	8/7	8/7	6/6	5/5	3/**4**
15	7/8	8/9	8/7	6/4	4/5	4/5	3/2
16	7/8	6/9	4/5	4/4	4/6	4/5	3/2
CIDP							
1	<u>**13/13**</u>	**17**/**13**	<u>**17**</u>/<u>**12**</u>	8/8	**11**/9	**10**/**11**	2/3
2	<u>**14**</u>/**12**	**13**/<u>16</u>	8/**10**	**12**/**11**	**13**/**11**	**15**/4	**4/4**
3	8/<u>**12**</u>	**12**/<u>**18**</u>	9/<u>**17**</u>	**28**/8	**35**/9	**19**/6	3/3
4	<u>**12**</u>/<u>**14**</u>	<u>**55/34**</u>	9/<u>**12**</u>	6/8	6/4	6/3	**4/4**
5	7/8	**13**/9	9/8	**10/10**	**9**/5	3/5	2/3
6	7/7	<u>**20**</u>/9	6/6	**10**/**11**	5/6	6/6	**4**/3

Cross sectional areas in mm² (right/left), **bold = enlarged**, <u>**underlined and bold = severe enlarged.**</u>

Axonal = axonal neuropathies, CIDP = chronic inflammatory demyelinating polyneuropathy, LSS = Lewis Sumner syndrome, Mfa = median nerve forearm, Mup = median nerve upper arm, Ps = plexus superior truncus, Pm= plexus median truncus, Pi = plexus inferior truncus, Su = sural nerve 14 cm above lateral malleolus, Uup = ulnar nerve upper arm 1/2 from elbow, WMSN = Wartenberg's migrant sensory neuritis
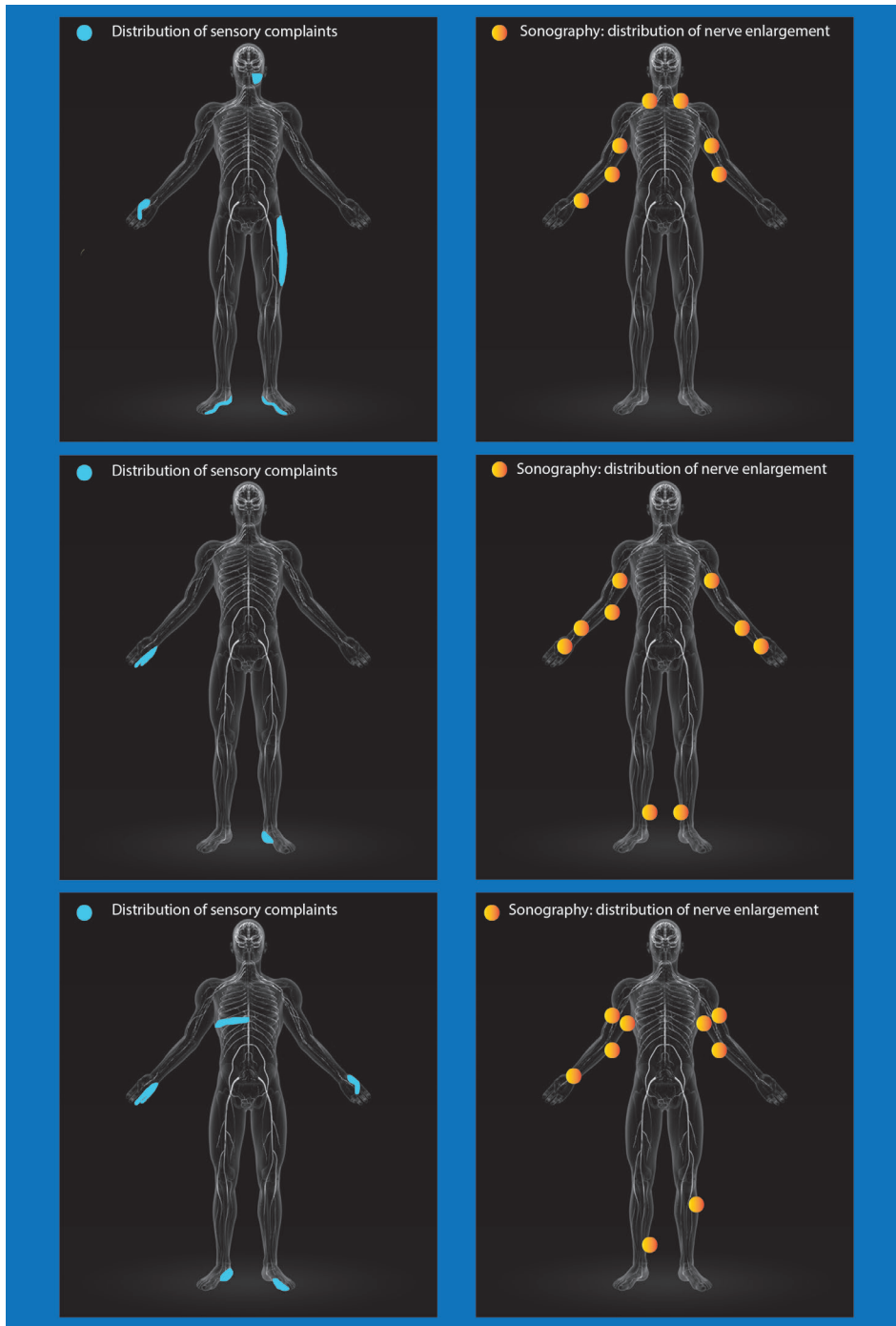
Figure 3.1 Sensory complaints versus sonographic enlargements of 3 patients with Wartenberg's migrant sensory neuritis

Correlation of sonography with clinical and electrodiagnostic findings

NCS revealed at least one absent or decreased sensory nerve action potentials (SNAPs) in 5 of 8 patients (63%) with WMSN and NCS abnormalities in 4 of 26 clinically affected nerves (15%). NCS showed no evidence of demyelination in all WMSN patients. We found sonographic nerve enlargement in 11 of 26 clinically affected nerves (42%) (**Supplemental Table 3.1**). Furthermore, HRUS showed nerve enlargement in 13 of 22 nerves (59%) with normal clinical findings and NCS tests.

DISCUSSION

As far as we are aware, this is the first study to describe HRUS findings in WMSN. We found multifocal nerve enlargement in all patients with WMSN, both at entrapment sites and proximal to these sites, the brachial plexus was involved in 3 of 8 patients. In comparison to sensory CIDP/LSS, sonographic nerve enlargement was milder, especially in proximal nerve segments. In contrast to controls with an axonal polyneuropathy nerve enlargement was found not only at, but also outside common sites of entrapment. This distinct pattern of mild, multifocal nerve enlargement in WMSN may, therefore, be of additional diagnostic value in distinguishing WMSN from other causes of pure sensory neuropathy.

Traditionally, WMSN has been evaluated in a clinical context and was regarded as a (multi)focal disease entity with selective involvement of sensory nerves and branches. In the present study, we examined the disease in a clinical context combined with HRUS and NCS. We observed a median of 7 clinically affected nerves per patient (range 4-9), a number comparable to the previously reported median of six affected nerves.[2] We found sonographic nerve enlargement in 11 of 26 clinically affected nerves (42%). This is in contrast to NCS which revealed abnormalities in only 4 of 26 clinically affected nerves (15%), suggesting that HRUS detects abnormalities more often than NCS, and that it may serve as an additional diagnostic tool for WMSN. Furthermore, we found sonographic enlargement in 13 of 22 nerves (59%) with normal clinical findings and NCS tests, showing that HRUS may be able to detect subclinical abnormalities and indicating a generalized or multifocal disease identity rather than a focal disease identity. The discrepancy between the nerve morphological alterations found with HRUS and NCS and clinical findings is a feature that is also observed in other types of peripheral nerve disease, and its pathophysiologic origin has yet to be clarified.[13]

The etiology of WMSN has not yet been elucidated, although an inflammatory cause has been suggested based on the combination of a specific clinical picture and evidence of perineuritis on nerve biopsy.[1,14] In our study we did not perform nerve biopsy to confirm an immune-mediated etiology, due to the limited extent of complaints in our patients and the fact that it is an invasive test. Still, HRUS has revealed different patterns of nerve involvement in vasculitic neuropathy and chronic inflammatory polyneuropathies. The pattern of proximal enlargement in upper extremity nerves observed in WMSN was similar to the one observed in patients with vasculitic neuropathy,

but with more frequent brachial plexus involvement, a feature found more often in chronic inflammatory polyneuropathies. The sonographic pattern in WMSN shares characteristics with both types of immune-mediated neuropathies, features which are not found in non-immune-mediated axonal polyneuropathies. This could support an immune-mediated etiology for WMSN. The combination of patchy sensory complaints and a distinct sonographic pattern of nerve enlargement also supports the notion that WMSN is a specific disease entity and that an underlying genetic cause cannot be totally excluded, since nerve enlargement is also a common characteristic of inherited neuropathies.[15-17]

WMSN and sensory CIDP/LSS are rare diseases; although we included a fair number of these patients, the sample size and the degree of clinical heterogeneity are clear limitations of this study. Nevertheless, WMSN could easily be distinguished from the disease controls. Another limitation was the relatively small number of cutaneous nerves investigated, due to the predefined sonographic protocol followed. However, the sural nerve, a pure sensory, cutaneous nerve, was significantly more enlarged in WMSN versus axonal neuropathies. In future research it might be of interest to extend the protocol to include more cutaneous nerves. Even though we aimed to match for age the difference between the non-inflammatory axonal group and WMSN is relatively large, this is due to the fact that the age of onset in WMSN is normally 35-50 years and in non-inflammatory axonal neuropathies >50 years.

We found multifocal nerve enlargement in WMSN. Compared to clinical examination and NCS, sonography was more sensitive in detecting nerve involvement and may, therefore, be of additional value in distinguishing WMSN from other sensory neuropathies. These findings suggest that HRUS may be of additional value in establishing the diagnosis of WMSN.

3

SUPPLEMENTAL MATERIAL

Supplemental Table 3.1 Correlation of clinical findings and sonography in arm nerves and sural nerve

WMSN	Median nerve R	Median nerve L	Ulnar nerve R	Ulnar nerve L	Sural nerve R	Sural nerve L
1	**_C-S_**	**_C-S_**	C	C		
2	C	**_C-S_**	C	C	**S**	**S**
3	**S**	**S**		**S**	C	C
4	**_C-S_**	**S**	C	**S**	**S**	
5	**_C-S_**	**_C-S_**	**_C-S_**	**_C-S_**	**S**	
6		**S**	**S**		C	C
7	**S**	**_C-S_**			C	C	**_C-S_**
8	C	**_C-S_**	C	C	**S**	**S**

C = clinically affected nerve without sonographic nerve enlargement, **S = sonographic enlargement in clinically unaffected nerve, _C–S = clinically affected nerve & sonographic enlargement._**

L = left, R = right, WMSN = Wartenberg's migrant sensory neuritis

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3

CHAPTER 4

Comparison of nerve ultrasound and electrodiagnostic studies in a cohort of 140 treatment-naive patients with chronic inflammatory neuropathies

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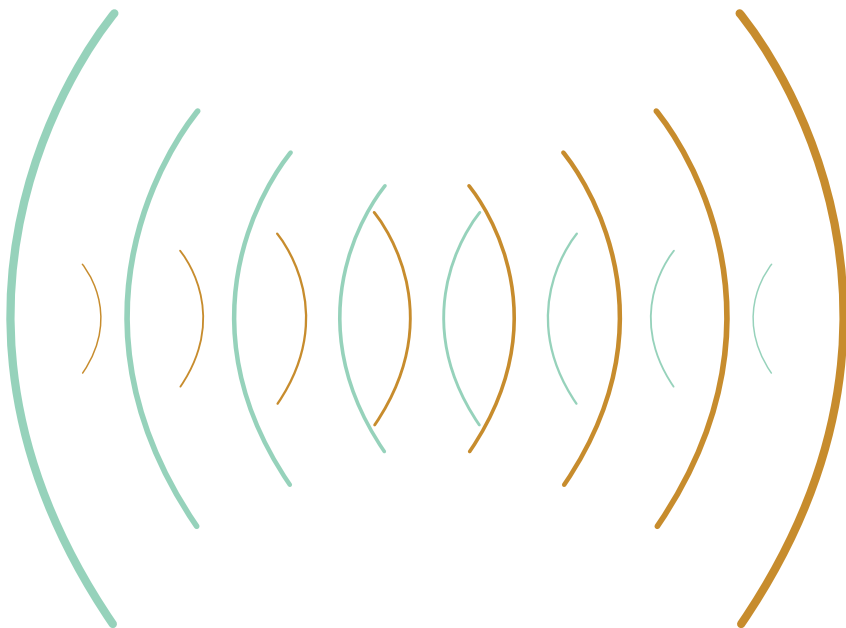
ABSTRACT

Objective

To study and compare clinical and electrodiagnostic characteristics and nerve morphology as detected by nerve ultrasound in incident treatment-naive patients with chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis Sumner syndrome (LSS) and multifocal motor neuropathy (MMN).

Methods

We enrolled 140 consecutive patients: 65 with a sensorimotor, 6 with pure sensory, 6 with sensory-ataxic and 4 with pure motor phenotypes of CIDP, 17 with LSS and 42 with MMN. In addition to detailed clinical examinations, all patients underwent standardized nerve conduction (NCS) and nerve ultrasound studies (US). We studied correlations of nerve conduction study parameters associated with axon loss or demyelination, nerve enlargement and clinical phenotypes.

Results

We found a high level of correspondence between distribution of electrodiagnostic features of demyelination and axon loss, and clinical phenotype. Although there were some differences in nerve sizes between LSS, MMN, CIDP ($p<0.001-0.05$) at several anatomical sites, and a trend to higher degree of nerve hypertrophy with sensory involvement, no particular sonographic pattern of enlargement aided in accurate distinction between these neuropathies. We found no relation between nerve size and distribution of axon loss or demyelination.

Conclusions

Nerve US does not allow reliable distinction between CIDP, LSS and MMN. Sonographic and electrodiagnostic abnormalities do not correlate and are likely to represent different dimensions of pathology in chronic inflammatory neuropathies.

INTRODUCTION

Chronic inflammatory neuropathies are rare disorders with unique clinical features, that respond to administration of steroids or immunoglobulins.[1-5] Chronic inflammatory demyelinating polyneuropathy (CIDP) is usually a stepwise or slowly progressive motor dominant neuropathy, but less typical presentations, such as pure sensory, pure motor, sensory-atactic and focal neuropathies as well as Lewis Sumner syndrome (LSS), have been identified.[6-10] Multifocal motor neuropathy (MMN) is an asymmetric pure motor neuropathy with onset in the forearm, hand or lower leg and slow progression of weakness.[11] The diagnostic criteria for CIDP and MMN primarily rely on clinical characteristics and results from nerve conduction studies.[12,13]

Neuro-imaging is emerging as an important adjunctive diagnostic tool in CIDP and MMN.[14-16] Several previous nerve ultrasound studies evaluated possible relations between nerve morphology and electrodiagnostic abnormalities.[14,17-22] Their interpretation was hampered by relatively small sample sizes, differences in nerve ultrasound and electrodiagnostic protocols, and substantial heterogeneity of relevant patient characteristics. Therefore, the aim of our study was to systematically document and compare clinical, sonographic and nerve conduction abnormalities using extensive standardized protocols in a large cohort of treatment-naive patients encompassing the full spectrum of CIDP, LSS and MMN presentations.

METHODS

Patients

We included consecutive incident patients, who visited our neuromuscular outpatient clinic between January 2013 and January 2017, at the University Medical Centre Utrecht (UMCU), with a diagnosis of chronic inflammatory neuropathy (definite, probable and possible).[12,13] All clinical presentations of CIDP, LSS and MMN were eligible for inclusion. Exclusion criteria were age <18 years, treatment, or a previous diagnosis of polyneuropathy. We enrolled 81 patients with CIDP, 16 with LSS and 43 with MMN.[12,13] All patients underwent routine ancillary investigations (**Supplemental Table 4.1**), including laboratory testing, standardised nerve conduction studies (NCS) and nerve ultrasound. Two authors (HSG, IJTH) assessed height, weight and muscle strength, using a previously described protocol.[16,23]

Furthermore, all initial clinical evaluations performed by treating physicians (WLvdP, LHvB, AFJEV) were used to reconstruct clinical presentation: distribution of weakness and/or sensory signs (upper and/or lower limb, and within the limbs distal and/or proximal), and stretch reflexes (generalized areflexia, reduced, normal or even brisk tendon reflexes). Using these clinical data, we stratified patients in the following CIDP phenotypes: sensorimotor (classic presentation, including motor dominant), pure sensory (exclusive sensory presentation, without weakness or significant ataxia on routine tests of walking and coordination), sensory-ataxia (predominance of ataxia combined with sensory involvement), and pure motor (sensory and coordination unaffected).[1,2,24-27] All studies were performed prior to treatment, and clinical improvement was

evaluated by treating physicians (WLvdP, LHvdB, AFJEV) based on relevant routine clinical assessments (including ≥1 year follow-up): increase >10% improvement in handgrip (CIDP, LSS and MMN), pinch or key-grip and myometry (LSS and MMN), and MRC sum-score ≥2 or standardized walk test (i.e. increase in walking distance on 6-minute walk test and/or reduction in time to cover fixed distance in sensory-ataxic CIDP).

Standard Protocol Approvals and Patient Consents

The local ethics committee of the UMC Utrecht reviewed and approved this study and its research protocol (14-328); we obtained written informed consent from all included participants.

Nerve conduction studies

We performed NCS after warming limbs in water at 37°C for 45 minutes [28], with a Nicolet VIKING IV EMG machine (CareFusion Japan) and standardized NCS protocol (**Supplemental Table 4.1**), as described previously.[16,29,30] We evaluated the distribution of demyelination and axon loss in long arm nerves (median and ulnar nerves, recordings from hand muscles) and leg nerves (fibular and tibial nerves, recordings from foot muscles; sural nerve) in all patients. In addition, in MMN patients we also evaluated intermediate length arm nerves (median and radial nerves, recordings from forearm muscles) and short arm nerves (musculocutaneus nerve, recording biceps). Hence, in order to improve electrodiagnostic yield, the NCS protocol was expanded in 9/16 patients with LSS to include intermediate and short arm nerves. We used normative values of our own lab[29,31], for distal CMAP and SNAP amplitudes per nerve, and defined axon loss based on more than 2SD below the lower limit of normal. All NCS were performed by two experienced clinical neurophysiologists (AFJEV, HF), blinded to the results of nerve ultrasound studies.

Nerve ultrasound studies

We performed nerve ultrasound studies of median, ulnar, fibular, tibial and sural nerves with a Philips iU22 and Epiq 7 (Philips Medical Instruments, 5-17 MHz respectively 5-18 MHz linear array transducers (**Supplemental Table 4.1**)). In addition, we also evaluated brachial plexus trunks (inter-scalene at the supraclavicular region). We used the ellipse tool to assess nerve size (cross-sectional area (CSA)) on transverse images.[32-35] We compared their nerve size with those previously obtained in disease controls.[16] One of us (HSG) performed all sonographic examinations and was blinded for the NCS results. We used previously described cut-off values for abnormal nerve size[23,36,37] and those that are specific for chronic inflammatory neuropathies (CSA median nerve: >10mm^2 at forearm and >13mm^2 at upper arm; >8mm^2 at any trunk of brachial plexus).[16]

Statistical analysis

Due to the ordinal nature or non-symmetrical distribution of variables, we used non-parametric tests to compare and evaluate associations between variables: Spearman's rho to test associations, Kruskal-Wallis and Mann-Whitney to compare continuous variables between groups. Chi-square test was used to evaluate associations and compare categorical variables between groups.

The multiple sonographic data points for the cross-sectional area (CSA) per anatomic site per individual were modelled using linear mixed models. CSA values were log-transformed because they were not normally distributed. The baseline model contained fixed effects for anatomic location (elbow, wrist or upper arm), nerve (median or ulnar), side (left or right), sex and disease type (CIDP, LSS or MMN). Per subject and nerve, a random intercept and random slope for anatomic location was modelled. A model with an additional random slope for side did not improve model fit ($p=0.65$). Subsequently we assessed the association between the CSA and electrodiagnostic variables (distal CMAP and SNAP amplitudes, distal motor latencies (DML), F-M interval, motor conduction velocity (MCV) and conduction block (CB) per nerve segment, presence of any and number of demyelinating features). The likelihood ratio test was used to determine its significance. All mixed models were fitted using the *lmer* function from the R lme4 package (version 1.1–12).[38] Findings with a p-value of <0.05 after adjustment for multiple testing with the Benjamini-Hochberg method[39], where appropriate, were considered significant.

RESULTS

Clinical characteristics

Patient characteristics are summarized in **Table 4.1**. We found a symmetric presentation of motor/sensory deficits in the majority of CIDP patients, with only mild differences between limbs (e.g. ≤ 2 points difference on MRC scale).[1,4] Striking asymmetry at onset was rare in our CIDP group, and exclusively seen in 3/65 (5%) patients with sensorimotor presentation. MMN initially presented with weakness in hand in 27/42 (64%) and lower leg (predominantly foot drop) in 13/42 (31%), progressing to upper and lower limb in another 12/42 (29%), and an upper arm onset in 2/42 (5%).[3]

Pain in the hand, forearm or leg was a common feature (10/17 (59%), mostly limited to a hand/forearm or leg) in LSS patients, but not in CIDP or MMN.[3,10,40] Concomitant disease was reported in 19/81 (23%) of patients with CIDP and 5/16 (31%) with LSS. We found concurrent malignancy in 5/81 (6%) patients with CIDP (seminoma, lymphoma, lung, and colon/rectal cancer). IgA or IgG kappa monoclonal gammopathy of unknown significance was found in 3/81 (4%) patients with CIDP and 1/16 (6%) with LSS. Diabetes mellitus was reported in 6/81 (7%) patients with CIDP and 4/16 (25%) with LSS. Other auto-immune disorders were only found in patients with CIDP; 2/81 (2%) with sarcoidosis, 2/81 (2%) with nephropathy (IgA and membranous), and 1/81 (1%) with myasthenia gravis.

Table 4.1 Summary patient characteristics

	CIDP					LSS	MMN	P-value
	Sensorimotor (n = 65)	Pure sensory (n =6)	Sensory-ataxic (n= 6)	Pure motor (n = 4)	Total (n = 81)	(n = 17)	(n = 42)	
Age (years)	62 (52-72)	50 (37-59)	58 (53-74)	61 (53-71)	61 (52-71)	58 (48-65)	51 (44-58)	0.002*
Gender (Male)	40 (62%)	5 (83%)	6 (100%)	2 (50%)	53 (65%)	14 (82%)	34 (81%)	0.23
Height (cm)	177 (170-185)	174 (160-184)	183 (178-186)	177 (170-185)	177 (170-185)	178 (175-187)	180 (175-184)	0.40
Weight (kg)	80 (70-86)	89 (71-97)	97 (89-108)	77 (66-82)	81 (71-90)	80 (75-89)	84 (75-95)	0.30
BMI	25 (22-28)	28 (24-31)	29 (27-32)	26 (23-29)	25 (23-28)	25 (24-28)	26 (24-29)	0.49
Disease duration (months)	12 (5-36)	40 (10-174)	19 (14-39)	14 (5-36)	14 (5-36)	36 (24-142)	24 (12-59)	0.001*
Clinical presentation								
Distal only	30 (46%)	6 (100%)	6 (100%)	-	42 (52%)	8 (48%)	31 (74%)	
Distal and proximal	35 (54%)	-	-	4 (100%)	39 (48%)	8(52%)	11 (26%)	
Upper limb only	-	-	-	-	-	6 (35%)	25 (60%)	
Lower limb only	11 (17%)	-	-	-	11 (14%)	2 (12%)	1 (2%)	
Upper and lower limb	54 (83%)	6 (100%)	6 (100%)	4 (100%)	70 (86%)	9 (53%)	16 (38%)	
Cranial nerve	4 (6%)	-	-	-	4 (5%)	3 (18%)	-	
Tendon reflexes decreased	13 (20%)	-	-	2 (50%)	15 (19%)	13 (76%)	24 (57%)	
Generalized areflexia	49 (75%)	4 (66%)	4 (66%)	2 (50%)	59 (73%)	-	4 (10%)	
Normal tendon reflexes	3 (5%)	1 (17%)	2 (34%)	-	6 (7%)	4 (24%)	6 (14%)	
Brisk tendon reflexes	-	1 (17%)	-	-	1 (1%)	-	8 (19%)	
MRC sum-score (0-120)	112 (101-117)	120	120	112 (102-118)	112 (102-118)	112 (110-117)	114 (112-116)	0.68
CSF protein content (g/L)	0.74 (0.58-1.26)	0.49 (0.49-1.21)	0.54 (0.39-0.75)	0.68 (0.51-1.06)	0.71 (0.54-1.12)	0.48 (0.34-0.86)	0.49 (0.35-0.62)	0.006*
Anti-GM1 antibodies	-	-	-	2 (50%)	-	-	15 (36%)	

Treatment (at follow-up)							
No	5 (8%)	3 (50%)	-	-	8 (10%)	2 (12%)	2 (5%)
IVIg	39 (60%)	3 (50%)	6 (100%)	4 (100%)	52 (64%)	14 (82%)	40 (95%)
Dexa/prednisone	13 (20%)	-	-	-	13 (16%)	-	-
IVIg + Dexa/prednisone	8 (12%)	-	-	-	8 (10%)	1 (6%)	-

All values are in median (IQR) or in number of patients (%).

Anti-GM1 = anti-GM1 antibodies, BMI = body mass index, CIDP = chronic inflammatory demyelinating neuropathy; categorized into clinical phenotypes (sensorimotor (classic presentation), pure sensor and pure motor, sensory-ataxia), Cranial nerve = cranial nerve involvement, Dexa = dexamethasone, IVIg = intravenous immunoglobulin, MRC = medical research council, CSF = cerebrospinal fluid, LSS = Lewis Sumner syndrome (also known as MADSAM or MIDN), MMN = multifocal motor neuropathy, *significant differences

CSF protein content was higher in older patients (p=0.006). MRC-sum-score was inversely related with disease duration (p=0.007). Although some patients remained stable without therapeutic intervention, most required treatment and improved subsequently (**Table 4.1**).

Nerve conduction studies

Results of nerve conduction studies are summarized in **Table 4.2** (**Supplemental Table 4.2**). We found electrodiagnostic features of demyelination predominantly in long arm nerves, whereas long leg nerves showed more axonal degeneration.[29,30,40,41] We observed considerable differences in electrodiagnostic abnormalities between the clinical phenotypes.

In CIDP we found more slowing of motor conduction (DML, MCV, temporal dispersion, F-M latency) than in LSS and MMN (p<0.001)[10,29,30,40] An exception was the pure motor phenotype of CIDP in which less slowing and more conduction block was found.[2,26,27] The symmetric pure motor type showed more features of distal and proximal demyelination (DML and F-wave abnormalities). Preservation of sensory conduction combined with demyelinating features in motor axons, comparable with MMN, was exclusively seen in pure motor CIDP (**Figure 4.1**).

Loss of sensory and motor axons, and features of demyelination were less frequent and more focal in LSS than in CIDP (p<0.001-0.05).[10,40] There was slight loss of sensory axons as reflected by reduced SNAP amplitudes in some of the MMN patients, but this did not affect the sensory conduction in segments over affected motor axons.

We found an association between lower MRC sum-score of hand and foot muscles with corresponding decrease of distal CMAP values of the fibular, median and ulnar nerves (p<0.001, respectively p=0.002 and p=0.003), and number of demyelinating features in ulnar nerve (p=0.006) in CIDP, but not in LSS. In MMN only weakness in median nerve innervated muscles showed correlation with lower distal CMAP values (p=0.01). We found no association between height, weight, BMI, disease duration and any of the electrodiagnostic parameters.

Nerve ultrasound studies

Sonographic findings are summarized in **Figure 4.2** (**Supplemental Table 4.3**). We found multifocal nerve enlargement in all patients[23], except for two patients with an atypical presentation of MMN (1 with upper arm weakness, and 1 with lower limb weakness compatible with sciatic nerve) who had normal nerve size in large arm nerves and the brachial plexus. There was a trend towards more frequent enlargement of brachial plexus trunks in CIDP than in LSS and MMN (p=0.05-0.14). Furthermore, pure sensory CIDP showed a trend for larger nerve size than the other CIDP phenotypes (sensorimotor, pure motor, sensory-ataxia) particularly at the brachial plexus (p=0.002-0.18).

Table 4.2 Summary of the distribution of axon loss and demyelination on nerve conduction studies

NCS abnormalities	CIDP					LSS	MMN
	Sensorimotor (n = 65)	Pure sensory (n = 6)	Sensory-ataxic (n = 6)	Pure motor (n = 4)	Total (n = 81)	(n = 17)	(n = 42)
Long axons arm nerves							
Demyelination							
MCV ↓	102/220 (46%)	7/20 (35%)	7/22 (32%)	4/16 (25%)	120/278 (43%)	21/61 (34%)	14/154 (9%)
DML ↑	91/220 (41%)	6/20 (30%)	7/22 (32%)	9/16 (56%)	113/278 (41%)	4/61 (7%)	6/154 (5%)
CMAP duration ↑	53/220 (24%)	3/20 (15%)	1/22 (5%)	4/16 (25%)	61/278 (22%)	1/61 (2%)	9/154 (6%)
F-M interval ↑	125/220 (57%)	3/20 (15%)	5/22 (23%)	6/16 (38%)	139/278 (50%)	27/61 (44%)	14/154 (1%)
Absent F-waves	34/220 (15%)	-	-	5/16 (31%)	39/278 (14%)	7/61 (11%)	13/154 (9%)
TD ↑	29/220 (13%)	2/20 (10%)	1/22 (5%)	2/16 (13%)	34/278 (12%)	12/61 (20%)	26/154 (17%)
CB	82/220 (37%)	5/20 (25%)	6/22 (27%)	8/16 (50%)	101/278 (36%)	14/61 (23%)	44/154 (28%)
Axon loss							
Motor	49/220 (22%)	3/20 (15%)	1/22 (5%)	5/16 (31%)	58/278 (21%)	11/61 (18%)	32/154 (21%)
Sensory	129/220 (59%)	19/20 (95%)	14/22 (70%)	-	162/278 (58%)	31/61 (51%)	9/154 (6%)
Long axons leg nerves							
Demyelination							
MCV ↓	16/72 (22%)	-	2/10 (20%)	-	18/110 (16%)	-	1/114 (1%)
DML ↑	8/72 (11%)	1/18 (6%)	-	-	9/110 (8%)	-	-
CMAP duration ↑	16/72 (22%)	-	-	1/10 (10%)	17/110 (15%)	-	-
F-M interval ↑	35/72 (49%)	6/18 (33%)	2/10 (20%)	3/10 (30%)	46/110 (42%)	8/37 (22%)	4/114 (4%)
Absent F-waves	23/72 (32%)	-	2/10 (20%)	3/10 (30%)	28/110 (25%)	3/37 (8%)	7/114 (6%)
TD ↑	4/72 (6%)	-	-	-	3/110 (3%)	-	4/114 (4%)
CB	-	-	-	-	-	-	1/114 (1%)
Axon loss							
Motor	136/179 (76%)	4/20 (20%)	10/16 (63%)	8/11 (73%)	158/226 (70%)	12/37 (32%)	38/114 (33%)
Sensory	69/106 (65%)	3/10 (30%)	8/9 (89%)	-	80/132 (61%)	4/23 (17%)	2/40 (5%)

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Table 4.2 continued

Intermediate axons arm nerves	
Demyelination	
MCV ↓	9/164 (5%)
DML ↑	3/83 (4%)
TD ↑	20/164 (12%)
CB	23/164 (14%)
Axon loss	
Motor	13/168 (8%)
Short axons arm nerves	
Demyelination	
MCV ↓	3/83 (4%)
TD ↑	2/83 (2%)
CB	11/83 (13%)
Axon loss	
Motor	5/83 (6%)

Data are shown as number of nerves (%) with abnormality. In the 9/16 patients with LSS that underwent the expanded the NCS protocol, we found features of demyelination or axon loss in intermediate arm nerves in 3/9 (33%, only 1 patient also demyelination in short arm nerve) respectively 1/9 (11%).

Long axons arm nerves (median and ulnar nerves, recordings from hand muscles), leg nerves (fibular and tibial nerves, recordings from foot muscles; sural nerve), intermediate length arm nerves (median and radial nerves, recordings from forearm muscles) and short axons arm nerves (musculocutaneus nerve, recording biceps).

CB = conduction block, CIDP = chronic inflammatory demyelinating neuropathy; categorized into clinical phenotypes (sensorimotor (classic presentation), pure sensor and pure motor, sensory-ataxia), CMAP = compound muscle action potential, DML = distal motor latency, LSS = Lewis Sumner syndrome (also known as MADSAM or MIDN), MCV = motor conduction velocity, MMN = multifocal motor neuropathy, TD = temporal dispersion
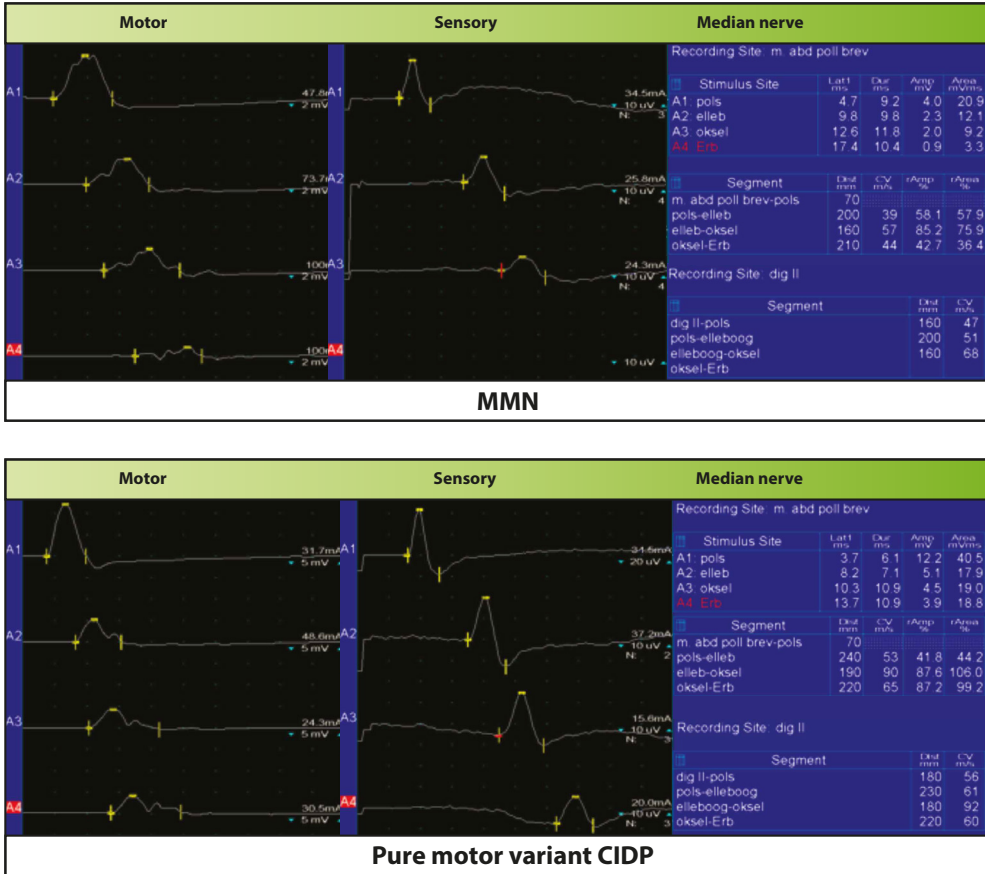
Figure 4.1 Examples of electrodiagnostic findings in MMN and pure motor CIDP

Electrodiagnostic proof of demyelination of motor axons with preservation of sensory axons in a patient with multifocal motor neuropathy (MMN (upper panels)) and similar findings in a patient with pure motor chronic inflammatory demyelinating neuropathy (CIDP (lower panels)).
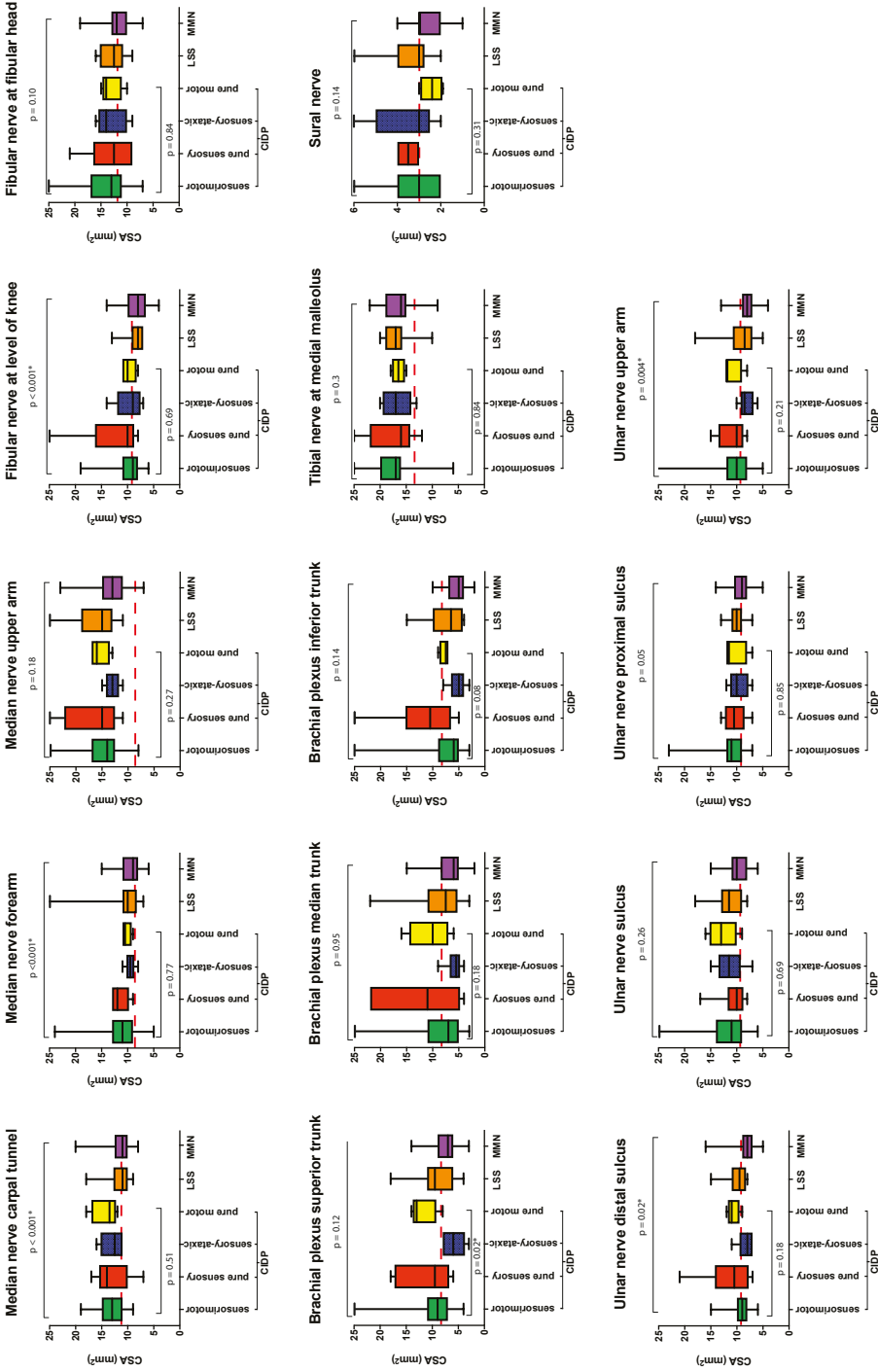
Figure 4.2 Summary sonographic nerve size in CIDP, LSS and MMN

Chronic inflammatory demyelinating neuropathy (CIDP (n=81); sensorimotor (n=65), pure sensory (n=6), sensory ataxic (n=6) and pure motor presentations (n=4)); Lewis Sumner syndrome (LSS (n=16)); multifocal motor neuropathy (MMN (n=42)).

*significant differences (after Benjamini-Hochberg correction between CIDP, LSS and MMN and between CIDP subgroups, using Kruskal-Wallis test)

We found no association between nerve size and baseline characteristic (age, gender, height, weight, BMI, disease duration, MRC sum-score, CSF protein content, presence of GM1 antibodies).

Combined analysis nerve conduction and nerve ultrasound studies

The results of the combined sonographic and electrodiagnostic analysis are summarized in **Table 4.3**. Nerve enlargement was frequently associated with clinical abnormalities, electrodiagnostic abnormalities, or both (**Figure 4.3)**. However, nerve enlargement was randomly distributed among nerves and segments with and without demyelination, or axon loss. We found no relation between nerve sizes and motor conduction velocities (adjusted p=0.065), presence of conduction block (adjusted p>0.99), temporal dispersion (adjusted p>0.99) or F-waves (adjusted p=0.56). Although the presence of demyelinating features was associated with a higher mean nerve size (mean difference log CSA 0.047, 95%-CI 0.012 – 0.081, adjusted p=0.040), there was still considerable overlap. The crude mean CSA of patients with and without demyelinating features was 11.4 mm^2 (95%-CI 11.1-11.8) respectively 10.1 mm^2 (95%-CI 9.7-10.5). The association between demyelinating features and CSA was identical for CIDP, LSS and MMN (interaction p=0.60). In addition, nerve ultrasound showed enlargement in a substantial number of nerves that showed no signs of clinical or electrodiagnostic involvement. Finally, in 18/35 (51%) forearm and 27/35 (77%) upper arm segments of median nerves without electrodiagnostic evidence of demyelination fulfilled previously described sonographic criteria compatible with chronic inflammatory neuropathy.[16]

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Table **4.3** Summary results of combined nerve ultrasound and nerve conduction studies

Number of nerves with	Sonographic involvement							
	CIDP					LSS	MMN	Total
	Sensorimotor (n = 65)	Pure sensory (n =6)	Sensory-ataxic (n= 6)	Pure motor (n = 4)	Total (n = 81)	(n = 17)	(n = 42)	
Clinical								
involvement	269/392 (69%)	34/45 (76%)	31/43 (72%)	15/16 (94%)	349/496 (70%)	52/69 (75%)	78/92 (85%)	479/657 (73%)
normal	77/91 (85%)	2/2 (100%)	-	8/12 (67%)	87/105 (83%)	35/58 (60%)	146/212 (69%)	268/309 (87%)
NCS								
Axon loss present	189/264 (72%)	19/21 (90%)	15/24 (63%)	10/12 (83%)	251/321 (74%)	36/42 (86%)	68/83 (82%)	355/446 (75%)
No axon loss	133/165 (81%)	13/19 (68%)	9/13 (69%)	13/14 (93%)	168/211 (80%)	45/65 (69%)	134/211 (64%)	347/487 (71%)
Demyelination	169/196 (86%)	13/16 (81%)	11/16 (69%)	14/17 (82%)	207/245 (84%)	33/39 (85%)	79/98 (81%)	319/382 (84%)
No demyelination	50/57 (88%)	13/14 (93%)	11/14 (79%)	5/5 (100%)	79/90 (88%)	32/39 (82%)	87/110 (79%)	198/239 (82%)
Normal	84/114 (73%)	12/14 (86%)	9/10 (90%)	4/4 (100%)	109/142 (77%)	40/116 (34%)	102/153 (67%)	251/411 (61%)

Data are shown as number (%) of affected nerves in the enrolled patients with chronic inflammatory neuropathy, comparing sonographic (enlargement) to clinical signs of involvement (sensory and/or motor) and electrodiagnostic abnormalities (evidence of loss of sensory/motor axons, demyelination).

CIDP = chronic inflammatory demyelinating neuropathy; categorized into clinical phenotypes (sensorimotor (classic presentation), pure sensor and pure motor, sensory-ataxia), LSS = Lewis Sumner syndrome (also known as MADSAM or MIDN), MMN = multifocal motor neuropathy
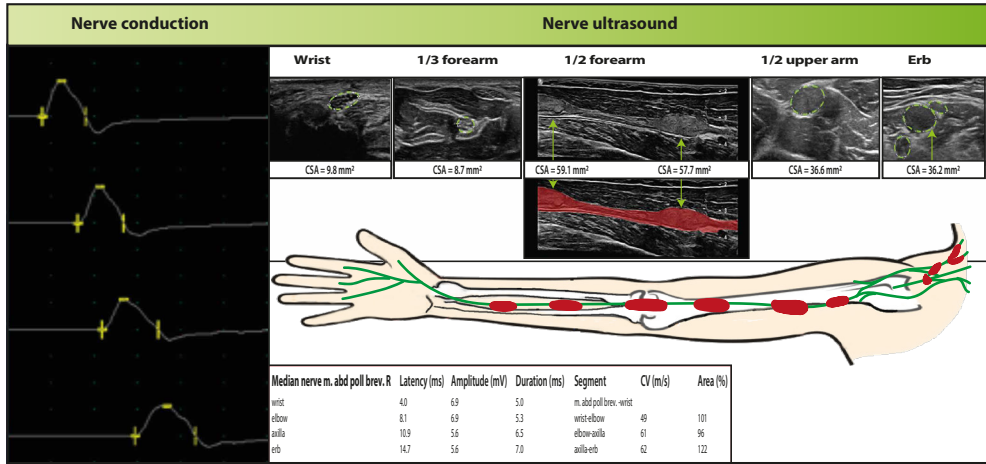
Figure 4.3 Example of electrodiagnostic and corresponding nerve ultrasound findings

Nerve ultrasound showed marked focal enlargements of right median nerve, extending from mid-forearm to brachial plexus. In contrast, nerve conduction was unremarkable even over segments with these pronounced morphological changes.

DISCUSSION

In this study, we systematically investigated electrodiagnostic, clinical and sonographic characteristics in a large cohort of incident and treatment-naive cases that encompass the full spectrum of chronic inflammatory neuropathies. We found three distinct electrodiagnostic patterns associated with different CIDP phenotypes: (1) lower frequency of demyelinating features and more pronounced loss of sensory axons in the pure sensory and sensory ataxic phenotypes, (2) generalized pattern of slowing in the more classic sensorimotor CIDP phenotype, and (3) sparing of sensory axons with predominance of conduction block rather than slowing in pure motor phenotypes. In contrast, electrodiagnostic features of demyelination and axon loss were more focal in LSS and MMN. Our study showed a trend towards more extensive and higher degree of nerve enlargement when there was sensory involvement. Nevertheless, our study revealed no particular sonographic pattern that helped to reliably distinguish between CIDP variants, LSS and MMN. Furthermore, we also found that nerve enlargement was distributed randomly among nerves and segments with and without demyelination, or axon loss.

There are no other studies that have systematically compared clinical features, electrodiagnostic and sonographic characteristics in a large cohort of incident and treatment-naive chronic inflammatory neuropathies. Our study allowed detailed analysis and comparison of functional and morphological abnormalities across the full spectrum of CIDP, LSS and MMN. We found a high level of correspondence between distribution of electrodiagnostic features of demyelination

and axon loss, and clinical phenotype. The finding of a lower occurrence of demyelinating features in sensory variants of CIDP, and more focal in LSS and MMN in our study are in line with previous studies and case-series.[2,3,10,25,30,42,43] Similarly, our study showed that the loss of sensory and/or motor axons is exclusively focal and more prominent distally in upper than lower limbs in LSS (sensory and motor) and MMN (only motor, occasionally also a focal discrete reduction of sensory amplitude but otherwise preserved sensory conduction).[10, 30] In contrast, relative generalized distal axonal loss was a common electrodiagnostic profile in leg nerves of our CIDP patients.[41] Taken together, our results indicate that longer axons are more prone to axonal dysfunction and subsequent Wallerian degeneration.[44-46] Interestingly, all of our four patients with a pure motor presentation of "CIDP" had less slowing of motor conduction and preservation of sensory conduction, a pattern that is also characteristic of MMN.[30] The presence of anti-GM1 antibodies in 2/4 (50%) cases of our 'pure motor CIDP', response to IVIg and previously documented deterioration on steroids all favour that this rather may belong to the MMN spectrum.[6,11,47-49]

The present study and other studies showed the most prominent increase in nerve size at proximal median nerve segments and brachial plexus.[50-54] Hence, we also found a trend towards a higher degree of nerve enlargement in the phenotypes with prominent sensory involvement. A recent quantitative nerve anatomy study showed that sensory axons dominate the axonal population in human arm nerves (>90%), with a gradient from nerve roots to terminal arm nerves.[55] In addition, the total number of (sensory) axons in human median nerve appears to be higher than the ulnar nerve.[55] Consequently, the density of potential axonal targets for random disease processes such as inflammation are highest in proximal segments of the median nerve and brachial plexus, thereby explaining our results. In line with this histological context, early descriptions of nerve pathology in CIDP and allergic experimental neuritis already reported that the processes of segmental demyelination and inflammation primarily affect nerve roots and proximal segments of terminal nerves.[56,57]

An important objective of our study was to analyze the association of electrodiagnostic and sonographic abnormalities. Previous nerve ultrasound studies that have reported findings regarding the relation of nerve size with nerve conduction parameters, showed no or only poor associations (correlation coefficients <0.6).[17,21,22,58,59] Interpretation of these studies is complicated by the differences in electrodiagnostic and sonographic protocols and the general lack of detailed information on temperature standardization and distances in electrodiagnostic protocols. To eliminate such unwanted methodological variation, we used previously described standardized electrodiagnostic and sonographic protocols.[16,28,29,60] We could not corroborate the previous findings of associations between increases in nerve size and motor conduction slowing or with focal conduction block.[22,58] This difference with some previous studies may be explained by several factors, such as larger sample size and inclusion of exclusively incident and treatment-naive patients in our study, and comparison of multiple nerve segments. Finally, discrepancy between function and morphology is not uncommon in neurologic disorders (e.g. silent strokes, MS lesions).

Strengths of this study are the use of standardized protocols and the inclusion of clinically well-characterized incident participants. Sample size may be a statistical weakness, but it should be noted that we included a large number of patients with these rare disorders.

In conclusion, nerve ultrasound and nerve conduction studies are complementary diagnostic tools for chronic inflammatory neuropathies. Although nerve ultrasound has high sensitivity for identification, our study does not support its use to further distinguish between CIDP, LSS and MMN. In contrast, electrodiagnostic profiling may be useful in their distinction. Hence, nerve ultrasound and NCS may detect different dimensions of the same pathological processes (i.e. edema, inflammation, dysmyelination versus nodal and axonal dysfunction).

4

SUPPLEMENTAL MATERIAL

Supplemental Table 4.1 Summary ancillary investigations

Ancillary investigations	
Neurological examination	
Standardized muscle strength testing (MRC scale)	Finger flexors, extensors, interossei, wrist extensors and flexors, biceps and triceps, deltoid muscles, iliopsoas, hamstrings and quadriceps, foot extensor, abductor pollicis brevis and opponens pollicis, abductor digiti minimi and first dorsal interosseus, antior tibial and peroneus longus muscles
Sensory testing	Gnostic (touch and vibration) hands and feet
Tendon reflexes	Upper and lower extremities
Lab screening	
Routine	Complete blood count and chemistry panel including glucose, C-reactive protein, serum protein immunofixation electrophoresis, vitamin B12, folic acid
Optional	Anti-GM1 antibodies, CSF cell count and protein content
Nerve conduction studies	
Motor	CMAP, DML, MCV, F-waves of median, ulnar, tibial and fibular nerve (bilateral) Optional in case of MMN: CMAP, DML and MCV of radial and musculocutaneous nerve (bilateral)
Sensory	SNAP, SNCV of ulnar, median, radial and sural nerve (bilateral).\
Sonographic protocol	
Median nerve	Screening for enlargement from axilla to wrist
Carpal tunnel	CSA
Forearm	CSA (1/3 of line between wrist and medial epicondyle)
Upper arm	CSA (1/2 of a line between medial epicondyle and axilla)
Ulnar nerve	Screening for enlargement from axilla to wrist
Distal sulcus	CSA
Sulcus	CSA
Proximal sulcus	CSA
Upper arm	CSA (1.2 of a line between medial epicondyle and axilla)
Brachial Plexus	
Superior truncus	CSA (supraclavicular between scalene muscles)
Median truncus	CSA (supraclavicular between scalene muscles)
Inferior truncus	CSA (supraclavicular between scalene muscles)
Fibular nerve	
Level of the knee	CSA (popliteal fossa)
Fibular head	CSA
Posterior tibial nerve	CSA (medial malleolus)
Sural nerve	CSA (14 cm above lateral malleolus)

Summary of ancillary investigations, including standardized clinical evaluation, laboratory testing, nerve conduction studies (NCS) and nerve ultrasound protocol.

A. For NCS, we further standardised assessments of distal CMAP, DML and CMAP duration using a 7 cm distance between recording and stimulation sites, in addition we used a 12 cm distance for sensory conduction of sural and radial nerves. Demyelination was defined as published previously: in the presence of a distal CMAP > 1 mV, a reduction in MCV by more than 2SD below the lower limit of normal, prolongation of DML, increased CMAP duration, temporal dispersion and F-wave latency 2SD above the upper limit of normal and presence of conduction block, were considered consistent with demyelination.[29,61] Criteria deployed to define conduction block were a CMAP area reduction of >30-50% (possible CB) or >50% (definite CB), in the presence of a distal CMAP > 1 mV.[61]

B. The nerve ultrasound protocol ascertained nerve size on transverse images with the ellipse tool inside the hyperechoic rim of nerves.[16]

CMAP = compound muscle action potential, CSA = cross-sectional area (mm^2), CSF = cerebrospinal fluid, DML = distal motor latency, MCV = motor conduction velocity, MRC scale = Medical Research Council scale, SNAP = sensory nerve action potential, SNCV = sensory nerve conduction velocity

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Supplemental Table 4.2 Summary nerve conduction studies

	CIDP					LSS	MMN	P-value
	Sensorimotor (n = 65)	Pure sensory (n =6)	Sensory-ataxic (n= 6)	Pure motor (n = 4)	Total (n = 81)	(n = 17)	(n = 42)	
Median nerve (APB)								
Distal CMAP (mV)	6.0 (3.5-9.0)	8.8 (4.4-10.4)	6.0 (5.5-7.0)	4.0 (3.6-5.8)	6.0 (3.7-8.8)	5.8 (3.6-11.7)	5.9 (2.0-9.7)	0.61
CMAP duration (ms)	7.0 (5.9-8.6)	6.8 (6.5-7.4)	6.4 (5.8-6.7)	7.0 (6.1-8.8)	6.8 (6.0-8.3)	6.1 (5.2-7.0)	6.1 (5.3-7.0)	0.03*
DML (ms)	5.1 (4.1-7.4)	4.2 (3.9-6.5)	5.0 (4.4-5.9)	5.2 (4.9-5.7)	5.0 (4.2-6.7)	4.1 (3.6-4.6)	4.0 (3.7-4.8)	< 0.001*
MCV forearm (m/s)	42 (33-50)	46 (41-50)	47 (41-51)	49 (43-52)	44 (34-50)	49 (46-57)	54 (50-56)	< 0.001*
MCV upper arm (m/s)	50 (41-58)	50 (44-59)	49 (43-56)	51 (46-65)	50 (42-58)	52 (43-58)	60 (55-67)	0.51
MCV shoulder (m/s)	57 (46-65)	53 (45-59)	58 (47-66)	58 (47-62)	57 (46-64)	58 (49-73)	63 (56-70)	0.10
F-M interval (ms)	32 (29-36)	31 (29-38)	30 (27-39)	29 (26-31)	32 (28-36)	31 (26-33)	26 (24-28)	0.005
Conduction block	45	3	4	4	56	5	20	
SNAP	4 (0-8)	1 (0-7)	4 (2-6)	16 (12-18)	4 (0-9.0)	10 (2-17)	18 (12-27)	< 0.001*
Ulnar nerve (ADM)								
Distal CMAP (mV)	5.5 (3.7-8.0)	7.4 (5.4-9.7)	6.5 (4.1-7.3)	4.5 (1.8-4.8)	5.7 (3.7-7.9)	7.1 (4.3-9.7)	6.6 (4.6-9.5)	0.25
CMAP duration (ms)	7.8 (6.5-9.5)	7.0 (6.2-9.1)	6.7 (5.7-7.5)	7.4 (6.0-7.4)	7.5 (6.4-9.3)	6.5 (5.6-7.0)	6.4 (5.6-7.3)	< 0.001*
DML (ms)	3.8 (3.1-5.1)	3.2 (3.0-5.7)	3.3 (2.9-3.6)	4.8 (4.0-5.0)	3.7 (3.1-5.1)	3.2 (3.0-3.6)	3.2 (2.9-3.6)	< 0.001*
MCV forearm (m/s)	43 (34-52)	52 (36-59)	49 (34-56)	41 (38-47)	43 (34-52)	51 (39-58)	57 (51-63)	< 0.001*
MCV elbow (m/s)	43 (33-52)	39 (29-61)	45 (27-64)	48 (35-57)	43 (32-53)	51 (42-63)	57 (48-64)	< 0.001*
MCV upper arm (m/s)	50 (40-58)	60 (30-70)	65 (48-67)	52 (44-59)	50 (41-62)	55 (50-65)	61 (55-70)	0.14
MCV shoulder (m/s)	55 (44-66)	54 (48-64)	61 (44-71)	51 (41-59)	55 (44-66)	56 (50-64)	62 (53-75)	0.06
F-M interval (ms)	34 (29-41)	30 (28-36)	31 (27-46)	50 (37-50)	33 (29-41)	32 (28-37)	27 (25-32)	0.001*
Conduction block	54	2	2	7	65	6	15	
SNAP	4 (0-9)	3 (0-4)	5 (2-6)	21 (15-25)	4 (0-9)	8 (15)	18 (12-28)	< 0.001*

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Tibial nerve (AH)								
Distal CMAP (mV)	0.9 (0-3.2)	3.9 (2.9-7.0)	1.0 (0-4.9)	2.3 (1.6-3.8)	1.3 (0-3.9)	6.2 (3.7-8.1)	6.1 (2.5-12.9)	< 0.001*
CMAP duration (ms)	6.7 (5.0-9.1)	6.4 (5.2-8.3)	6.5 (5.7-10.9)	5.2 (4.9-6.6)	6.4 (5.1-8.8)	5.6 (5.1-6.3)	5.5 (4.8-6.1)	0.002*
DML (ms)	5.7 (4.6-7.5)	4.7 (4.4-7.6)	4.3 (4.1-7.6)	5.2 (5.0-6.0)	5.4 (4.6-7.2)	4.5 (3.6-4.8)	4.4 (4.0-4.9)	0.01*
MCV lower leg (m/s)	39 (30-44)	40 (33-50)	32 (23-42)	37 (22-37)	39 (30-44)	40 (36-44)	44 (41-48)	0.10
F-M interval (ms)	62 (53-69)	60 (53-71)	56 (52-64)	49 (46-58)	60 (52-69)	54 (50-65)	53 (47-57)	0.36
Fibular nerve (EDB)								
Distal CMAP (mV)	0.7 (0-1.7)	5.1 (3.2-6.3)	0.7 (0-2.7)	1.9 (0.5-3.2)	0.7 (0-2.6)	4.4 (1.5-6.9)	3.6 (1.8-5.7)	< 0.001*
CMAP duration (ms)	6.5 (5.4-8.5)	5.8 (5.3-6.7)	7.1 (6.3-7.7)	5.8 (4.89-9.0)	6.2 (5.4-8.0)	5.4 (4.7-5.9)	5.5 (4.8-6.3)	0.03*
DML (ms)	5.5 (4.8-6.9)	4.9 (4.3-6.4)	4.6 (3.7-7.5)	5.1 (4.7-5.4)	5.3 (4.6-6.7)	4.5 (4.2-5.1)	4.5 (4.2-5.0)	< 0.001*
MCV lower leg (m/s)	35 (29-41)	39 (33-43)	44 (33-48)	40 (33-44)	36 (30-42)	39 (36-45)	46 (42-56)	< 0.001*
MCV fibular head (m/s)	41 (30-53)	43 (40-47)	44 (38-47)	34 (25-49)	42 (32-50)	42 (37-49)	51 (48-57)	0.25
F-M interval (ms)	65 (55-70)	55 (49-72)	52	49 (48-49)	56 (49-69)	52 (47-55)	51 (48-57)	0.15
Sural nerve								
SNAP	0 (0-4)	5 (2-8)	0	9 (3-10)	0 (0-4)	9 (4-12)	9 (5-15)	< 0.001*
Median nerve (FCR)								
Distal CMAP (mV)							8.3 (5.9-10.8)	
DML (ms)							2.5 (2.2-2.9)	
MCV upper arm (m/s)							67 (58-75)	
MCV shoulder (m/s)							67 (61-74)	
Conduction block							13	
Radial nerve (ECR)								
Distal CMAP (mV)							6.3 (3.8-8.7)	
MCV upper arm (m/s)							59 (53-68)	
MCV shoulder (m/s)							70 (59-79)	
Conduction block							15	
SNAP	6 (0-11)	7 (0-9)	5 (2-6)	14 (9-21)	6 (0-11)	11 (7-15)	16 (12-24)	< 0.001*

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Supplemental Table 4.2 continued

Musculocutaneous nerve (BB)	
Distal CMAP (mV)	6.6 (4.8-8.0)
MCV shoulder (m/s)	66 (55-78)
Conduction block	11

The NCS parameter values are displayed in median (interquartile range) values, except for conduction block.

*significant differences (after Benjamini-Hochberg correction between CIDP, LSS and MMN, using Kruskal-Wallis test)

ADM = abductor digiti minimi, AH = abductor hallucis, APB = abductor pollicis brevis, BB = biceps brachii, CIDP = chronic inflammatory demyelinating neuropathy; categorized into clinical phenotypes (sensorimotor (classic presentation), pure sensor and pure motor, sensory-ataxia), CMAP = compound muscle action potential, DML = distal motor latency, ECR = extensor carpi radialis, EDB = extensor digitorum brevis, FCR = flexor carpi radialis, LSS = Lewis Sumner syndrome (also known as MADSAM or MIDN), MCV = motor conduction velocity, MMN = multifocal motor neuropathy, SNAP = sensory nerve action potential

Supplemental Table 4.3 Summary nerve ultrasound studies

	Cut-off in mm²[#]	CIDP					LSS	MMN	P-value
		Sensorimotor (n = 65)	Pure sensory (n =6)	Sensory-ataxic (n= 6)	Pure motor (n = 4)	Total (n = 81)	(n = 17)	(n = 42)	
Median nerve									
Carpal tunnel	>11	12.7 (11.4-14.8)	13.8 (10.1-15.7)	12.4 (10.9-15.0)	13.6 (12.6-16.9)	12.8 (11.2-14.8)	10.8 (9.9-12.3)	11.0 (9.7-12.6)	<0.001*
Forearm	>9	10.9 (9.2-13.0)	12.2 (9.8-13.1)	9.7 (8.8-10.6)	10.4 (9.3-10.8)	10.8 (9.3-12.8)	10.3 (8.5-11.9)	8.9 (7.6-10.7)	<0.001*
Upper arm	>9	14.2 (12.5-17.3)	14.6 (12.3-22.5)	13.2 (12.0-14.2)	15.7 (13.3-17.1)	14.2 (12.5-17.1)	14.6 (13.0-19.2)	13.2 (10.6-15.0)	0.18
Ulnar nerve									
Distal sulcus	>9	9.2 (8.1-10.3)	10.5 (8.0-14.0)	8.1 (7.0-9.8)	10.9 (9.1-11.9)	9.3 (8.1-10.6)	9.5 (8.5-10.8)	7.7 (7.0-9.2)	0.02*
Sulcus	>9	11.1 (8.8-13.5)	10.0 (8.7-12.0)	11.4 (9.4-13.8)	12.8 (9.9-15.1)	11.0 (9.0-13.5)	11.3 (8.9-13.3)	10.1 (8.1-11.2)	0.26
Proximal sulcus	>9	10.5 (9.1-12.2)	10.5 (8.9-12.1)	9.7 (8.0-11.6)	11.5 (8.4-11.7)	10.6 (9.0-11.9)	10.2 (8.9-10.9)	9.2 (7.7-10.9)	0.05
Upper arm	>9	10.1 (8.0-11.9)	10.0 (8.7-13.6)	8.7 (6.8-9.4)	11.8 (9.1-12.2)	9.8 (8.1-11.9)	8.5 (6.8-10.5)	8.0 (6.7-9.6)	0.004*
Brachial plexus									
Superior trunk	>8	8.6 (6.5-10.7)	9.6 (6.5-17.5)	6.0 (3.8-8.4)	13.1 (9.6-13.6)	8.6 (6.4-11.2)	9.6 (5.8-11.2)	7.1 (5.7-9.0)	0.12
Median trunk	>8	7.1 (5.4-10.8)	10.8 (4.6-22.1)	5.6 (4.8-7.0)	9.8 (7.0-14.5)	7.1 (5.4-10.8)	7.2 (5.4-11.3)	6.1 (4.7-8.5)	0.95
Inferior trunk	>8	6.3 (5.1-9.6)	10.1 (6.4-15.6)	5.1 (4.0-6.4)	7.6 (6.8-8.5)	6.6 (5.1-9.4)	6.6 (4.4-9.6)	5.3 (4.4-7.0)	0.08
Fibular nerve									
At level of knee	>9	9.4 (8.1-11.1)	9.7 (8.5-16.3)	8.6 (7.5-12.4)	10.2 (9.2-10.2)	9.4 (8.1-11.1)	8.4 (7.4-9.0)	7.6 (6.5-9.6)	<0.001*
At fibular head	>11	13.2 (11.5-16.0)	12.2 (8.9-16.3)	14.0 (10.1-15.4)	14.0 (13.9-14.0)	13.2 (11.1-15.3)	12.8 (11.1-15.0)	11.9 (9.7-13.1)	0.10
Tibial nerve									
Medial malleolus	>13	17.3 (16.0-19.6)	16.1 (14.2-21.9)	17.3 (14.3-19.6)	17.6 (17.4-17.6)	17.3 (15.6-19.5)	17.1 (16.1-18.7)	15.9 (15.0-18.8)	0.35
Sural nerve									
At level of ankle	>3	3.0 (2.3-3.7)	3.4 (2.9-4.2)	2.9 (2.5-5.0)	2.4 (2.1-2.4)	3.0 (2.4-3.7)	2.9 (2.4-4.1)	2.5 (2.1-3.1)	0.14

The CSA values are displayed in median (interquartile range) values. Cross-section area (CSA) values for each of the predetermined sites of measurements (median, ulnar, fibular, posterior tibial and sural nerve, brachial plexus), in the enrolled patients with chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis Sumner syndrome (LSS, also known as MADSAM or MIDN) and multifocal motor neuropathy (MMN).

*significant differences (after Benjamini-Hochberg correction, using Kruskal-Wallis test), [#] as published previously[16,23,37]

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CHAPTER 5

Sonographic patterns of nerve enlargement in Charcot-Marie-Tooth type 1a and inflammatory neuropathies

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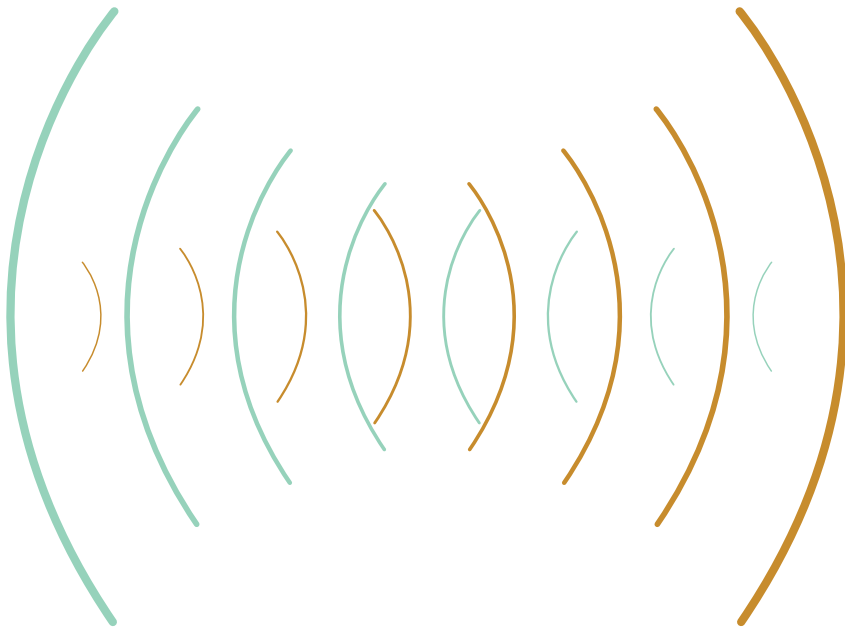
In preparation

ABSTRACT

Objective

To examine the distribution of nerve enlargement in polyneuropathies by performing extensive sonographic assessment along the entire tract of the median and ulnar nerves.

Methods

This cross sectional study was performed between May 2017 and August 2019. We included in total 85 patients of whom 70 patients were diagnosed with chronic inflammatory neuropathies (chronic inflammatory demyelinating polyneuropathy (CIDP) (n=30), multifocal motor neuropathy (MMN) (n=30), Lewis Sumner syndrome (LSS) (n=10)). Ten had chronic idiopathic axonal polyneuropathy (CIAP) and 5 Charcot-Marie-Tooth type 1a (CMT1a). All patients underwent extensive nerve ultrasound of the median and/or ulnar nerves, which consisted of bilateral assessment of the cross sectional area (CSA) at the wrist and every 2 cm up to the level of the axilla. Mean nerve CSA was compared between CIDP and CMT1a and also between different chronic inflammatory neuropathies.

Results

The mean nerve CSA of the median nerve from 0 cm (wrist) up to 14 cm (1/2 forearm) and from 28 up to 32 cm (1/2 upper arm) and along the entire tract of the ulnar nerve was significantly larger in CMT1a compared to CIDP (all $p<0.01$). Chronic inflammatory neuropathies were characterized by predominant enlargement of proximal nerve segments of the median nerve, more pronounced in CIDP and LSS than in MMN. CIDP and LSS were also characterized by enlargement of the ulnar nerve in both distal and proximal segments.

Conclusions

Related polyneuropathies differ in patterns of nerve enlargement. Bilateral evaluation of the sonographic pattern of nerve enlargement can easily be performed and may be useful to discriminate between different types of polyneuropathy e.g. CMT1a and CIDP.

INTRODUCTION

Nerve ultrasound is a relatively new technique for the diagnostic workup of suspected polyneuropathy. Nerve enlargement was reported first in mononeuropathies and in later years this feature has also been found in several types of polyneuropathy.[1-7] Patterns of nerve enlargement may be associated with specific neuropathies, such as diffuse and severe enlargement in hereditary demyelinating polyneuropathies (e.g. Charcot-Marie-Tooth type 1a (CMT1a), multifocal enlargement of proximal nerve segments (median nerve and brachial plexus) in chronic inflammatory neuropathies, pronounced ulnar nerve enlargement above the medial epicondyle in Hansen's neuropathy and no or only limited enlargement at entrapment sites in axonal neuropathies.[8-11]

Previous studies have primarily focused on evaluating the discriminative properties of extensive sonographic protocols in which several nerve sites were combined.[12-14] We developed a short sonographic protocol that showed high diagnostic accuracy to discriminate chronic inflammatory neuropathies i.e. chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and Lewis Sumner syndrome (LSS) from disease mimics.[8,15] However, this and other studies have not evaluated distribution of nerve enlargement along the entire tract of individual nerves. Such an approach could give insight on the localization of maximum nerve cross sectional areas and the presence of marked asymmetry that would favor bilateral assessment. Also, these patterns could potentially give additional insight in the potentially different pathophysiological processes in different polyneuropathies.

In this study we therefore analyzed the distribution of nerve enlargement in median and ulnar nerves in chronic inflammatory neuropathies, CMT1a and in chronic idiopathic axonal polyneuropathy (CIAP).

METHODS

Study design and patients

This cross-sectional study was performed between May 2017 and August 2019 in the UMC Utrecht, a tertiary referral center for neuromuscular disorders and the Elisabeth-Tweesteden Hospital Tilburg (ETZ), a large general teaching hospital. The study was approved by the Brabant Regional Ethics Committee (NL50375.028.14). All participants gave written informed consent. Inclusion criteria were 1) age ≥18 2a) a diagnosis of CIDP, MMN or LSS according to the EFNS/PNS criteria, 2b) a diagnosis of CIAP according to previously published clinical criteria, nerve conduction studies (NCS) results and laboratory testing or 2c) a confirmed molecular genetic diagnosis of CMT1a.[16-20] Exclusion criterion was physical inability to undergo nerve ultrasound.

Nerve ultrasound

Nerve ultrasound was performed with a high frequency probe of 5-18 MHz with a Philips EPIQ7 (Philips Medical Instruments, Bothell, WA) at the UMC Utrecht and a Toshiba Xario XG (Toshiba, Tokyo, Japan) at the ETZ Tilburg. Nerve cross-sectional area (CSA) was assessed within the hyperechoic rim. We examined CSA of the median and ulnar nerve using an inching technique in which CSA was obtained at wrist and every 2 centimeters (cm) proximal from the wrist up to the level of the axilla.[11] We used this inching technique to assess the median or the ulnar nerve bilaterally, each in half of the included patients with CIDP, MMN, LSS or CIAP. We investigated the median nerve first in consecutive patients; in the second half of the study we investigated the ulnar nerve in consecutive patients. We assessed both the median and ulnar nerve bilaterally in patients with CMT1a. Nerve ultrasound was performed by two investigators with ≥1 year of nerve ultrasound experience (IJTH, JAT).

Statistical Analysis

All baseline characteristics are summarized as median (range) for continuous variables and n (%) for categorical variables. Mean nerve size per disease group was calculated for all nerve sites assessed with the inching technique. Missing values along the nerve tract were imputed by taking the mean of two adjacent nerve sites (missing observations: 29/3960 (0.7%)). Mean CSA was compared between chronic inflammatory neuropathies using the one-way ANOVA test and between CIDP and CMT1a using the independent t-test. Absolute differences in nerve size between right and left median or ulnar nerve were calculated. Due to the exploratory nature of this study, we did not adjust for multiple testing and results were considered significant when the *p*-value was lower than 0.05.

RESULTS

We included a total of 85 patients with a median age of 58 years (range 27-85); 30 had CIDP, 30 had MMN, 10 had LSS, 10 had CIAP and 5 had CMT1a. Baseline characteristics are shown in **Table 5.1.** Mean CSA of the median and ulnar nerve per nerve site assessed with the inching technique is shown in **Table 5.2** and **Supplemental Table 5.1**.

Sonographic patterns of median nerve enlargement

Figure 5.1 summarizes the distribution of nerve enlargement along the course of the median nerve per disease group. The mean CSA of the median nerve was significantly higher in patients with CMT1a at 0-14 cm and at 28-32 cm compared to CIDP (p<0.01). In chronic inflammatory neuropathies (i.e. MMN, LSS and CIDP) the median nerve was especially enlarged at the level of the upper arm. Enlargement seemed to be more pronounced in CIDP and LSS compared to MMN. Significant differences in mean nerve size were found between CIDP, MMN and LSS especially in the distal part of the upper arm (at 30 cm p=0.041, 32 cm p=0.019, and 34 cm p=0.046). The absolute differences between the right and left median nerve in individual patients are shown in **Figure 5.2**.

Table 5.1 Baseline characteristics

	Total cohort	CIDP	MMN	LSS	CIAP	CMT1a
Number of patients	85 (100)	30 (35)	30 (35)	10 (12)	10 (12)	5 (6)
Age (median, range)	58.0 (27-85)	58.5 (27-85)	59.0 (36-77)	52.5 (32-71)	60.5 (50-80)	50.0 (37-65)
Sex: male (%)	62 (73)	23 (77)	21 (70)	8 (80)	7 (70)	3 (60)
Disease duration in months	77.5 (8-636)	48.0 (8-324)	126.0 (24-562)	112.0 (10-252)	78.0 (32-104)	360 (120-636)
Treatment duration in months	30.0 (0-311)	19.5 (6-311)	45.0 (0-306)	23.5 (0-91)	NA	NA

Baseline characteristics are shown of all inclusions and per disease group. Data are shown as number of patients (%) or median (range).

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy, NA = not applicable

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Table 5.2 Mean nerve cross sectional area in mm^2

	Median nerve					Ulnar nerve			
Site	CIDP	MMN	LSS	p-value	Site	CIDP	MMN	LSS	p-value
0	12.67	10.53	11.30	0.060	0	6.00	5.07	6.10	0.001
2	12.57	10.00	10.60	0.002	2	5.77	5.23	5.70	0.009
4	12.03	9.00	8.90	0.003	4	5.43	4.97	6.30	0.001
6	12.27	8.63	9.30	0.005	6	5.50	4.90	8.60	0.001
8	10.80	8.73	9.20	0.133	8	6.07	4.87	10.20	0.002
10	10.73	8.10	9.50	0.022	10	6.73	5.10	9.70	0.001
12	10.53	8.07	9.20	0.136	12	6.50	5.03	9.20	0.004
14	10.27	8.17	9.10	0.353	14	6.67	5.23	9.70	0.001
16	11.23	8.13	8.70	0.234	16	6.73	5.37	12.60	0.004
18	11.10	8.00	9.90	0.147	18	6.70	5.17	9.30	<0.001
20	12.00	8.17	10.50	0.037	20	6.90	5.37	9.80	0.004
22	12.60	8.10	9.90	0.018	22	7.43	5.83	6.90	0.004
24	13.63	9.90	12.20	0.046	24	8.07	6.60	7.10	0.001
26	17.93	12.00	16.20	0.066	26	9.77	9.37	8.70	0.479
28	18.90	12.87	18.60	0.037	28	8.57	8.37	8.20	0.003
30	19.57	13.20	18.60	0.041	30	9.07	6.83	8.00	<0.001
32	19.33	12.53	18.70	0.019	32	9.10	7.00	8.00	0.001
34	18.07	12.43	19.30	0.046	34	9.97	6.87	7.30	0.003
36	17.70	12.57	17.30	0.160	36	9.93	7.17	6.70	0.007
38	17.63	12.30	17.70	0.057	38	9.33	7.07	7.50	0.018
40	17.07	11.97	19.60	0.075	40	9.87	7.27	12.10	0.113
					42	10.07	7.07	8.70	0.067
					44	9.97	7.03	7.90	0.028
					46	9.47	6.90	9.80	0.142

CIDP = chronic inflammatory demyelinating polyneuropathy, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy

Figure 5.1 Sonographic pattern of enlargement of the median nerve stratified per neuropathy

The mean nerve cross sectional area in mm² of the median nerve along its tract stratified per subgroup. The reference line was set at 12 mm2 (carpal tunnel), at 9 mm² (forearm), at 9 mm² (elbow) and at 13 mm² (1/2 upperarm), according to previously published cut-off values.[29]

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy

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Figure 5.2 Absolute difference of right and left median nerve per disease group

The absolute difference between the right and left median nerve per individual patient (grey lines) in the different disease groups in mm². The red line shows the mean absolute difference per disease group.

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy

Sonographic patterns of ulnar nerve enlargement
Figure 5.3 shows the distribution of nerve enlargement along the course of the ulnar nerve per disease group. The mean CSA of the ulnar nerve was significantly higher in CMT1a along its entire tract compared to CIDP (all p<0.01). Significant differences in mean nerve size were found between CIDP, MMN and LSS at all nerve sites except at the sulcus (26cm) and around the axilla (40-46cm). In LSS the mean CSA of the ulnar nerve was higher at the forearm compared to CIDP and MMN and enlargement was more focal. In MMN the ulnar nerve was only enlarged around the ulnar sulcus (26 cm) while in CIDP and LSS there was more pronounced enlargement in both forearm and upper arm. The absolute differences between right and left ulnar nerves in individual patients are shown in **Figure 5.4**.
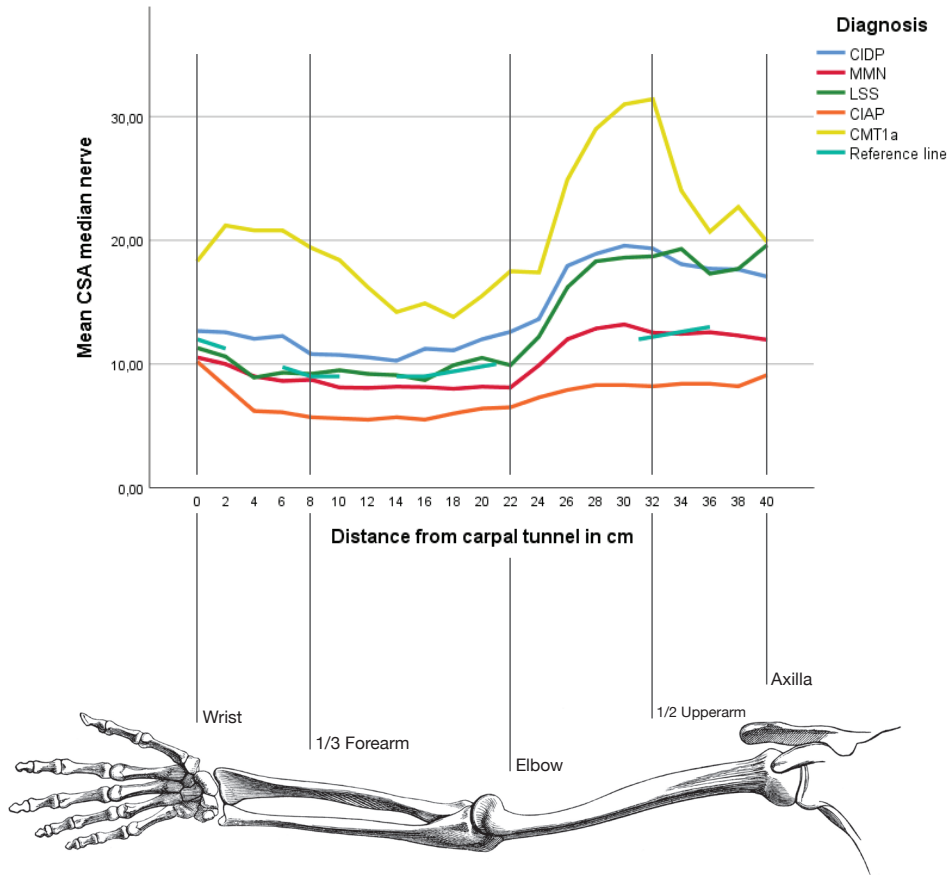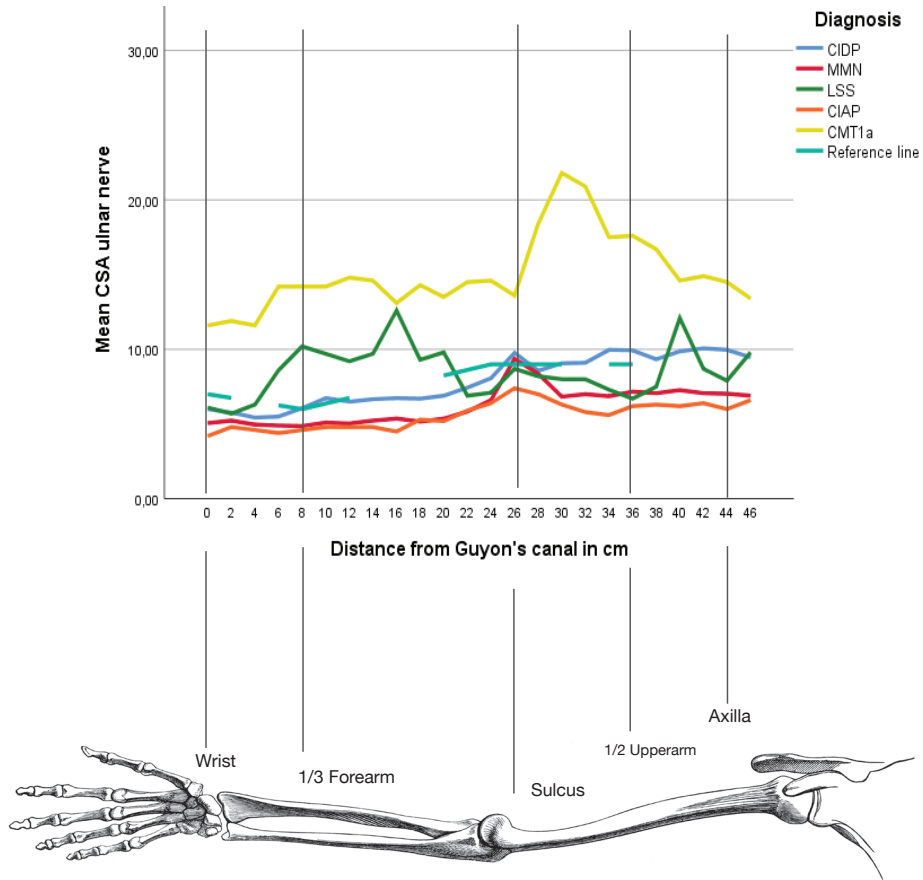
Figure 5.3 Sonographic pattern of enlargement of the ulnar nerve stratified per neuropathy

The mean nerve cross sectional area in mm2 of the ulnar nerve along its tract stratified per subgroup. The reference line was set at 7 mm² (wrist), at 6 mm² (forearm) at 9 mm² (sulcus) and at 9 mm² (1/2 upperarm) according to previously published cut-off values.[29]

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy
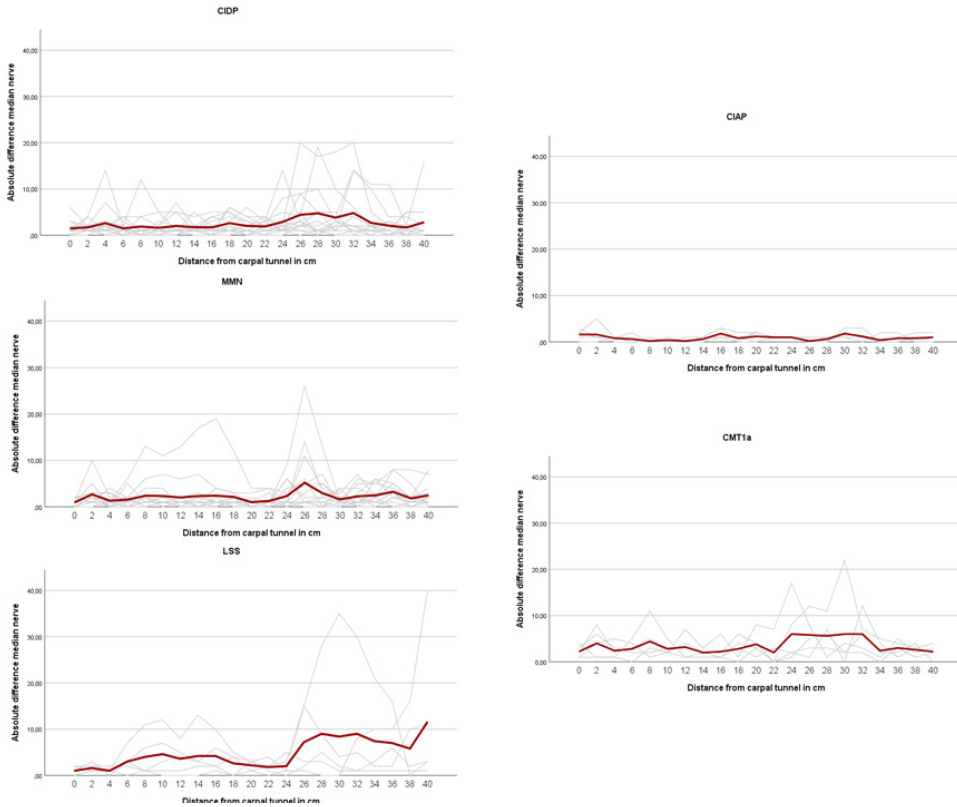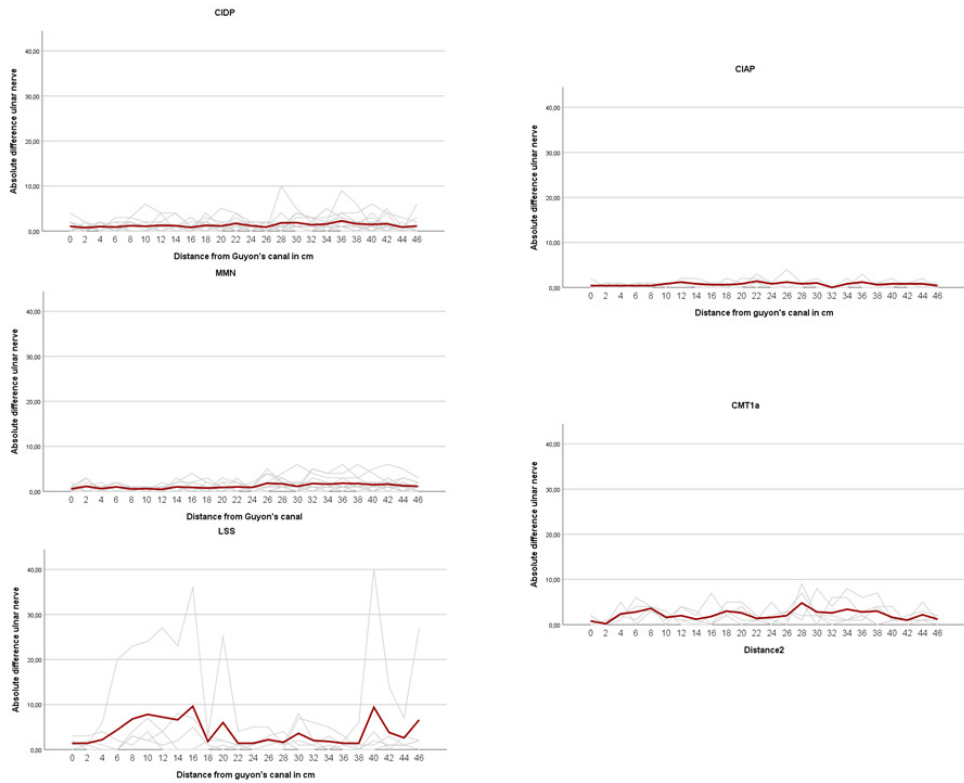
Figure 5.4 Absolute difference of right and left ulnar nerve per disease group

The absolute difference between the right and left ulnar nerve per individual patient (grey lines) in the different disease groups in mm². The red line shows the mean absolute difference per disease group.

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy

DISCUSSION

This study shows that the patterns of nerve enlargement differ between polyneuropathies. Nerve enlargement is most pronounced in patients with CMT1a, followed by CIDP, LSS and MMN. CIAP is not characterized by enlargement outside entrapment sites. The pattern of enlargement in CMT1a and inflammatory neuropathies was most obvious in the proximal segments of the upper arm. Asymmetrical nerve enlargement was observed in several patients, indicating that bilateral ultrasonographic assessment should be advised when a patient is suspected of chronic inflammatory neuropathy or CMT1a.

Previous studies have shown that nerve enlargement can be found in various types of polyneuropathy.[9,10,13,21] We previously showed that a short sonographic protocol is a useful tool to identify patients with inflammatory neuropathies.[8] In this large nested case control study we found that the median nerve at 1/2 of the upper arm was one of the most discriminative nerve sites to identify chronic inflammatory neuropathies.[8] However, until now nerve ultrasound has not been performed along the full tract of the median and ulnar nerves. In this study, nerve enlargement was most pronounced in the proximal segments of the median nerve, even more so in hereditary than inflammatory neuropathies. Importantly, assessment of the ulnar nerve seems to be of additional value to discriminate between chronic inflammatory neuropathies. This possibly indicates differences in pathophysiology but can also be relevant for the discrimination of (pure motor) CIDP and relatively symmetric MMN. Marked enlargement of both the median and ulnar nerve at the upper arm especially are more compatible with the diagnosis of CIDP. This could suggest that CIDP is a more generalized and MMN a more focal inflammatory process. These findings indicate that extensive assessment of both median and ulnar nerve could be of additional value to discriminate between chronic inflammatory neuropathies.

Observations from previous studies suggest that the distinction of CMT1a from CIDP may sometimes be difficult.[22] This study indicates that sonographic assessment of the ulnar nerve along its entire tract and the median nerve from wrist to 1/2 of the forearm or at 1/2 of the upper arm could discriminate CMT1a from CIDP. Since the number of observations in CMT1a in this study is limited and sonographic pattern of nerve enlargement differ considerably in individual patients, the discriminative value of such a pattern has to be established in larger patient groups.

Nerve ultrasound and NCS both seem to differ between forms of inflammatory neuropathy.[23] MMN is characterized by conduction block, whilst in CIDP a combination of several demyelinating features e.g prolonged distal and F-wave latencies, slow conduction velocities and abnormal temporal dispersion is more common.[18,19,24-28] The more focal and less pronounced thickening of nerves in MMN compared to CIDP may fit with the hypothesis that it is caused by a targeted attack at (para)nodal structures, whereas in CIDP the inflammation is more dispersed.

Our study had some limitations. Because chronic inflammatory neuropathies and CMT1a are rare diseases, sample sizes may fall short of what is desirable. The limited number of patients per disease group precludes a comparison between clinical characteristics and sonographic patterns. However, previous studies have described that nerve size is not associated with

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muscle strength, age or sex.[8,9] Arm length could be variable between men and women and therefore measuring every 2 cm could cause differences in position of assessment, but our study population consisted primarily of male patients. Another limitation was the fact that we performed exploratory data analysis.

This study shows that different sonographic patterns of nerve enlargement can be found in hereditary and inflammatory polyneuropathies. These specific patterns of nerve enlargement may be useful to discriminate between polyneuropathies.

SUPPLEMENTAL MATERIAL

Supplemental Table 5.1 Mean nerve cross sectional area in mm^2

Median nerve			Ulnar nerve		
Site	CIAP	CMT1a	Site	CIAP	CMT1a
0	10.20	18.3	0	4.20	11.6
2	8.20	21.2	2	4.80	11.9
4	6.20	20.8	4	4.60	11.6
6	6.10	20.8	6	4.40	14.2
8	5.70	19.4	8	4.60	14.2
10	5.60	18.4	10	4.80	14.2
12	5.50	16.2	12	4.80	14.8
14	5.70	14.2	14	4.80	14.6
16	5.50	14.9	16	4.50	13.1
18	6.00	13.8	18	5.30	14.3
20	6.40	15.5	20	5.20	13.5
22	6.50	17.5	22	5.90	14.5
24	7.30	17.4	24	6.40	14.6
26	7.90	24.9	26	7.40	13.6
28	8.30	29.0	28	7.00	18.4
30	8.30	31.0	30	6.30	21.8
32	8.20	31.4	32	5.80	20.9
34	8.40	24.0	34	5.60	17.5
36	8.40	20.7	36	6.20	17.6
38	8.20	22.7	38	6.30	16.7
40	9.10	19.9	40	6.20	14.6
			42	6.40	14.9
			44	6.00	14.5
			46	6.60	13.4

CIAP = chronic idiopathic axonal polyneuropathy, CMT1a = Charcot-Marie-Tooth type 1a

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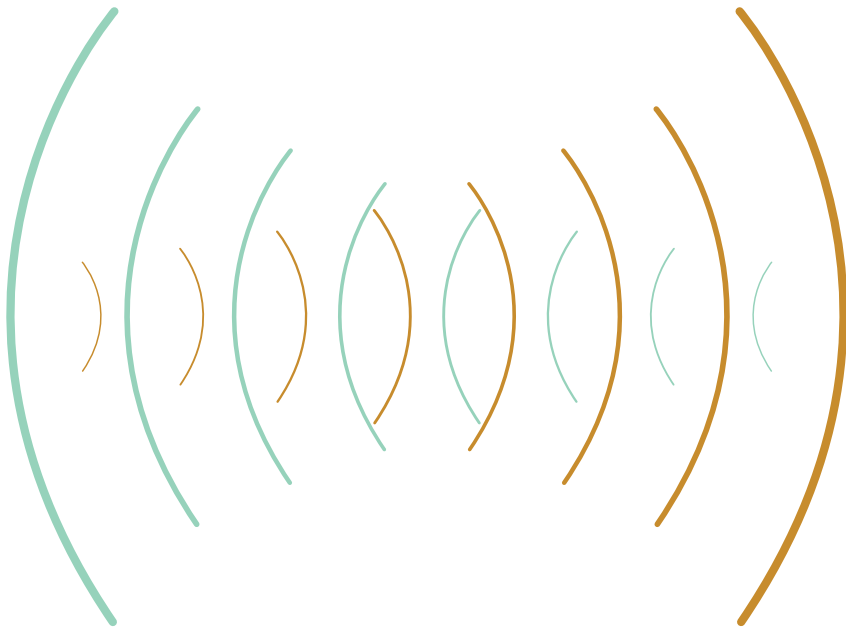
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CHAPTER 6

Nerve ultrasound can identify treatment-responsive chronic neuropathies without electrodiagnostic features of demyelination

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ABSTRACT

Objective

To present a case series of six treatment-naive patients with clinical phenotypes compatible with chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, without electrodiagnostic features of demyelination but with abnormal peripheral ultrasound findings who responded to treatment.

Methods

All six patients underwent a complete set of ancillary investigations, including extensive nerve conduction studies (NCS). We also performed standardized nerve ultrasound of median nerves and brachial plexus as part of a larger effort to evaluate diagnostic value of sonography.

Results

NCS did not show conduction block or other signs of demyelination in any of the six patients. Sonographic nerve enlargement was present in all patients and was most prominent in proximal segments of the median nerve and brachial plexus. Treatment with intravenous immunoglobulin resulted in objective clinical improvement.

Conclusions

Our study indicates that nerve ultrasound represents a useful complementary diagnostic tool for the identification of treatment-responsive inflammatory neuropathies.

INTRODUCTION

The presence of persistent conduction block or other nerve conduction study (NCS) abnormalities suggestive of (multifocal) demyelination helps to distinguish chronic motor neuropathies that respond to immune modulating treatment, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), from the more common neurodegenerative lower motor neuron (LMN) disorders. According to consensus diagnostic criteria, a combination of a compatible clinical phenotype and these NCS characteristics is sufficient for a diagnosis of 'probable' or 'definite' CIDP or MMN, which predicts a high chance of response to treatment.[1,2] Patients without electrodiagnostic features of demyelination are classified as having 'possible' CIDP or MMN if results of additional ancillary investigations, such as brachial plexus magnetic resonance imaging (MRI), albumino-cytological dissociation in cerebrospinal fluid (CSF), or the titre of anti-GM1 IgM antibodies (only for MMN), are abnormal.[3] However, treatment response rates in such cases are relatively low. Other diagnostic strategies are needed to limit the number of unsuccessful trials with intravenous immunoglobulin (IVIg).

We recently showed that high-resolution ultrasound (HRUS) is a sensitive technique to identify patients with MMN and CIDP with characteristic NCS abnormalities.[4] Only a few previous reports in single patients and a retrospective chart review have noted abnormal ultrasound findings in patients without these characteristic NCS findings.[5-8] Here we describe six patients suspected of an inflammatory neuropathy who lacked electrodiagnostic features of demyelination but had abnormal ultrasound findings. Response to treatment in the majority of these patients provides evidence that peripheral nerve ultrasound is a complementary diagnostic tool for evaluation of inflammatory neuropathies.

METHODS

Patients and routine ancillary investigations

All patients in this study presented with a clinical phenotype of a subacute or chronic symmetric or asymmetric LMN syndrome, compatible with a diagnosis of CIDP or MMN.[1,2] All were newly referred and treatment-naive patients at the neuromuscular outpatient clinic at the University Medical Centre Utrecht (UMCU), who were seen between January 2014 and January 2016.[4] They did not meet the inclusion criteria of the ongoing study to evaluate the diagnostic accuracy of HRUS in patients with inflammatory neuropathies because their NCS showed no electrodiagnostic features of demyelination.[2,4,9-11] They underwent extensive NCS according to a previously published standardized protocol, after warming extremities in water at 37 degrees Celcius for 45 minutes and routine ancillary investigations according to consensus diagnostic guidelines.[1,2,4,9] We used a previously published HRUS protocol of median nerves and brachial plexus trunks. The physiotherapist and clinical neurophysiologist (H.F.) were blinded to the HRUS

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results. The treating physicians (W.L.P, L.B.) were blinded to the details of HRUS evaluations, and not allowed to read the degree of (any) enlargement.

Five patients received IVIg treatment at a cumulative dose of 2 g/kg. We evaluated treatment effects assessed at intervals of 3 to 4 weeks after initial doses, using the Medical Research Council (MRC) scale and an experienced physiotherapist independently tested for muscle strength using dynamometry of hand, pinch- and key-grip, myometry of large arm and leg muscles, and 10-m walking tests.[12,13] Objective improvement was defined as an increase of ≥2 points on MRC scores (≥1 muscle group for hand and leg muscles, ≥1 muscle in upper arm), >10% increment of dynamometry/myometry (≥1 muscle group), or >10% improvement in pinch/key-grip or 10-m walking test times.

Standard approval of protocols and consent

The ethics committee of the UMC Utrecht approved the study protocol (14-328), and we obtained informed consent from all included participants.

RESULTS

Five patients had a subacute or chronic onset of asymmetric weakness of the arms or symmetric weakness of the legs and one patient had progressive sensory ataxia. Patient characteristics are presented in **Table 6.1**, and results from ancillary investigations in **Table 6.2** (**Supplemental Table 6.1**): chronic progressive asymmetric weakness compatible with MMN (patient 1), subacute/chronic progressive symmetric weakness of the legs and a single case of sensory ataxia fitting CIDP (patients 2-5, and patients 6) according to the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) diagnostic consensus criteria. None of the patients met any of the electrodiagnostic criteria for demyelination (motor conduction velocity > 2 SD below the lower limit of normal or other specified nerve conduction variables); most met only two of the required supportive criteria needed for CIDP (patients 2-6) and one met only the current diagnostic criterion for possible MMN (patient 1).[1,2] Repeated NCS at a >6-month interval revealed features of multifocal demyelination fulfilling the EFNS/PNS electrodiagnostic criteria in patient 6, but not in the other patients (1-5).[1,2] Sonography results are presented in **Table 6.3** (**Supplemental Figure 6.1**). High-resolution ultrasound was performed on the same day as NCS in all but patient 6 (3-week interval). One patient with progressive symmetric weakness and normal brachial plexus MRI results (patient 3) had lymphadenopathy according to HRUS and MRI. Non-Hodgkin lymphoma (NHL) was eventually diagnosed in this patient, and hematological treatment resulted in clinical improvement of muscle strength. Consecutive courses of IVIg in the other five patients resulted in significant reduction of sensory ataxia (patient 6) and improvement of muscle strength (patients 1, 2, 4 and 5; **Table 6.1**, **Supplemental Table 6.2**).

Table 6.1 Patient characteristics

Patient	Sex	Age (years)	Disease duration (months)	First symptoms	Clinical findings	Clinical phenotype	Improvement after treatment
1	F	50	34	Weakness right hand	Weakness and atrophy both hands	MMN	Increased muscle strength both hands
2	M	61	3	Weakness both legs	Symmetric distal > proximal weakness legs, low tendon reflexes, reduced vibration sense feet, postural tremor	CIDP	Increased muscle strength legs
3	M	66	6	Weakness both hands	Symmetric distal > proximal weakness and atrophy arms, proximal weakness legs, reduced vibration sense feet, absent tendon reflexes	CIDP	Increased muscle strength arms and legs
4	M	75	2	Paraesthesia feet	Symmetric distal > proximal weakness legs, reduced vibration sense lower legs and hands, absent tendon reflexes, tremor and sensory ataxia	CIDP	Increased muscle strength legs, reduced sensory ataxia
5	M	58	2	Paraesthesia feet	Symmetric proximal weakness arms and legs, absent tendon reflexes, postural tremor	CIDP	Increased muscle strength arms and legs
6	M	75	24	Paraesthesia feet	Symmetric hypoesthesia lower legs, absent tendon reflexes, sensory ataxia	CIDP	Reduced sensory ataxia, gain in balance

Sex: M = male, F = female, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy

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Table 6.2 Summary routine ancillary investigations

Patient	NCS (EFNS/PNS criteria are not fulfilled)	MRI brachial plexus	CSF protein content (mg/dL)	Supportive criteria EFNS/ PNS[a]	Diagnostic criteria EFNS/ PNS
1	CMAP ↓ median bilateral, right tibial + left fibular nerves	Normal	37	1 (treatment)	Not compatible
2	CMAP ↓ of left and absent on right fibular nerve	Normal	**103**	2 (CSF, treatment)	Not compatible
3	SNAP ↓ right median, both sural nerves	Normal[b]	-	1 (treatment)	Not compatible
4	DML ↑ and SNAP ↓ of right median nerve (CTS), CMAP⁻ fibular and tibial nerves, SNAP ↓ sural nerves	Normal	**54**	2 (CSF, treatment)	Not compatible
5	Only chronodispersion F-waves (median, ulnar, fibular + tibial)	Normal	**52**	2 (CSF, treatment)	Not compatible
6	SNAP ↓ right median, ulnar and radial, absent CMAP fibular and tibial nerves + SNAP both sural nerves	Enlargement + hyperintense T2-signal right trunks	42	2 (MRI, treatment)	Not compatible

[a]Abnormal MRI brachial plexus (enlargement and/or T2 hyperintense signal (nerve)root(s), gadolinium contrast enhancement), increased CSF protein, objective improvement following treatment, and in the case of MMN, presence of anti-GM1 antibodies.

[b]additionally diagnosed with non-Hodgkin lymphoma.

CMAP = compound muscle action potential, CSF = cerebrospinal fluid (elevated protein content was defined as > 40 mg/dL, indicated in bold type), NCS = nerve conduction studies, SNAP =sensory nerve action potential

Table 6.3 Summary sonographic nerve size median nerves and brachial plexus

Patient	Cross-sectional area (mm²)									
	Right median nerve		Left median nerve		Right brachial plexus			Left brachial plexus		
	Forearm	Upper arm	Forearm	Upper arm	Upper trunk	Middle trunk	Lower trunk	Upper trunk	Middle trunk	Lower trunk
Normal value	<9	<9	<9	<9	<8	<8	<8	<8	<8	<8
Disease specific cut-off value[a]	>10	>13	>10	>13	>8	>8	>8	>8	>8	>8
1	5.5	7.9	7.0	6.8	3.3	**8.5**	**9.4**	5.4	**9.4**	8.3
2	**10.6**	11.0	10.2	**13.7**	5.3	7.0	4.9	6.5	6.1	5.5
3	**11.8**	**18.6**	**12.1**	**18.9**	6.0	5.7	**.5**	5.2	**8.5**	**8.8**
4	**13.0**	**14.1**	9.6	10.7	6.1	3.4	4.8	5.9	4.9	5.4
5	**11.0**	11.9	**11.8**	**15.6**	7.3	5.0	5.2	**9.8**	**10.6**	**8.8**
6	9.5	**14.2**	10.4	**13.8**	7.3	5.4	4.1	**9.7**	7.5	6.2

[a]Sonographic enlargement of nerve size (median nerve at forearm and upper arm and brachial plexus any trunk) compatible with chronic inflammatory neuropathy indicated in boldface type.

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DISCUSSION

Enlargement of nerves of the upper arm and brachial plexus detected with HRUS is a hallmark for inflammatory neuropathies including CIDP and MMN.[4] The results from this case series provide evidence that HRUS may also be helpful in identifying the more elusive patients in which electrodiagnostic features of demyelination are absent. Only a small minority of patients (< 15%) with a clinical phenotype that may suggest MMN, but without the characteristic conduction block in combination with abnormal ancillary investigations, respond to IVIg treatment.[14] High-resolution ultrasound, therefore, may represent not only a useful complementary diagnostic tool, but may also eventually help to reduce the cost of IVIg trials that are the consequence of the current guidelines for the treatment of patients with lower motor neuron syndromes.

The six patients had the same pattern of sonographic nerve enlargement of proximal segments of median nerve and brachial plexus that we observed in our larger series of untreated patients with CIDP or MMN.[4] This supports the hypothesis that the six patients presented here had CIDP/MMN, and not another as yet unspecified treatment-responsive LMN syndrome. However, the patient with nerve enlargement and NHL is a clear illustration of the requirement for clinical caution when HRUS and NCS diverge. Therefore, electrodiagnostic and HRUS results should always be viewed in the clinical context because treatment decisions should not be based on a single abnormal test such as nerve size or only one enlarged nerve site.

We do not think that we failed to identify electrophysiological abnormalities because we used and even repeated an extensive NCS protocol that did not yield characteristics of demyelination in our patients. Our findings are in agreement with previous studies that noted sonographic enlargement in nerves without apparent demyelinating nerve conduction abnormalities.[15-18] The complementary role of HRUS and NCS in the diagnostic evaluation of chronic inflammatory neuropathies mirrors that of focal neuropathies.[19-23] In addition, HRUS may also have prognostic value in chronic inflammatory neuropathies.[24-28] Magnetic resonance imaging results of the brachial plexus were abnormal in only one patient, which may suggest that the larger field of view of HRUS offers a diagnostic advantage compared to MRI. The sonographic protocol presented here takes less than 15 minutes and is time and cost efficient. Taken together, nerve ultrasound is warranted in patients in whom CIDP and MMN are suspected, both for helping to minimize overtreatment and, particularly, for early identification of treatable patients.

SUPPLEMENTAL MATERIAL

Supplemental Table 6.1 Summary nerve conduction studies

Nerve and NCS parameters	Normal values (cut-off values demyelination)	Patient					
		Right/left					
		1	2	3	4	5	6
Median nerve (APB)							
Distal CMAP amplitude (mV)	≥3.5	**1.6/1.4**	14.0/11.1	6.0/5.4	8.9/6.1	13.0/13.5	4.7
CMAP duration (ms)	(>9.0)	3.7/3.5	7.0/5.2	6.0/5.7	6.4/6.6	5.4/6.0	5.5
DML (ms)	≤4.2 (>5.3)	3.7/3.8	3.2/3.5	3.9/3.8	**5.9/5.5**	3.8/3.5	4.2
MCV forearm (m/s)	≥50 (<38)	55/51	62/60	59/53	51/**48**	53/53	**44**
MCV upper arm (m/s)	≥50 (<38)	**45**/66	63/69	55/51	**47**/54	56/62	59
MCV shoulder (m/s)	≥50 (<38)	-/74	76/71	73/57	70/58	80/76	54
F-M interval (ms)	≤27 (>32)	-	25/24	27/**30**	27/26	19/20	**30**
SNAP amplitude (µV)	a	32/36	24/27	**4**/9	**6/4**	12/24	**4**
Ulnar nerve (ADM)							
Distal CMAP amplitude (mV)	≥2.8	5.4/3.3	12.0/9.2	5.7/3.3	7.1/7.3	13.1/9.1	6.1
CMAP duration (ms)	(>9.0)	3.9/3.5	5.6/5.0	6.0/5.0	7.3/6.7	5.7/6.5	6.3
DML (ms)	≤3.4 (>4.3)	**3.7/3.6**	3.0/3.1	2.8/3.4	3.3/**3.6**	2.7/3.1	3.0
MCV forearm (m/s)	≥50 (<38)	63/56	67/62	51/50	**49**/50	53/60	50
MCV elbow (m/s)	≥50 (<38)	57/85	58/**45**	67/74	45/**44**	56/**44**	51
MCV upper arm (m/s)	≥50 (<38)	56/54	71/68	66/50	**47**/66	73/56	65
MCV shoulder (m/s)	≥50 (<38)	71/-	75/60	61/73	-/70	72/98	54
F-M interval (ms)	≤29 (>35)	24/24	27/26	**32**/27	**32**/29	29/-	33
SNAP amplitude (µV)	a	40/42	23/23	7/11	6/7	20/16	**3**

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Supplemental Table 6.1 continued

Measurement	Reference						
Fibular nerve (EDB)							
Distal CMAP amplitude (mV)	≥2.5	**0**/0.2	0/2.6	1.3/**0**	**0.7/0.7**	4.9	**0/0**
CMAP duration (ms)	(>9.0)	-/4.5	-/4.5	5.0/-	7.9/8.2	7.2	-
DML (ms)	≤5.5 (>6.9)	-/4.7	-/4.5	5.5/-	**6.5/8.5**	4.6	-
MCV lower leg (m/s)	≥40 (<32)	-/46	-/47	41/-	**33/33**	42	-
MCV fibular head (m/s)	≥40 (<32)	-/50	-/40	67/-	48/44	63	-
F-M interval (ms)	≤52 (>62)	-	-	-	-	-	-
Tibial nerve (AH)							
Distal CMAP amplitude (mV)	≥2.9	**2.2**/8.3	12.2/10.3	3.6/**2.1**	**1.0**/0.5	10.1	**0/0**
CMAP duration (ms)	(>9.0)	4.8/3.7	4.9/4.3	5.2/5.0	7.5/14.2	6.5	-
DML (ms)	≤6.2 (>7.5)	4.5/3.6	5.2/4.6	5.3/5.1	**7.4/7.7**	4.7	-
MCV lower leg (m/s)	≥40 (<33)	51/42	43/44	41/40	**35/41**	48	-
F-M interval (ms)	≤53 (>64)	**55/46**	53/52	-	**65**/-	-	-
Sural nerve							
SNAP amplitude (µV)	a	-	12/15	**0/0**	**0/0**	11/8	**0/0**
Median nerve (FCR)							
Distal CMAP amplitude (mV)	≥2.8	12.6/9.2				4.4	
DML (ms)	≤2.7 (>3.8)	2.0/2.0				2.4	
MCV upper arm (m/s)	≥50 (<40)	70/72				66	
MCV shoulder (m/s)	≥50 (<40)	74/71				62	
Radial nerve (ECR)							
Distal CMAP amplitude (mV)	≥2.8	7.6/9.4					
MCV upper arm (m/s)	≥50 (<40)	69/72					
MCV shoulder (m/s)	≥50 (<40)	65/68					
SNAP amplitude (µV)	a	27/35			6/5	10/17	**4**

Musculocutaneous (BB)		
Distal CMAP amplitude (mV)	≥2.8	6.7/7.0
MCV shoulder (m/s)	≥50 (<40)	77/77

We used previously established cut-off values of our lab.[9, 10]

Repeated NCS at a > 6-month interval showed features of multifocal demyelination in patient 6 fulfilling the EFNS/PNS electrodiagnostic criteria[1,2], but not in the patients 1-5. We documented carpal tunnel syndrome (CTS) in patient 4.

[a]Normal values for SNAP according to age categories: for median nerve ≥11 (18-60 years) or ≥5 (>60 years); ulnar and radial nerve ≥11 (18-39 years), ≥7 (40-60 years) or ≥5 (>60 years); sural nerve ≥11 (18-39 years), ≥5 (40-60 years) or ≥2 (>60 years).

ADM = abductor digiti minimi, AH = abductor hallucis, APB = abductor pollicis brevis, BB = biceps brachii CMAP = compound muscle action potential, DML = distal motor latency, ECR = extensor carpi radialis, EDB = extensor digitorum brevis, FCR = flexor carpi radialis, MCV = motor conduction velocity, SNAP = sensory nerve action potential

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Supplemental Table 6.2 Summary baseline and follow-up of clinical evaluations

Patients	1	2	3	4	5	6
Baseline measurements						
MRC MN	14	20	16	20	16	20
MRC UN	12	20	16	20	16	20
MRC sum	111	117	109	120	102	120
Hand dynamometry (kg)	16				32	36
Pinch grip (kg)	1				6	8
Key grip (kg)	3				8	8
Ataxia (sensory)				Severe		Severe
After 1st course IVIg			NA			
MRC MN	14	20		20	20	20
MRC UN	12	20		20	20	20
MRC sum	113	118		120	118	120
Hand dynamometry (kg)	21				39	38
Pinch grip (kg)	2.25				7,25	8
Key grip (kg)	3.25				9,5	8
Ataxia (sensory)				Improved		Improved
After 2nd course IVIg			NA			
MRC MN		20		20	20	20
MRC UN		20		20	20	20
MRC sum		120		120	120	120
Hand dynamometry (kg)					47	
Pinch grip (kg)					8	
Key grip (kg)					8.75	
Ataxia				Improved	9,75	Improved
Total follow-up (years)		1	2	1	1	1
MRC sum		120	117	120	120	120
Ataxia				Improved		Improved

IVIg = Intravenous immunoglobulin treatment at a cumulative dose of 2 g/kg.

MRC MN = MRC score 2 muscles per median nerve on both sides, MRC UN = MRC score 2 muscles per ulnar nerve on both sides, NA = not applicable
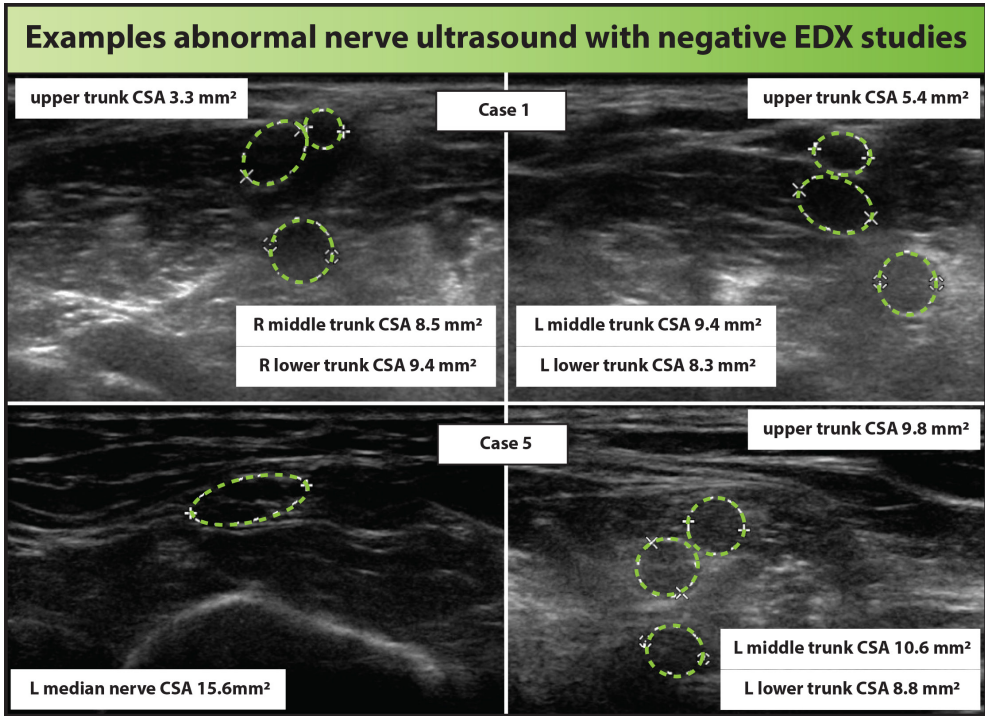
Supplemental Figure 6.1 Sonographic findings of patient 1 and patient 5

CSA = cross sectional area, R = right, L = left

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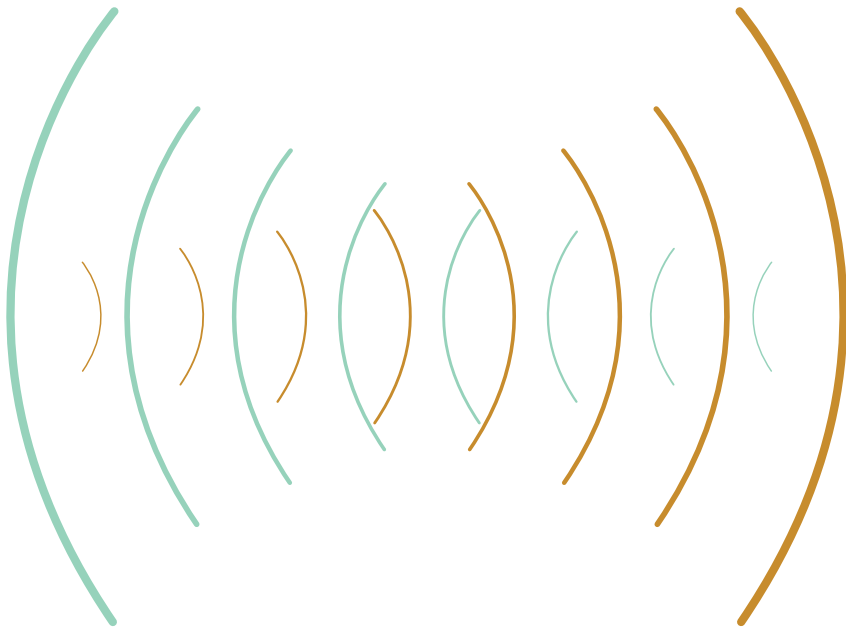
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CHAPTER 7

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 EFNS/PNS) 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 patients 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.

INTRODUCTION

Polyneuropathy is one of the most common disorders in neurological practice.[1] 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 outcomes.[2-6]

Nerve ultrasound is an emerging tool for the diagnostic work-up of polyneuropathies.[7-11] 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.[8]

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 can therefore not be used to exlude a diagnosis of treatment-responsive neuropathy.[12-15] Nerve ultrasound is a reliable and reproducible diagnostic tool.[16] The use of nerve ultrasound could shorten the time to diagnosis and could possibly improve identification of patients with chronic inflammatory neuropathies.[17]

The diagnostic performance of nerve ultrasound has, however, 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.[8] In addition, we assessed whether nerve ultrasound could improve the identification of treatment-responsive patients compared to NCS.

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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 out 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.[18-22] 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 and 3) physical inability to undergo nerve ultrasound investigation.

Routine diagnostic work-up

Diagnostic work-up 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).[23-25] 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, Tuttlingen, Germany) and testing of sensory function with the modified INCAT Sensory Sum Score (ISS).[26]

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.[8] 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). All NCS were graded following the EFNS/PNS criteria for CIDP (definite, probable or possible) or MMN (definite conduction block, probable conduction block, no conduction block).[21,22] 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.[8] 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) with a 5-18 MHz linear array transducer. In short, we assessed nerve size (cross sectional area (CSA)) 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 uni- or bilateral nerve enlargement was found at ≥1 of the measured sites.[8]

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.[21, 22] 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 one-year follow-up period, and 3a) either NCS abnormalities in accordance with the respective EFNS/PNS criteria, or 3b) nerve ultrasound abnormalities as defined previously in combination with treatment response.[8]

For the purpose of this study, we stratified patients into four 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 intravenous immunoglobulins (IVIg) and/or corticosteroids (**Figure 7.1**). 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 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 (HHD, in Newton): an increase in strength of ≥10% in two 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.[24, 27-29] 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 one-year follow-up period.

Statistical analysis

All data were summarized as mean (standard deviation (SD)) for normally distributed variables, median (interquartile range (IQR)) for non-normal 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 chi-square test (categorical). Results were considered significant when alpha 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 (PPV) and negative predictive value (NPV) from 2x2 tables. All analyses were conducted in SPSS 22 (SPSS Inc., Chicago IL, USA).

Standard protocol approvals, registration and patient consents

Our study protocol was approved by the medical ethics committee Brabant (NL42895.008.12) and all patients gave written informed consent.
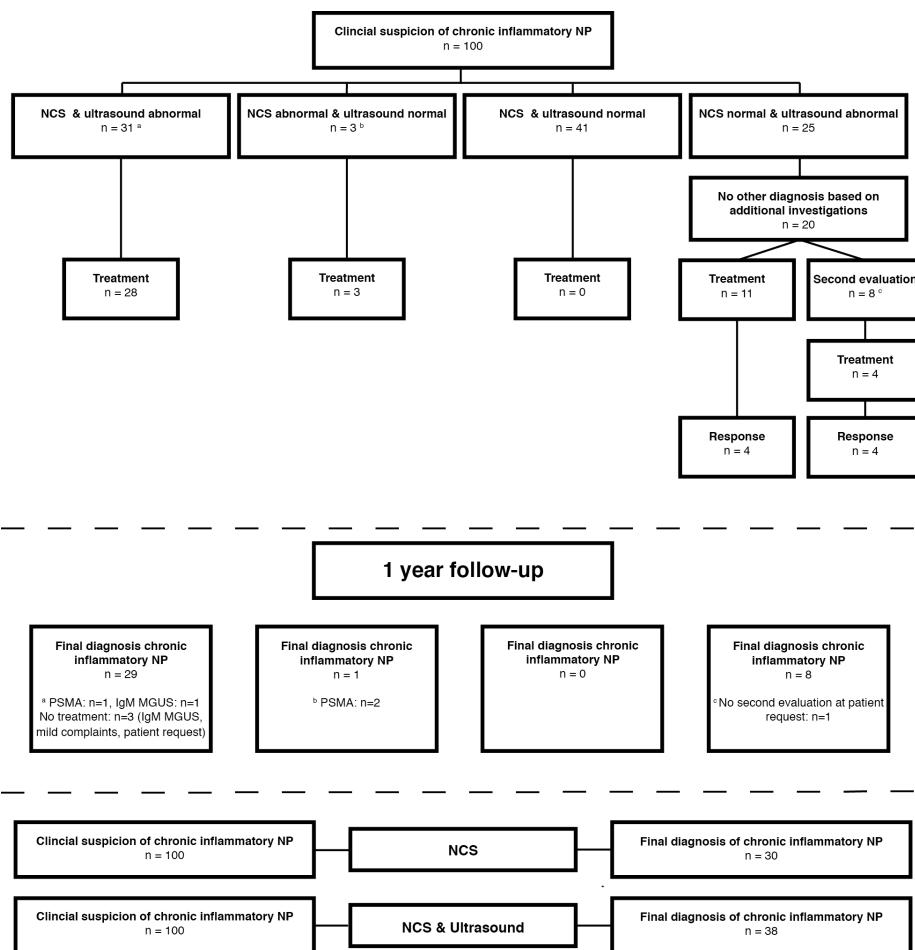
Figure 7.1 Flowchart of study

The diagnostic work-up, follow-up and final diagnoses established in the four groups.

[a] and [b] = other diagnosis, [c] = no second evaluation

Chronic inflammatory NP = chronic inflammatory neuropathy, IgM MGUS = IgM MGUS polyneuropathy, MGUS = monoclonal gammopathy of undetermined significance, NCS = nerve conduction studies, PSMA = progressive spinal muscular atrophy, Response = treatment response based on predefined criteria, Ultrasound = nerve ultrasound

RESULTS

Baseline Characteristics

Baseline characteristics of the 100 patients initially suspected of a chronic inflammatory neuropathy are shown in **Table 7.1.** All final diagnoses are presented in **Supplemental Table 7.1**.

Table 7.1 Baseline characteristics

	Inclusions (n=100)
Age in years (median, IQR)	58.9 (19.5)
Sex	
Male	78
Female	22
Duration of symptoms in months (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

Baseline characteristics of 100 patients in whom there is a clinical suspicion of a chronic inflammatory neuropathy; data are shown as number of patients unless stated otherwise.

CIDP = chronic inflammatory demyelinating polyneuropathy, Classical = classical phenotype of CIDP, IQR = interquartile range, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy, Pure motor = pure motor phenotype of CIDP, Pure sensory = pure sensory phenotype of CIDP

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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)) (**Supplemental Table 7.2 and Supplemental Table 7.3**). Distribution of the patients among groups is shown in **Figure 7.1**. Group 4 consisted of 25 patients, of whom 15 were treated despite normal NCS results. Of the 15 treated patients, eight 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 7.2**). There were no significant differences in clinical characteristics between patients with normal NCS and abnormal NCS (**Table 7.3**).

In addition to the eight patients with a final diagnosis of CIDP and MMN based on the combination of normal NCS, abnormal nerve ultrasound, and response to treatment, three 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 baselinescore but improvement in ≥1 of the other modalities was fulfilled (n=1)) (**Supplemental Table 7.3**). 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 7.2**. 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 7.4**). Based on the results of this study we devised two potential strategies to diagnose treatment-responsive chronic inflammatory neuropathy (**Figure 7.3**).

Supportive criteria

Results from ancillary investigations are presented in **Supplemental Table 7.2**.

Table 7.2 Treatment response

Patient	Diagnosis	Follow-up duration (months)	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	+

Treatment response of the 8 patients with normal NCS and abnormal nerve ultrasound with a diagnosis of chronic inflammatory neuropathy. The score per modality shown in the figure was calculated as the difference between pretreatment and posttreatment.

NA = not applicable, NP = not performed; "-" = 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, ODSS = Overall Disability Sum Score, RODS = Rasch-built Overall Disability Scale, Vig = vigorimetry

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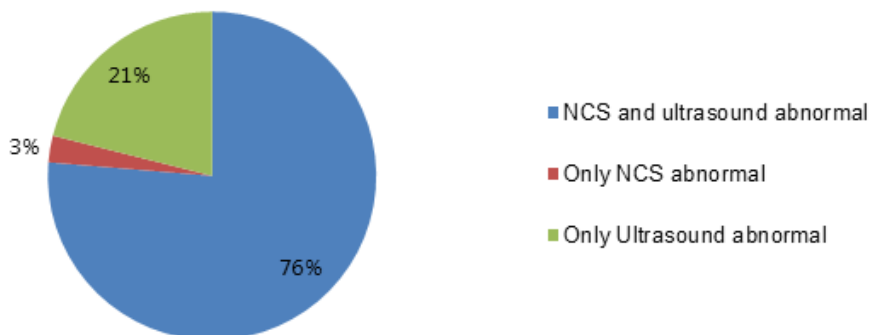
Diagnosis of CIN

Total cohort
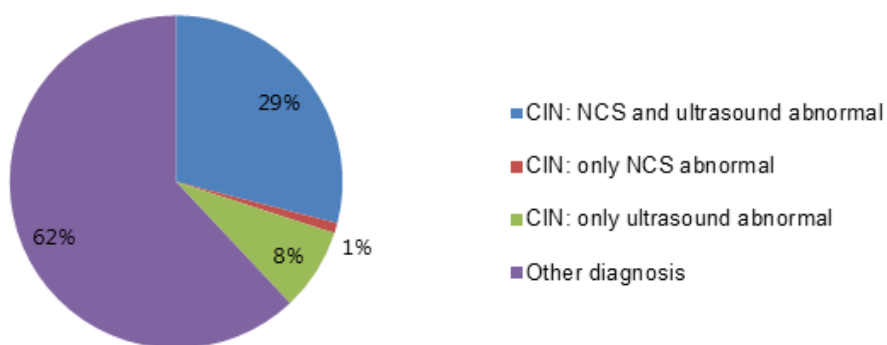

Figure 7.2 Added value of nerve ultrasound

The distribution of the diagnoses of chronic inflammatory neuropathy established with abnormal NCS, abnormal nerve ultrasound, or both; in the group with a diagnosis of chronic inflammatory neuropathy (n=38) and in the total cohort (n=100).

CIN = chronic inflammatory neuropathy, NCS = nerve conduction studies, Ultrasound = nerve ultrasound

Table 7.3 Clinical characteristics

	CIDP/MMN/LSS Abnormal NCS (n=30)	CIDP/MMN/LSS Normal NCS (n=8)	P-value
Age in years (mean, SD)	56.5 (12.6)	58.6 (12.7)	0.67
Sex			
Male	23	8	0.31
Female	7	0	
Duration of symptoms in months (median, IQR)	33.0 (72.3)	24.0 (21.0)	0.74
Number of sites with nerve enlargement (median, IQR)	3.0 (3.0)	3.0 (1.8)	0.77
CSF protein			
Normal	3	0	0.58
Abnormal	10	3	
MRI brachial plexus			
Normal	7	3	0.66
Abnormal	6	5	
Clinical phenotype			
CIDP			
Classical	11	3	0.85
Pure motor	2	0	
Pure Sensory	3	1	
LSS	4	0	
MMN	10	4	
Anti-GM1 antibodies			
Absent	12	5	1.0
Present	1	1	

Clinical characteristics of 38 patients with a diagnosis of chronic inflammatory neuropathy; data are shown in number of patients unless stated otherwise.

CIDP = chronic inflammatory demyelinating polyneuropathy, Classical = classical phenotype of CIDP, IQR = interquartile range, LSS = Lewis Sumner syndrome, MMN = multifocal motor neuropathy, NCS = nerve conduction studies, Pure motor = pure motor phenotype of CIDP, Pure sensory = pure sensory phenotype of CIDP

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Table 7.4 Diagnostic accuracy of nerve ultrasound and NCS

	Nerve ultrasound	NCS
Test positive/total positive Sensitivity (%)	37/38 (97.4)	30/38 (78.9)
Test negative/total negative Specificity (%)	43/62 (69.4)	58/62 (93.5)
NPV (%)	97.7	87.9
PPV (%)	66.1	88.2

Diagnostic accuracy of nerve ultrasound and nerve conduction studies for the diagnosis of chronic inflammatory neuropathy.

NCS = nerve conduction studies, NPV= negative predictive value, PPV = positive predictive value
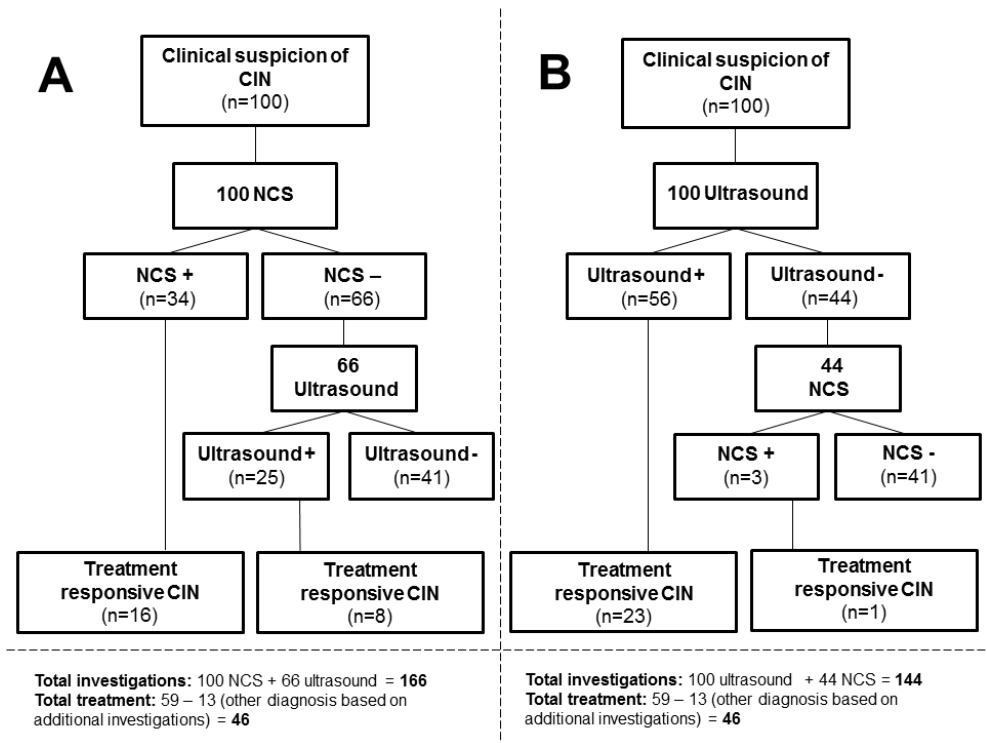

Figure 7.3 Possible diagnostic strategies of chronic inflammatory neuropathy

Possible diagnostic strategies based on a subset of patients with documented treatment response.

Strategy 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

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 work-up 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 AAN consensus criteria was a source of potential bias.[7,8,30] 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 eight 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.[21,22] 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 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 previously been described, which suggest 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

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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 cerebrospinal fluid, presence of anti-GM1 IgM antibodies) and to be similar to the rate of treatment response in patients with NCS abnormalities. Our sonographic protocol, has low inter-rater and inter-hospital 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 7.3**: Strategy B) for patients suspected of 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 labour intensive NCS and the burden to patients and may thus improve cost-effectiveness.

Our study also 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 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 were treated with abnormal nerve ultrasound, abnormal NCS or a combination of both. Another limitation was the difference in follow-up duration. Nevertheless, we followed all patients for at least one year. Lastly, the treating physician was free in his/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.

In conclusion, 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%.

SUPPLEMENTAL MATERIAL

Supplemental Table 7.1 Final diagnoses

	Inclusions (n=100)
Adult polyglucosan body disease	1
ALS	1
Axonal neuropathy, not CIAP	3
Benign muscle cramp fasciculation syndrome	1
Cervical radiculopathy	2
CIAP	12
CIAP in combination with mitochondrial neuromyopathy	1
CIDP	
Classical	14
Pure motor	2
Pure sensory	4
Working diagnosis; definition of treatment response not fulfilled; in analysis regarded as false positive (no chronic inflammatory neuropathy)	3
Distal myopathy	1
Functional disorder	1
Hirayama Syndrome	4
HNLPP	1
IgM-MGUS polyneuropathy	1
Immune-mediated polyradiculitis associated with Sjögren syndrome	1
LSS	4
Lumbar spinal stenosis	2
MMN	14
Multifocal axonal neuropathy associated with Crohn's disease	1
Neuralgic amyotrophy	1
Neurolymphomatosis	1
Post-infectious axonal polyneuropathy	1
PSMA	15
Post-Guillain Barre Syndrome	3
Ulnaropathy	1
Vasculitis	4

The final diagnoses of 100 patients in whom there is a clinical suspicion of chronic inflammatory neuropathy; data are shown as number of patients.

ALS = amyotrophic lateral sclerosis, CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, Classical = classical phenotype of CIDP, GBS = Guillain-Barré syndrome, HNLPP = hereditary neuropathy with liability to pressure palsies, MGUS = monoclonal gammopathy of undetermined significance, MMN = multifocal motor neuropathy, LSS = Lewis Sumner syndrome, PSMA = progressive spinal muscular atrophy, Pure motor = pure motor phenotype of CIDP, Pure sensory = pure sensory phenotype of CIDP

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Supplemental Table 7.2 Patient characteristics per subgroup

	Diagnosis	Clinical phenotype	EFNS/PNS NCS classification	Ultrasound	Supportive criteria CSF Protein	MRI brachial plexus	Anti-GM1	Comments
Group 1								
1	CIDP	Classical	Definite	+	+	NP	NP	
2	CIDP	Pure sensory	Definite	+	NP	NP	NP	
3	LSS		Possible	+	NP	-	NP	
4	MMN		Definite	+	+	+	-	
5	LSS		Possible	+	NP	-	NP	
6	LSS		Possible	+	NP	-	NP	
7	CIDP	Classical	Definite	+	+	NP	NP	
8	MMN		Definite	+	-	NP	-	
9	CIDP	Classical	Possible	+	NP	NP	NP	
10	MMN		Definite	+	+	NP	-	
11	MMN		Definite	+	NP	NP	-	
12	CIDP	Classical	Definite	+	NP	NP	NP	
13	CIDP	Classical	Definite	+	+	NP	NP	
14	LSS		Probable	+	-	-	NP	
15	CIDP	Pure sensory	Possible	+	+	-	NP	
16	CIDP	Classical	Definite	+	+	NP	NP	
17	MMN		Definite	+	NP	NP	-	
18	CIDP	Classical	Possible	+	NP	NP	NP	
19	CIDP	Pure sensory	Definite	+	NP	NP	NP	
20	MMN		Definite	+	NP	+	-	
21	CIDP	Pure motor	Definite	+	NP	+	-	

No.	Diagnosis	Type						Comment
22	CIDP	Classical	Definite	+	+	+	NP	
23	MMN		Definite	+	+	-	-	
24	CIDP	Classical	Definite	+	NP	NP	NP	
25	MMN		Probable	+	NP	NP	+	
26	MMN		Probable	+	NP	+	-	
27	CIDP	Classical	Definite	+	NP	NP	NP	
28	CIDP	Pure motor	Definite	+	NP	NP	NP	
29	CIDP	Classical	Possible	+	-	-	NP	
30	PSMA		Possible (proximal demyelination)	+	+	-	NP	Respiratory failure and no treatment response
31	IgM-MGUS PNP		Definite	+	NP	NP	NP	Diagnosis based on additional investigations
Group 2								
1	MMN		Probable	-	+	+	-	Respiratory failure and no treatment response
2	PSMA		Probable (CB of ulnar nerve at the shoulder)	-	+	NP	-	
3	PSMA		Possible (proximal demyelination)	-	+	+	NP	Respiratory failure and no treatment response
Group 4								
1	CIDP	Pure sensory	Negative	+	NP	-	NP	
2	CIDP	Classical	Negative	+	NP	+	NP	
3	MMN		Negative	+	+	+	-	
4	CIDP	Classical	Negative	+	+	+	NP	
5	MMN		Negative	+	+	+	-	
6	MMN		Negative	+	NP	-	+	
7	MMN		Negative	+	NP	-	-	

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Supplemental Table 7.2 continued

#	Diagnosis	Subtype						Comment
8	CIDP	Classical	Negative	+	NP	+	NP	
9	Working diagnosis CIDP	Pure sensory	Negative	+	+	+	NP	Loss to follow-up due to depression; second NCS 5 months after primary work-up: definite according to EFNS/PNS NCS criteria
10	Working diagnosis CIDP	Classical	Negative	+	+	NP	NP	Exacerbation COPD; deceased
11	Working diagnosis CIDP	Classical	Negative	+	+	+	NP	Decline due to cerebral infarction
12	PSMA		Negative	+	NP	+	NP	Respiratory failure and no treatment response
13	CIAP		Negative	+	NP	NP	NP	No treatment response; no progression without treatment
14	PSMA		Negative	+	NP	+	-	Respiratory failure and no treatment response
15	Functional disorder		Negative	+	NP	+	-	No treatment response and no objective weakness with repeated neurological examination
16	Status after GBS		Negative	+	+	-	NP	Symptoms resolved without treatment
17	Neuralgic amyotrophy		Negative	+	+	+	NP	Symptoms stable without treatment
18	Post-infectious axonal PNP		Negative	+	+	NP		Symptoms stable without treatment
19	CIAP		Negative	+	NP	NP		Symptoms stable without treatment
20	CIAP		Negative	+	+	-		No treatment; loss to follow-up
21	Vasculitis		Negative	+	NP	NP	NP	Diagnosis based on additional investigations
22	Cervical radiculopathy		Negative	+	NP	NP	NP	Diagnosis based on additional investigations
23	Mononeuropathy		Negative	+	+	NP	-	Diagnosis based on additional investigations
24	Vasculitis		Negative	+	+	NP	NP	Diagnosis based on additional investigations

		Lumbar radiculopathy	Negative	+	+	-	NP	Diagnosis based on additional investigations
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NA= not applicable, NP = not performed; "-" = normal test result, "+" = abnormal test result

Anti-GM1 = anti-GM1 antibodies, CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, CSF = cerebrospinal fluid, GBS = Guillain-Barre syndrome, MGUS = monoclonal gammopathy of undetermined significance, MMN = multifocal motor neuropathy, NCS = nerve conduction studies, PNP = polyneuropathy, PSMA = progressive spinal muscular atrophy, Ultrasound = nerve ultrasound

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Supplemental Table 7.3 Treatment response per subgroup

	Diagnosis	MRC sum score	RODS MCID	Vigorimetry right	Vigorimetry left	ODSS	ISS	HHD	Treatment response
Group 1									
1	CIDP	+9	-	+2	-24	-1	-3	-	+
2	CIDP	-2	-	-20	-5	-1	+3	NP	-
3	CIDP	-6	-	+15	+19	+4	+11	NP	-
4	MMN	-1	-	-12	-13	-3	NA	+	-
5	CIDP	-6	-	-7	+16	0	+5	NP	-
6	CIDP	-17	-	-82	-35	+1	NA	+	-
7	CIDP	+4	NP	+15	+50	NP	NA	NP	+
8	MMN	0	+	+32	+5	-1	NA	+	-
9	CIDP	+7	+	-2	-4	-3	-9	NP	+
10	MMN	-3	-	+8	+9	0	NA	+	-
11	MMN	+4	-	-9	-5	0	NA	NP	-
12	CIDP	+11	+	+57	+38	-3	0	NP	+
13	CIDP	+8	-	+12	+12	0	-4	NP	+
14	CIDP	+6	+	-25	+35	0	+1	+	+
15	CIDP	0	+	+8	+3	-1	-7	NP	-
16	CIDP	+69	+	+47	+46	-5	-10	NP	+
17	MMN	-1	-	-23	-5	-1	NA	+	-
18	CIDP	+6	-	0	-15	0	-8	NP	+
19	CIDP	NA	NA	NA	NA	NA	NA	NA	Loss to follow-up
20	MMN	+4	-	+80	+5	-1	NA	NP	+
21	CIDP	+50	+	+10	+10	-3	+1	NP	+
22	CIDP	+6	+	+25	+20	-6	-5	NP	+
23	MMN	+1	-	+8	+7	+1	NA	-	+
24	CIDP	+3	-	-12	-24	+1	-4	NP	+

	Diagnosis								
25	MMN	0	+	NP	NP	0	NA	NP	-
26	MMN	+13	+	+6	+6	-3	NA	+	+
27	CIDP	+21	-	+102	+94	-3	-17	NP	+
28	PSMA	-16	NA	NA	NA	NA	NA	-	-
Group 2									
1	MMN	+5	+	+7	+11	-1	NA	+	+
2	PSMA	-11	NA	NA	NA	NA	NA	-	-
3	PSMA	-4	NA	NA	NA	NA	NA	-	-
Group 4									
1	Working diagnosis CIDP	Max	NP	NP	NP	+1	0	-	-
2	Working diagnosis CIDP	+10	-	-11	0	0	NP	NP	-
3	Working diagnosis CIDP	+10	-	-15	-32	+1	+6	NP	-
4	PSMA	+1	NP	NP	NP	+1	NP	NP	-
5	CIAP	0	NP	-15	-10	0	+2	-	-
6	PSMA	-1	NP	NP	NP	NP	NP	-	-
7	Functional disorder	0	NP	NP	NP	NP	NP	-	-

NA = not applicable, NP = not performed, NT = not treated, "-" = no improvement or no response, "+" = improvement or response

CIAP = chronic idiopathic axonal polyneuropathy, 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, ODSS = Overall Disability Sum Score, PSMA = progressive spinal muscular atrophy, RODS = Rasch-built Overall Disability Scale, Treatment response = treatment response according to predefined criteria

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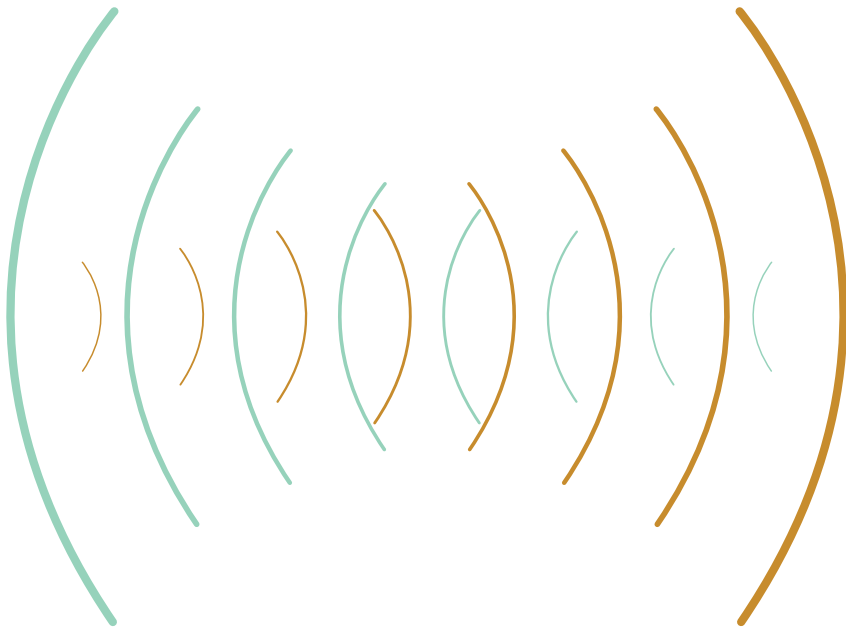
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CHAPTER 8

Nerve ultrasound for the diagnosis of chronic inflammatory neuropathy: a multicenter validation study

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ABSTRACT

Objective

To validate the diagnostic accuracy of a previously described short sonographic protocol to identify chronic inflammatory neuropathy (CIN), including chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis Sumner Syndrome (LSS) and multifocal motor neuropathy (MMN) and to determine the added value of nerve ultrasound to detect treatment-responsive patients compared to nerve conduction studies (NCS) in a prospective multicenter study.

Methods

We included 100 consecutive patients clinically suspected of CIN in three centers. The study protocol consisted of neurological examination, laboratory tests, NCS and nerve ultrasound. We validated a short sonographic protocol (median nerve at forearm and arm, and C5 nerve root) and determined its diagnostic accuracy using the EFNS/PNS criteria of CIDP/MMN (reference standard). In addition, to determine the added value of nerve ultrasound in detecting treatment-responsive patients, we used previously published diagnostic criteria based on clinical, NCS, sonographic findings and treatment response (alternative reference standard).

Results

Sensitivity and specificity of the sonographic protocol for CIN according to the reference standard were 87.4% and 67.3%, respectively. Sensitivity and specificity of this protocol according to the alternative reference standard were 84.6% and 72.8%, respectively, and of NCS 76.1% and 93.4%. With addition of nerve ultrasound 44 diagnoses of CIN were established compared to 33 diagnoses with NCS alone.

Conclusions

A short sonographic protocol shows high diagnostic accuracy for detecting CIN. Nerve ultrasound is able to detect up to 25% more patients who respond to treatment.

INTRODUCTION

Polyneuropathy is a spectrum of disorders with prevalences ranging from 800 to 3200/100.000 across ages.[1] Treatable chronic inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis Sumner Syndrome (LSS) and multifocal motor neuropathy (MMN) are much rarer (estimated prevalences ranging from 0.1 to 9.0/100.000).[2-5] Distinction of CIDP, LSS and MMN from the more common, predominantly axonal polyneuropathies is presently primarily achieved by nerve conduction studies (NCS).[6,7] However, NCS protocols designed to detect conduction blocks or other demyelinating features are time and labour intensive, and the sensitivity for proximal conduction failure is limited.[8-10]

Nerve ultrasound is a relatively recent diagnostic tool to identify patients with chronic inflammatory neuropathies.[11-13] We previously showed that a short sonographic protocol that consisted of five nerve sites along the median nerve and brachial plexus has a high sensitivity and specificity for discriminating CIDP, LSS and MMN from disease mimics.[14] This protocol showed good reproducibility between observers and hospitals, and improved detection of patients with treatment responsive inflammatory neuropathy that lacked the characteristic NCS abnormalities in a single center study.[15,16] To validate this sonographic protocol for use across different centers, we tested its performance in consecutive patients clinically suspected of chronic inflammatory neuropathy enrolled in three hospitals in The Netherlands. We also compared the diagnostic accuracy of nerve ultrasound to NCS and determined the added value of nerve ultrasound for detecting treatment-responsive patients who do not fulfil the NCS criteria of demyelination.[6,7]

METHODS

Study design and patients
This prospective cohort study was performed between January 2014 and January 2018 at two tertiary neuromuscular centers, i.e. the Amsterdam UMC (location Amsterdam Medical Center) and the Radboudumc Nijmegen, and one large teaching hospital, i.e. the Elisabeth-Tweesteden Hospital Tilburg (ETZ). The study was approved by the METC Brabant (NL42895.008.12) and all patients gave written informed consent.

In- and exclusion criteria have been published previously.[16] In summary, consecutive patients presenting at any of the (neuromuscular) outpatient clinics of the participating hospitals with a "clinical suspicion of a chronic inflammatory neuropathy" were eligible for inclusion (**Supplemental Figure 8.1**). Exclusion criteria were: 1) previous diagnosis of (and treatment for) polyneuropathy; 2) age <18 or >80; and 3) physical inability to undergo nerve ultrasound or NCS investigation. Diagnostic work-up consisted of a neurological examination, appropriate laboratory investigations, NCS and nerve ultrasound as described previously **(Supplemental Table 8.1)**.[16] Further investigations (e.g. MRI of the brachial plexus, antibody testing or lumbar

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puncture, as outlined in diagnostics standards) could be performed if thought necessary by the treating physician.

Nerve conduction studies

NCS were performed by experienced clinical neurophysiologists with a Synergy EDX (Amsterdam UMC, Radboudumc and ETZ) and Nicolet™ Viking EDX (ETZ). We used the NCS criteria of the EFNS/PNS to interpret NCS results for CIDP/LSS (definite/probable/possible) and MMN (definite conduction block, probable conduction block, no conduction block).[6,7] For the aim of this study, we considered NCS that met the 'definite/probable/possible' criteria for CIDP or the presence of at least one definite or probable conduction block in case of MMN as 'abnormal' and other outcomes as 'normal'.[16]

Nerve ultrasound

Nerve ultrasound was performed by experienced ultrasonographers. Investigations were performed using a Esaote MyLabTwice (Esaote, Genoa, Italy) with a 6 – 18 MHz linear-array transducer (LA435, for upper and lower extremity nerves, Amsterdam UMC and Radboudumc) and a 3 – 13 MHz linear-array transducer (LA533, for brachial plexus, Amsterdam UMC), and a Toshiba Xario XG (Toshiba, Tokyo, Japan) with a 7 – 18 MHz linear-array transducer (PLT-1204BT, ETZ). We used a previously published protocol in which nerve cross-sectional areas (CSA) were measured bilaterally within the hyperechoic rim at standardized sites. Enlargement was defined based on previously described cut-off values; uni- or bilateral nerve enlargement at ≥1 of the measured sites (median nerve at the forearm and arm, and C5, C6, and C7 nerve roots) was considered abnormal.[14] Because the inter-observer variability of C6 and C7 nerve roots measurement is relatively high, this may affect performance of the diagnostic protocol in a multicenter setting.[15] Therefore, we validated the protocol both with and without the inclusion of these nerve roots (sonographic protocols A (with inclusion of C6 and C7) and B (without C6 and C7) respectively) (**Supplemental Figure 8.2**).

Treatment

Physicians treated patients if they fulfilled the EFNS/PNS criteria for chronic inflammatory neuropathy or if they fulfilled the clinical criteria of the EFNS/PNS in combination with nerve enlargement, compatible with chronic inflammatory neuropathy, and if no other diagnosis was more likely. No standardized treatment schedule was used, but treatment consisted of immunoglobulins in case of MMN, of immunoglobulins or corticosteroids or a combination of both in LSS and CIDP; only in exceptional cases if patients did not improve after the first treatment regimen, plasmapheresis was considered. Treatment response was evaluated based on the discretion of the treating physician.

Diagnostic criteria and outcome measures

We assessed the diagnostic accuracy, i.e. sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), of both sonographic protocols using a diagnosis of CIDP/MMN according to the EFNS/PNS criteria as reference standard. In addition, we compared diagnostic accuracy of both sonographic protocols and NCS, using a previously described alternative reference standard that consisted of the clinical picture of CIDP and MMN according to the EFNS/PNS clinical criteria, in combination with an abnormal nerve ultrasound result as defined previously, and a positive response to treatment (**Supplemental Table 8.2**).[6,7,16] Based on these results we determined the additional value of nerve ultrasound in the identification of treatment-responsive patients that did not fulfil the NCS criteria for demyelination of the EFNS/PNS.

Statistics

Statistics were performed with SPSS 25 (SPSS Inc., Chicago IL, USA), and the R-library metafor version 1.9-9, Viechtbauer W, 2016). We used a mean (standard deviation (SD)) for normally distributed variables, a median (range) for non-normal distributed variables and n (%) for categorical variables to summarize data. We compared results from participating hospitals using a one-way ANOVA (Tukey HSD post hoc test) for normally distributed continuous variables, a Kruskal Wallis test (Mann-Whitney U post hoc test) for non-normal distributed continuous variables and the Chi-square test or Fisher's-exact for categorical variables. Results were considered significant when alpha was below 0.05.

To validate the previously described sonographic protocol, nerve ultrasound was coded as abnormal (1) or not (0), and a similar approach was used for patients with a diagnosis of chronic inflammatory neuropathy according to the reference standard (EFNS/PNS) (1) or not (0).

To determine the additional value of nerve ultrasound based on the alternative reference standard, both NCS and nerve ultrasound were coded as abnormal (1) or not (0) and a similar approach was used for patients with CIDP/LSS/MMN according to the alternative reference standard (1) or not (0). We calculated for both approaches the sensitivity and specificity, NPV and PPV from 2x2 tables. Results across centres were pooled using a random-effects meta-analysis. In case one of the cells contained a zero, a small constant (0.5) was added to each cell.[17]

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RESULTS

Baseline characteristics

We included a total of 100 patients with a clinical suspicion of chronic inflammatory neuropathy in three participating hospitals (Amsterdam UMC, Radboudumc and ETZ). Baseline characteristics of these patients are shown in **Table 8.1**. The number of included patients was evenly distributed among hospitals (Amsterdam UMC n=35, ETZ n=31, Radboudumc n=34). The specification of all diagnoses established in this cohort can be found in **Supplemental Table 8.3**.

Table 8.1 Baseline characteristics

	Total cohort (n=100)	Amsterdam UMC (n=35)	ETZ (n=31)	Radboudumc (n=34)	p-value
Sex					
Male	73	23	22	28	0.28
Female	27	12	9	6	
Age in years (mean, SD)	60.7 (12.6)	58.7 (13.5)	61.9 (10.9)	61.5 (13.1)	0.53
Disease duration in months (median, range)	15 (1-720)	18.0 (1-240)	6.0 (1-120)	28.5 (2-720)	<0.01
Clinical criteria set A					
Sensorimotor	42	14	16	11	0.02
Motor > sensory	14	1	6	7	
Pure motor	31	17	7	8	
Pure sensory	13	3	2	8	
Clinical criteria set B					
Asymmetrical complaints	55	26	15	14	0.02
Proximal weakness	33	18	11	4	<0.01
Areflexia	40	9	15	16	0.10
Sensory ataxia	7	1	2	4	0.34
Rapid progression	28	9	14	5	0.02
Postural tremor	6	3	0	3	0.27
Pain	30	7	11	12	0.28

Baseline characteristics of 100 patients with a clinical suspicion of a chronic inflammatory neuropathy. Data are stratified per hospital and shown as number of patients unless stated otherwise.

CSA of nerves

Mean values of nerve CSA at the sites included in the protocol are shown stratified per hospital in **Table 8.2**. Mean CSA of the C5, C6, and C7 nerve roots was higher in the Amsterdam UMC compared to the other hospitals (all *p*<0.001), while no other significant differences were found.

Diagnostic accuracy of nerve ultrasound according to the reference standard (EFNS/ PNS criteria)

In total 39 patients were diagnosed with a chronic inflammatory neuropathy according to the reference standard (CIDP n=24, MMN n=11, LSS n=4) of whom 33 patients fulfilled the NCS criteria of the EFNS/PNS. The pooled sensitivity and specificity of nerve ultrasound for the diagnosis of chronic inflammatory neuropathy were 96.4% and 40.0% respectively for sonographic protocol A, and 87.4% and 67.3% for sonographic protocol B (**Table 8.3**).

Table 8.2 Nerve cross sectional area (CSA) stratified per hospital

	Total cohort (n=100)	Amsterdam UMC (n=35)	ETZ (n=31)	Radboudumc (n=34)	P-value
Median nerve at forearm	7.0 (4-33)	8.0 (5-33)	8.0 (4-13)	7.0 (5-21)	0.11
Median nerve at arm	12.0 (6-44)	12.0 (9-42)	12.0 (6-19)	11.0 (6-44)	0.80
Nerve root C5	7.0 (1-33)	9.0 (5-33)	5.0 (2-14)	6.0 (1-20)	<0.01
Nerve root C6	7.0 (2-35)	13.0 (8-35)	4.0 (2-14)	5.0 (3-24)	<0.01
Nerve root C7	6.0 (1-44)	17.0 (11-44)	4.0 (2-14)	5.0 (1-24)	<0.01

Nerve size for different nerve points stratified per hospital; data are shown in median (range).

Table 8.3 Diagnostic accuracy of nerve ultrasound according to the reference standard (EFNS/PNS criteria)

	Amsterdam UMC		ETZ		Radboudumc		Total	
	A	B	A	B	A	B	A	B
Sensitivity test positive/total positive (%)	21/21 (100.0)	18/21 (85.7)	9/10 (90.0)	9/10 (90.0)	7/8 (87.5)	7/8 (87.5)	96.4%	87.4%
Specificity test negative/total negative (%)	0/14 (0.0)	9/14 (64.3)	13/21 (61.9)	14/21 (66.7)	15/26 (57.7)	18/26 (69.2)	40.0%	67.3%
NPV (%)	0.0	75.0	92.9	93.3	93.8	94.7	93.0	92.4
PPV (%)	60.0	78.3	52.9	56.3	38.9	46.7	52.4	62.3

Data are shown in number of patients (%).

A = sonographic protocol A, B = sonographic protocol B, NPV = negative predictive value, PPV = positive predictive value, Total = pooled data three hospitals

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Diagnostic accuracy of nerve ultrasound according to the alternative reference standard[16]

A diagnosis of chronic inflammatory neuropathy according to the alternative reference standard was established in 44 patients (CIDP n=29, MNN n=11, LSS n=4). The pooled sensitivity and specificity of nerve ultrasound for the diagnosis of chronic inflammatory neuropathy were 96.4% and 44.9%, respectively, for sonographic protocol A, and 84.6% and 72.8% for sonographic protocol B.The pooled sensitivity and specificity of NCS were 76.1% and 93.4%, respectively **Table 8.4 and Supplemental Table 8.2**).[16]

Table 8.4 Diagnostic accuracy of nerve ultrasound and NCS according to the previously described alternative reference standard[16]

	Amsterdam UMC			ETZ			Radboudumc			Total		
	A	B	NCS	A	B	NCS	A	B	NCS	A	B	NSC
Sensitivity test positive/total positive (%)	22/22 (100.0)	19/22 (86.4)	16/22 (72.7)	11/12 (91.7)	10/12 (83.3)	9/12 (75.0)	10/11 (90.9)	9/11 (81.8)	8/11 (72.7)	96.4%	84.6%	76.1%
Specificity test negative/total negative (%)	0/13 (0.0)	9/13 (69.2)	13/13 (100.0)	13/19 (68.4)	14/19 (73.7)	17/19 (89.5)	15/23 (65.2)	17/23 (73.9)	21/23 (91.3)	44.9%	72.8%	93.4%
NPV (%)	0.0	75.0	68.4	92.9	87.5	85.0	93.8	89.5	87.5	93.0	86.5	83.0
PPV (%)	62.9	82.6	100	64.7	66.7	81.8	55.6	60.0	80.0	61.5	72.4	90.5

Data are shown in number of patients (%).

A = sonographic protocol A, B = sonographic protocol B, NPV =negative predictive value, PPV = positive predictive value, Total = pooled data 3 hospitals (Amsterdam UMC, ETZ, Radboudumc)

Treatment response

Of the 37 patients with abnormal NCS results, 31 (83.7%) were treated (in the remaining 6 patients we either established another diagnosis than CIN (n=3), or complaints were mild (n=3)). Twenty-five patients (80.6%) responded to treatment. We treated 36 out of 53 (67.9%) patients with abnormal nerve ultrasound results. We established an alternative diagnosis (n=13), or complaints of CIN were mild (n=4). Thirty patients (83.3%) responded to treatment. **Figure 8.1** summarizes treatment response and classification according to the alternative reference standard.
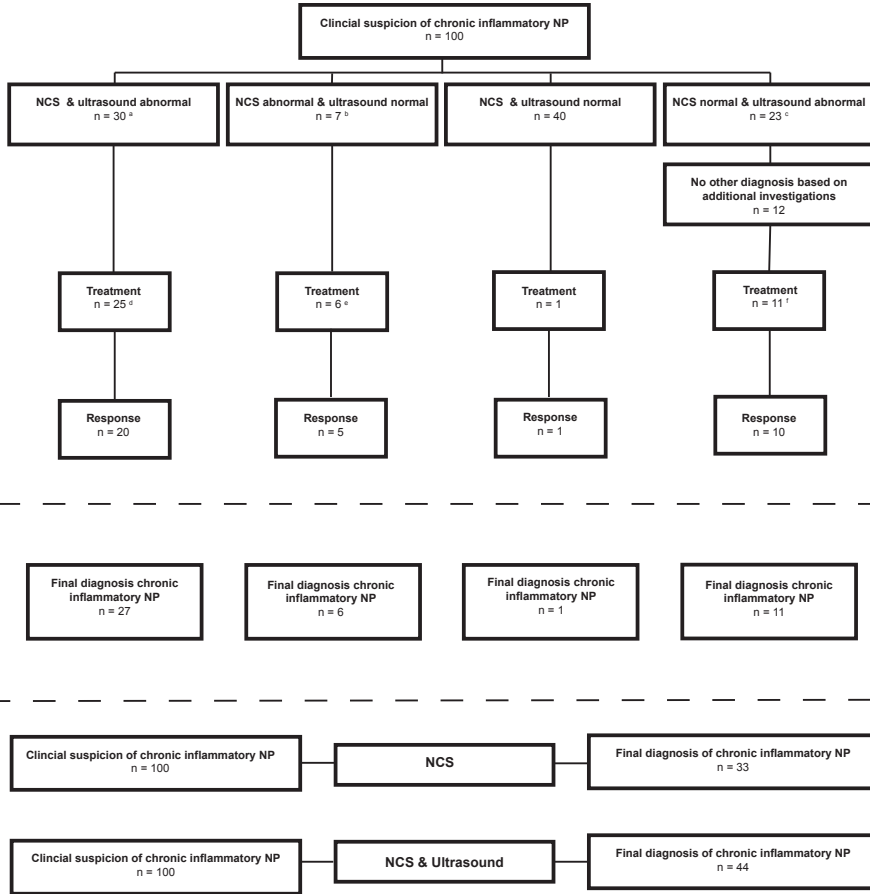
Figure 8.1 Flowchart study and treatment response

The diagnostic work-up, treatment response and final diagnoses established in the four subgroups based on results of nerve conduction studies and sonographic protocol B.

a = polyneuropathy of unknown origin, HMSN type 1, IgM MGUS neuropathy, b = mononeuritis multiplex, c = ALS, cervical radiculopathy, CIAP (n=2), critical illness polyneuropathy, HMSN type 2, IgM MGUS neuropathy, neuralgic amyotrophy, paraneoplastic demyelinating polyneuropathy, peripheral nerve demyelination in multiple sclerosis, progressive spinal muscular atrophy, vasculitis

Chronic inflammatory NP = chronic inflammatory neuropathy, NCS = nerve conduction studies

Additional value of nerve ultrasound compared to NCS

We identified 11 patients with normal NCS findings but abnormal nerve ultrasound findings who responded to treatment (CIDP n=5, MMN n=6). The added value of nerve ultrasound in identifying treatment-responsive chronic inflammatory neuropathies compared to NCS alone was therefore 25% (11 out of 44, 95% CI 13.2% to 40.3%), and showed little variance (from 20.0% to 27.0%) among hospitals (**Figure 8.2)**.
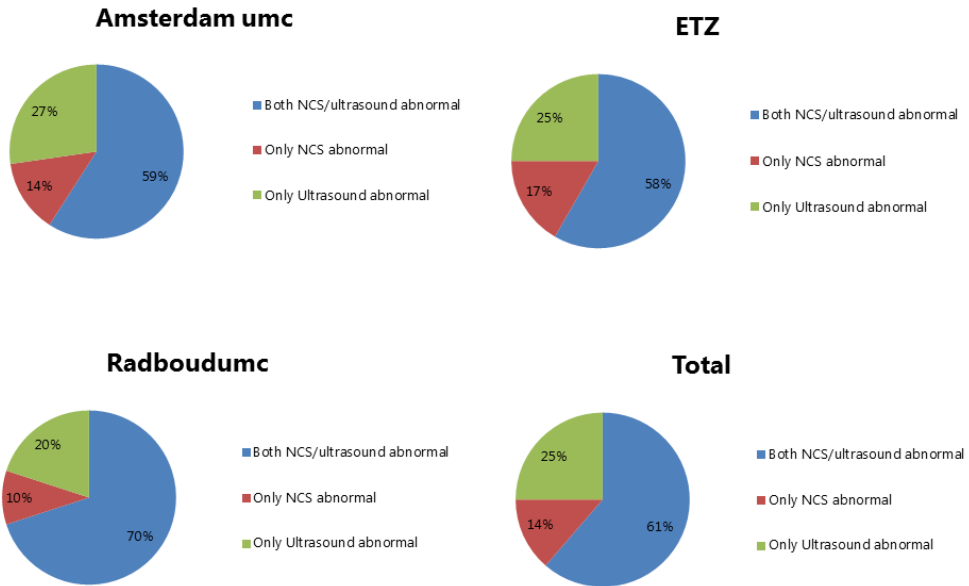

Figure 8.2 Additional value of nerve ultrasound per center and the total cohort

The distribution of the diagnoses of chronic inflammatory neuropathy established with abnormal NCS,abnormal nerve conduction studies or both in the three participating hospitals and in the total cohort.

NCS = nerve conduction studies, Ultrasound = nerve ultrasound

Possible diagnostic strategies

We developed two possible diagnostic strategies to identify all treatment-responsive patients with chronic inflammatory neuropathy based on the results of our study, in which either NCS (strategy A) or nerve ultrasound (strategy B) serves as a screening tool (**Figure 8.3**). In strategy B the number of NCS was reduced by 53%.
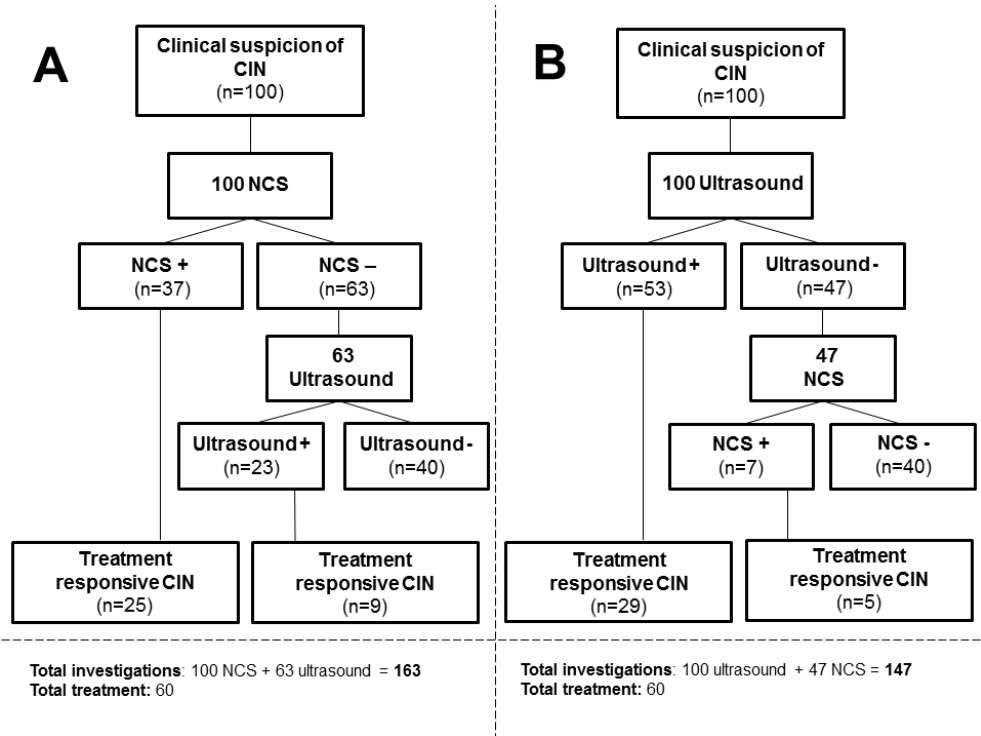
Figure 8.3 Possible diagnostic strategies

Possible diagnostic strategies based on a subset of patients with documented treatment response.
Strategy 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

DISCUSSION

We show that a short sonographic protocol has a high sensitivity, but a low specificity to identify patients with chronic inflammatory neuropathies in a multicenter study setting. Slight modification of the previously published protocol, i.e. exclusion of the technically more challenging assessment of spinal nerve roots that previously showed high inter-observer variability (protocol B), significantly improved specificity while sensitivity remained high. The diagnostic test characteristics of nerve ultrasound and NCS were complementary, with a high sensitivity of the former and high specificity of the latter. Nerve ultrasound, which has low burden for patients, relatively low-cost and low inter-observer variability, identified not only patients with

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an inflammatory neuropathy according to EFNS/PNS criteria, but also an additional 25% of patients with normal NCS results who responded to treatment.[15]

Previous studies exploring the usefulness of different nerve ultrasound protocols for the diagnosis of chronic inflammatory neuropathies reported high levels of sensitivity and specificity but lacked an unbiased approach by inclusion of patients with a clinical phenotype compatible with CIDP, LSS or MMN.[18,19] Prior to this study we developed a short nerve ultrasound protocol by ROC analysis in a cross-sectional study.[14] This protocol uses CSA of median nerve at arm and forearm and nerve roots bilaterally and is shorter than the more extensive protocols suggested by other authors.[15,20-22]. It showed good clinical performance in a prospective single-center study.[16] In this study that aimed at assessing performance in clinical practice across different hospitals, we found significantly larger nerve CSA of the brachial plexus in the Amsterdam UMC compared to the other hospitals which is in line with our previous findings of higher inter-observer variability in nerve roots C6 and C7,[15] but the slightly modified protocol (B) showed high diagnostic accuracy to identify patients with chronic inflammatory neuropathy. These findings show that this nerve ultrasound protocol is useful in clinical practice.

In accordance with two previous studies we found that nerve ultrasound improves detection of patients with a treatment responsive inflammatory neuropathy but without characteristic NCS abnormalities.[16,23] The additional yield was approximately 25% across centres. Patients with normal NCS but abnormal nerve ultrasound results who responded to treatment were found in all hospitals, making the possibility of physician or hospital-based bias less likely. The available evidence strongly suggests that sensitivity of nerve ultrasound exceeds that of NCS, whilst for specificity the opposite is true.[16] Therefore, in future diagnostic strategies nerve ultrasound should ideally be applied as screening test (**Figure 8.3:** Strategy B), followed by NCS to identify potentially treatment responsive patients without sonographic abnormalities, or in case of no treatment response to further confirm the diagnosis. Abnormal nerve ultrasound but normal NCS results have a higher likelihood of false positivity. Therefore, a definite diagnosis of chronic inflammatory neuropathy would require both high clinical suspicion and an objective response to treatment. This approach would have multiple advantages, amongst others a decrease in the number of patients that need to undergo NCS by 53% and improved detection of treatment-responsive patients. However, local availability of techniques and considerations of cost-effectiveness, in particular the use of high cost of treatment trials with IVIg, will probably shape diagnostic approaches in the future. Nerve ultrasound could be introduced as a complementary technique to routine NCS in patients with a clinical suspicion of chronic inflammatory neuropathy. Nerve ultrasound should not replace NCS since NCS since their test characteristics differ, but given the large group of treatment-responsive patients that were identified by nerve ultrasound alone, NCS should not remain the sole diagnostic technique for chronic inflammatory neuropathy either.

Our study has some limitations. Logistic limitations (such as only one physician able to perform NCS and nerve ultrasound) precluded blinding in all cases in one of the participating centers.

However, in the large majority of investigations (i.e. 93 %), investigators were blinded for NCS results. NCS protocols slightly differed between hospitals, but this reflects clinical practice and all NCS were evaluated following the EFNS/PNS NCS criteria. Nerve ultrasound was performed on different sonography devices, but we previously found that this did not cause significant variability.[15] Treatment response was defined by the treating physician, which may have led to some overestimation of the success rate.

Strengths are the prospective design that mimics clinical practice (i.e. inclusion of patients with a clinical suspicion of chronic inflammatory neuropathy rather than patients with an already confirmed diagnosis). Our findings also corroborate our previous single center study findings that nerve ultrasound has an added value of approximately 25% for the detection of treatment-responsive chronic inflammatory neuropathy.[16] The data support the use of this sonographic protocol in the diagnostic workup of patients who might have CIDP, LSS or MMN.

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SUPPLEMENTAL MATERIAL

Supplemental Table 8.1 Specification of diagnostic work-up

Modality	Description
MRC score	Bilateral measurement of motor function of:
	Abduction of the arm
	Flexion and extension of the forearm and wrist
	Spreading of the fingers
	Abduction of the thumb
	Flexion of the hip
	Flexion and extension of the ankle and foot
	Eversion of the foot
	Extension of the hallux
	MRC sum score: 0-140 points
ISS	INCAT Sensory Sum Score Measurement of gnostic and vital sensibility in arms and legs[26]
Vigorimetry	Bilateral measurement of grip strength in Kilopascals (kPa) with the Martin Vigorimeter (Martin Medizintechnik, Tuttlingen, Germany)
RODS	Rasch-built Overall Disability Scale Standardized questionnaire for CIDP or MMN (depending on clinical phenotype)[27, 28]
INCAT ODSS	INCAT Overall Disability Sum Score Standardized questionnaire[29]
Laboratory investigations	To exclude other causes of polyneuropathy:
	Kidney, liver, and thyroid function
	Glucose
	Vitamins
	Complete blood count
	Protein spectrum
NCS	Amsterdam UMC
	Bilateral evaluation of demyelination and axonal loss in:
	Median and ulnar nerves (recordings from hand muscles)
	Musculocutaneous nerve (recordings from biceps)
	Radial nerve (recordings from forearm)
	Fibular and tibial nerves (recordings from foot muscles)
	Sural nerve
	If not yet fulfilling the criteria and negative peak CMAP amplitude < 1 mV:
	Median nerve (recordings from forearm muscles)
	ETZ/Radboudumc
	Bilateral evaluation of demyelination and axonal loss in:
	Median and ulnar nerves (recordings from hand muscles) Fibular and tibial nerves (recordings from foot muscles)
	Sural nerve

Nerve ultrasound	Bilateral measurement of cross sectional area (CSA) of:
	Median nerve at the forearm and arm
	Nerve roots C5, C6, and C7 at the interscalene level
	Cut-off values for nerve enlargement:
	Median nerve at the forearm $>$10 mm^2
	Median nerve at the arm $>$13 mm^2
	Nerve roots C5,C6, or C7 $>$8 mm^2

MRC = medical research council, NCS = nerve conduction studies

Supplemental Table 8.2 Diagnostic criteria of chronic inflammatory neuropathy[16]

Criteria	Definition
1	A clinical phenotype fitting the EFNS/PNS clinical criteria for CIDP/MMN in combination with
2	A clinical course fitting CIDP/MMN during 1 year follow-up period, and with either
3 a	NCS in accordance with the respective EFNS/PNS criteria **or,**
3 b	Abnormal nerve ultrasound as defined previously in combination with treatment response

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Supplemental Table 8.3 Diagnoses established in the cohort of 100 patients with a clinical suspicion of a chronic inflammatory neuropathy

Diagnoses	Multicenter cohort (n=100)
ALS	3
Axonal neuropathy, not CIAP	10
BSCL2 mutation associated peripheral nerve demyelination in MS; Silver syndrome	1
Cervical radiculopathy	1
CIAP	8
CIDP: EFNS/PNS criteria fulfilled	24
CIDP: EFNS/PNS criteria not fulfilled	6
Critical illness polyneuropathy	1
HMSN type 1	1
HMSN type 2	4
HNLPP	1
IgM-MGUS polyneuropathy	2
Immune mediated polyradiculitis associated with Sjögren syndrome	1
LSS	4
MMN: EFNS/PNS criteria fulfilled with abnormal NCS	5
MMN: EFNS/PNS criteria fulfilled with normal NCS	6
Mononeuritis multiplex	1
Multiple compression neuropathies, no genetic diagnosis	2
Neuralgic amyotrophy	5
Neurosarcoidosis	1
Paraneoplastic demyelinating polyneuropathy	1
Peripheral nerve demyelination in multiple sclerosis	1
PNP of unknown origin (no CIDP/MMN); loss to follow-up	1
PSMA	5
Small fiber neuropathy	1
Spinal muscular atrophy	2
Vasculitis	2

ALS = amyotrophic lateral sclerosis, CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, HMSN = Hereditary Motor and Sensory Neuropathy, HNLPP = Hereditary Neuropathy with Liability to Pressure Palsies, MGUS = Monoclonal Gammopathy of Undetermined Significance, MMN = multifocal motor neuropathy, MS = multiple sclerosis, PSMA = progressive spinal muscular atrophy

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┌────────────────────────────────────────────────┐
│        Chronic or subacute polyneuropathy       │
│            (complaints ≥ 6 weeks)               │
└────────────────────────────────────────────────┘

┌──────────────────┐   ┌──────────────────┐   ┌──────────────────┐
│  Sensorimotor +  │   │ Motor > Sensory +│   │ Pure motor/sensory +│
│  ≥2 criteria of B│   │  ≥1 criteria of B│   │  ≥1 criteria of B │
└──────────────────┘   └──────────────────┘   └──────────────────┘

            ┌────────────────────────────────────┐
            │             Criteria B             │
            └────────────────────────────────────┘

┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐
│ Proximal │ │Asymmetric│ │Areflexia │ │Sensory   │ │  Rapid   │ │Postural  │ │  Pain    │
│ weakness │ │involvement│ │          │ │ataxia    │ │progression│ │Tremor   │ │(symmetric/│
│          │ │          │ │          │ │          │ │          │ │          │ │multifocal)│
└──────────┘ └──────────┘ └──────────┘ └──────────┘ └──────────┘ └──────────┘ └──────────┘
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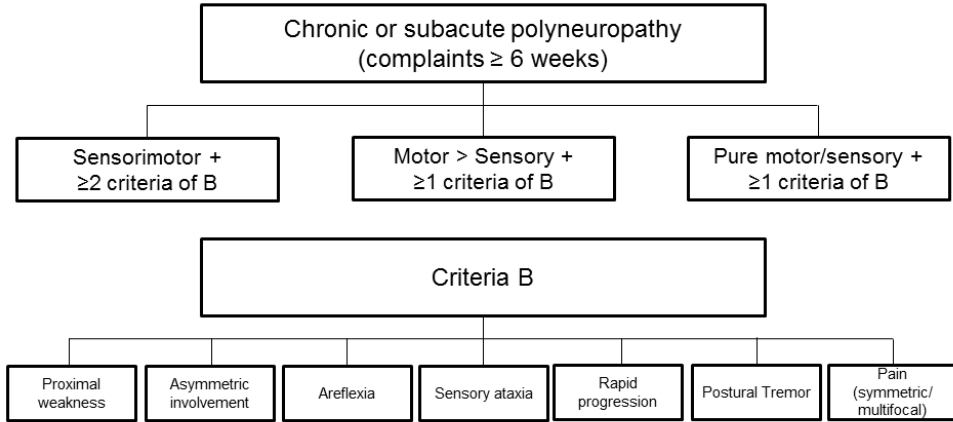
Supplemental Figure 8.1 Definition of clinical suspicion of a chronic inflammatory neuropathy
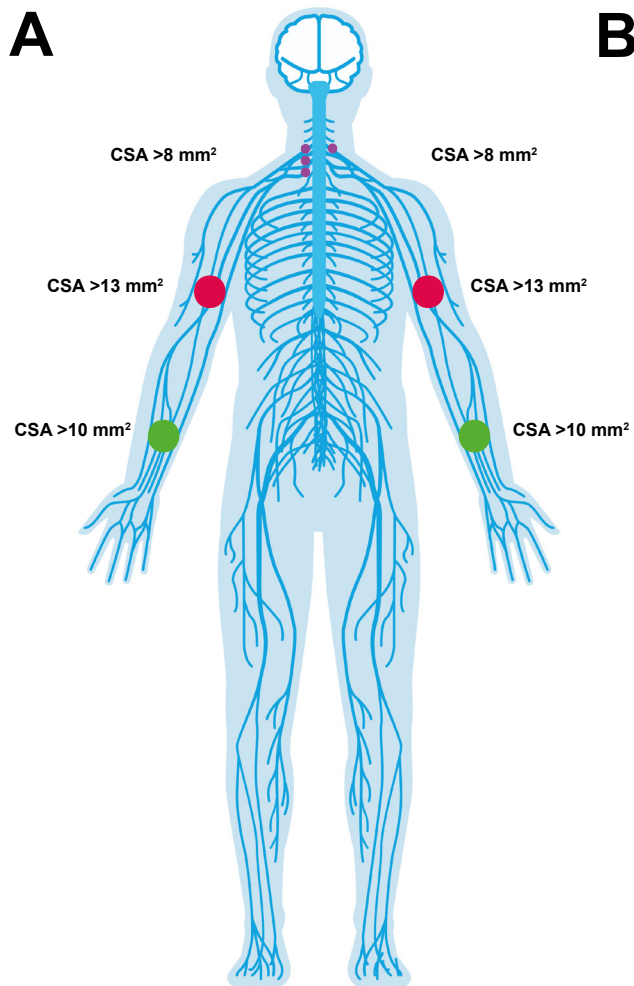
Supplemental Figure 8.2 Sonographic protocols

Sonographic protocol A (left side of the figure; median nerve forearm, upper arm and C5, C6 and C7. Sonographic protocol B (right side of the figure); median nerve forearm, upper arm and C5.

CSA = cross sectional area

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CHAPTER 9

Natural history of multifocal motor neuropathy

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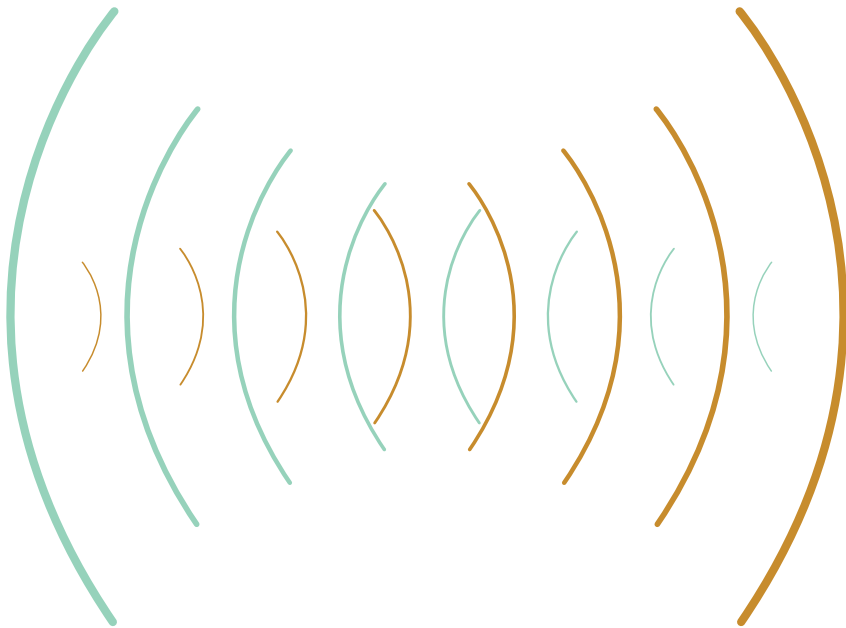
ABSTRACT

Objective
To assess the natural history of multifocal motor neuropathy (MMN) in a large cohort of patients and to identify predictive factors of a progressive disease course.

Methods
Between May 2015 and February 2016, we collected clinical data from 100 patients with MMN of whom 60 had participated in a nationwide cross-sectional cohort study in 2007. We documented clinical characteristics using standardized questionnaires and performed a standardized neurological examination. We used multiple linear regression analysis to identify factors that correlated with worse outcome.

Results
We found that age of diagnosis (45.2 *vs.* 48.6 years, $p<0.02$) significantly increased between 2007 and 2015-2016 with a reduction of the diagnostic delay (42.0 *vs.* 27.0 months, $p = 0.10$). Seven out of ten outcome measures deteriorated over time (all $p<0.01$). Patients, who had a lower MRC sum score and absence of reflexes at the baseline visit showed a greater functional loss at follow up ($p=0.016$ and $p=0.007$).

Conclusions
MMN is a progressive disease. Although 87% of patients received maintenance treatment, muscle strength, reflexes, vibration sense, and the Self-Evaluation Scale significantly deteriorated over time. Lower MRC sum score and absence of reflexes predicted a more progressive disease course.

INTRODUCTION

Multifocal motor neuropathy (MMN) is a slowly progressive pure motor disorder characterized by asymmetric distal weakness that predominates in the hands, the absence of upper motor neuron signs and presence of one or more abnormal ancillary investigations, i.e. abnormal nerve conduction or conduction block, thickening or T2 hyperintensity on MRI of the brachial plexus, sonographic nerve thickening, mildly increased protein content in the cerebrospinal fluid or the presence of anti-GM1 IgM antibodies in serum.[1-7] Administration of intravenous or subcutaneous immunoglobulins improves muscle strength, but only transiently and maintenance treatment is therefore needed.[4,8-10]

Consensus criteria have facilitated diagnosis of MMN and shortened diagnostic delays, but we know less of its longer-term disease course and outcome.[4] Early case reports suggested that its course is not benign, but few studies have longitudinally addressed the natural history of MMN.[11-13] Early treatment may improve long-term outcome, but accumulating axonal damage nevertheless results in significant disability in up to one fifth of patients.[4,14] More insight in MMN's natural history would help to identify correlates of worse outcome and thereby patients at higher risk for developing severe deficits, and eventually to investigate efficacy of other treatment approaches.

We have previously reported the characteristics of a relatively large cross sectional cohort of patients with MMN in The Netherlands.[4] In order to gain more insight in natural history of MMN, we performed a combined cross-sectional and follow-up study in a cohort of 100 patients with the aim to identify factors that predict a progressive disease course of MMN.

METHODS

Study design and patients

This cross-sectional cohort study was performed between May 2015 and February 2016 in the UMC Utrecht, a large tertiary referral center for neuromuscular disorders in The Netherlands. We invited all patients listed in the MMN database of the UMC Utrecht who met the following inclusion criteria: 1) a diagnosis of definite, probable or possible MMN according to the EFNS/PNS criteria and 2) age ≥18 years.[7] A subgroup of our patients previously participated in a similar cross-sectional cohort study in 2007.[4]

Neurological examination and questionnaires

We documented clinical characteristics of patients with MMN (including but not limited to site of onset and age at symptom onset) using a standardized questionnaire and collected the Overall Disability Sum Score (ODSS), the Self-Evaluation Scale (SES), the Rasch-built Overall Disability Score for MMN (MMN-RODS) and the Fatigue Severity Scale (FSS).[15-20] All patients underwent a standardized neurological examination (**Supplemental Table 9.1**).[4] This consisted of bilateral

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grading of motor function of 18 muscle groups using the Medical Research Council (MRC) scale to calculate the MRC sum score with a maximum of 180 points. Sensory function was tested using a Rydell-Seiffer tuning fork to assess vibration sense in arms and legs bilaterally. Vibration sense was graded from normal (grade 0) to abnormal at the acromioclavicular joint or anterior superior iliac spine (grade 4).[4,21] Tendon reflexes of biceps, triceps, knee and ankle were performed on both sides and scored as normal, brisk or absent. We used data obtained during a previous study in 2007 as baseline data.[4] To minimize inter-observer variability, one of the authors (EAC) who collected clinical data during the 2007 study[4] trained the author (BAJ) who performed the clinical examination in 2015-2016, with special emphasis on the interpretation of MRC and Rydell-Seiffer scales.

Nerve conduction studies and other ancillary investigations

One of the authors (HSG), who has extensive experience in clinical neurophysiology, evaluated available nerve conduction study results using the EFNS/PNS criteria for conduction block and other abnormalities.[7] We defined axonal loss as a decreased distal CMAP (distal CMAP amplitude below the lower limit of normal) in ≥1 nerves, including the median, ulnar, radial, musculocutaneous, peroneal, and tibial nerves.[4,22,23] We also collected all available results of laboratory studies (in particular the presence of anti-GM1 IgM antibodies in serum and analysis of cerebrospinal fluid) and of MRI of the brachial plexus.

Statistical analyses

MMN cohort data

We stratified the MMN patients into two groups; (1) patients diagnosed before 2007 our previous study and (2) after 2007, to explore differences in clinical characteristics.[4] Depending on the distribution of the variable, we compared groups using the Mann-Whitney U test (for continuous data) and the χ^2 test (for categorical data). To account for right skew in time-related covariates, we log-transformed (natural) duration of treatment, months untreated and time to diagnosis. Univariate linear regression analyses were performed to identify changes in clinical characteristics over calendar time. Dependent variables were age at diagnosis, time to diagnosis (log-transformed) and age at onset of symptoms. The independent variable was the year of diagnosis. Subsequently, we calculated the mean MRC score per muscle group for patients with longer and shorter disease duration (defined as equal to or larger than the median disease duration). We corrected the obtained p-values for multiple testing using the Benjamini Hochberg method. Multiple linear regression analysis was used with backward elimination based on p-value selection to predict the MRC sum score 2015-2016 based on sex, symptom onset in a leg, presence of anti-GM1 IgM antibodies, FSS (0-63), duration of treatment in months (log-transformed), months untreated (log-transformed) and age at onset of symptoms in years.

Longitudinal follow-up data

The mean yearly rate of decline of each outcome measure was estimated between visit 1 (2007) and visit 2 (2015-2016) and tested using a one-sample t-test (i.e. assessing whether the yearly rate of decline is other than zero). Multiple linear regression analysis was performed with backward elimination based on *p*-value selection to predict the yearly rate of decline in MRC sum score based on sex, presence of anti-GM1 IgM antibodies, symptom onset in leg, months untreated (log-transformed), age at onset of symptoms in years, ODSS (0-8), MRC sum score (0-180) and sum score of reflexes (0-8). The last three variables were analysed with data of the first visit (2007).

Standard protocol approvals, registrations and patient consent

The local medical ethics committee of the UMC Utrecht approved the research protocol (NL50354.041.14). All included patients gave written informed consent.

RESULTS

We identified a total of 142 patients with MMN. Hundred patients (70.4%) agreed to participate of whom 60 patients previously participated in a nationwide cross sectional cohort study in 2007.[4] Reasons for not participating are shown in **Figure 9.1**.

Clinical characteristics

Patient characteristics (sex, age at onset of symptoms, MMN diagnosis according to EFNS/PNS criteria and additional investigations i.e. NCS, MRI brachial plexus, CSF protein and presence of anti-GM1 IgM antibodies) between participants (n=100) and non-participants (n=42), were not significantly different, except for the onset of muscle weakness (*p*=0.04). Median age at onset of symptoms and age of diagnosis were significantly higher in patients diagnosed after 2007 (*p*<0.01 and *p*=0.02; **Table 9.1**). We performed univariate linear regression analysis with year of diagnosis as independent variable. Both median age at onset of symptoms and median age of diagnosis significantly increased over time (both *p*<0.01) (**Figure 9.2**). Median time from symptom onset to diagnosis (i.e. diagnostic delay) decreased over time (6.4 years (range 1-27) in period 1996 to 2000; 1,8 years (range 1-29) in period 2011-2015) but was significantly longer for patients with onset of symptoms in leg and for patients with higher age at diagnosis (*p*=0.01, *p* <0.01). The starting dose of immunoglobulins per week was significantly higher for patients diagnosed before 2007 (*p*<0.01), probably due to a different treatment regime with repeated loading doses of immunoglobulins in the period before 1995 rather than lower-dosed weekly to monthly maintenance therapy. No significant differences in clinical characteristics between males and females were found.

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Table 9.1 Clinical characteristics

	Diagnosis before 2007 (n=64)	Diagnosis in or after 2007 (n=36)	p-value
Male	46 (72)	29 (81)	0.34
Age at symptom onset	40.3 (21.4-53.8)	45.2 (30.1-67.2)	<0.01
Age of diagnosis	45.2 (25.2-71.1)	48.6 (30.9-73.5)	0.02
Time to diagnosis (months)[a]	42.0 (3.0-433.0)	27.0 (6.0-345.0)	0.10
Time from disease onset until treatment (months)	42.0 (3.0-435.9)	27.5 (3.9-346.0)	0.09
Maintenance treatment immunoglobulins	55 (86)	32 (89)	0.67
Starting maintenance therapy IVIg per week (gram)	10.0 (5.0-33.0)	8.0 (4.0-12.0)	<0.01
Onset of muscle weakness			
Distal arm	41 (64)	25 (70)	0.08
Proximal arm	3 (4)	3 (8)	
Distal leg	18 (28)	4 (11)	
Proximal leg	1 (2)	-	
Distal symmetrical	1 (2)	4 (11)	
Number of affected limbs at inclusion			
0	2 (3)	1 (3)	0.15
1	7 (11)	8 (22)	
2	12 (19)	12 (33)	
3	18 (28)	7 (20)	
4	25 (39)	8 (22)	
Electrophysiological criteria according to EFNS/PNS criteria			
Definite	45 (70)	29 (81)	0.32
Probable	15 (23)	4 (11)	
Negative	4 (6)	3 (8)	
NCS with axonal degeneration	31 (48)	13 (36)	0.23
MRI abnormalities brachial plexus	22/43 (51)	8/17 (47)	0.77
Laboratory: increased CSF protein	12/16 (75)	8/10 (80)	0.77
Anti-GM1 IgM antibodies	38/61 (62)	17/29 (59)	0.74
MMN diagnosis according to EFNS/PNS criteria			
Definite	45 (70)	29 (81)	0.32
Probable	15 (24)	4 (11)	
Possible	4 (6)	3 (8)	

Data are shown in median (range) or number of patients (%), unless stated otherwise.

[a] log transformed variable

Anti-GM1 IgM antibodies = presence of anti-GM1 IgM antibodies, IVIg = intravenous immunoglobulins
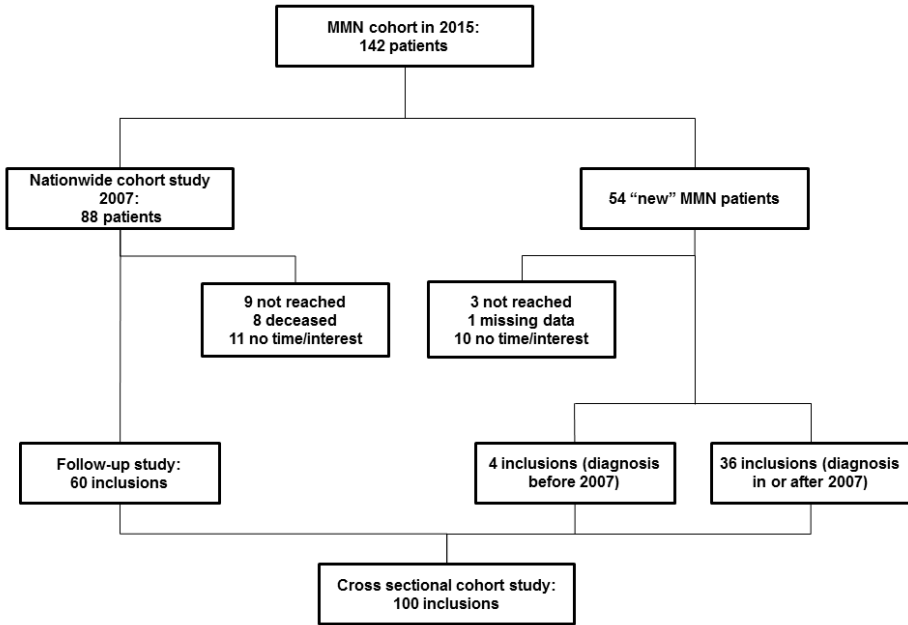
Figure 9.1 Flowchart of study

We included 100 patient of whom 60 patients previously participated in a nationwide cross sectional cohort study in 2007.[4]
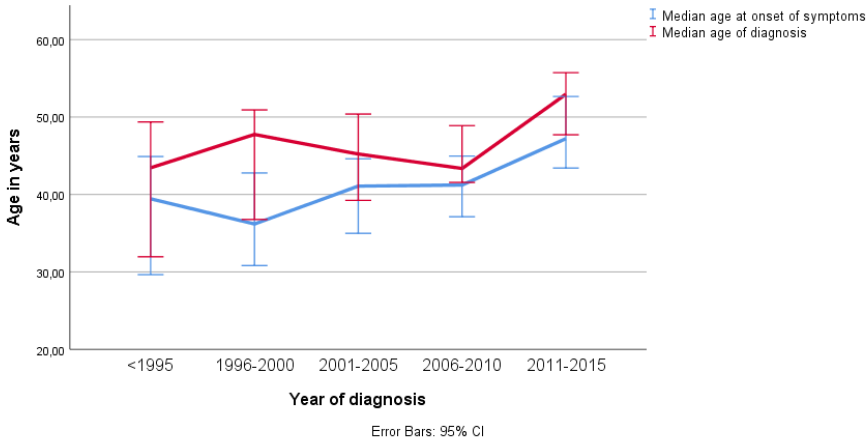
MMN = multifocal motor neuropathy

Figure 9.2 Clinical characteristics over time

The median age at onset of symptoms and median age of diagnosis over time.

95% CI = 95% confidence interval

Weakness, sensory function and tendon reflexes

The distribution of muscle weakness was distal more than proximal and more pronounced in hand than in foot or lower leg muscles (**Supplemental Table 9.2**). Finger flexion and plantar foot flexion were relatively spared compared to hand and finger extension and dorsal foot flexion. Patients with longer disease duration had significantly more weakness in hand and lower leg/foot muscles compared to patients with shorter disease duration (all $p<0.05$) (**Figure 9.3, Supplemental Table 9.2**).

We found abnormal vibration sense on the toes in 57 patients (57.6%). Median disease duration was longer in these patients compared to those without sensory symptoms (median 16.1 years, range (1.3-46.5) versus 11.5 range (1.9-30.5); $p=0.03$). At least one absent reflex was found in 63 patients (63.6%) and generalized areflexia in 16 patients (16.2 %) (**Supplemental Table 9.3**).
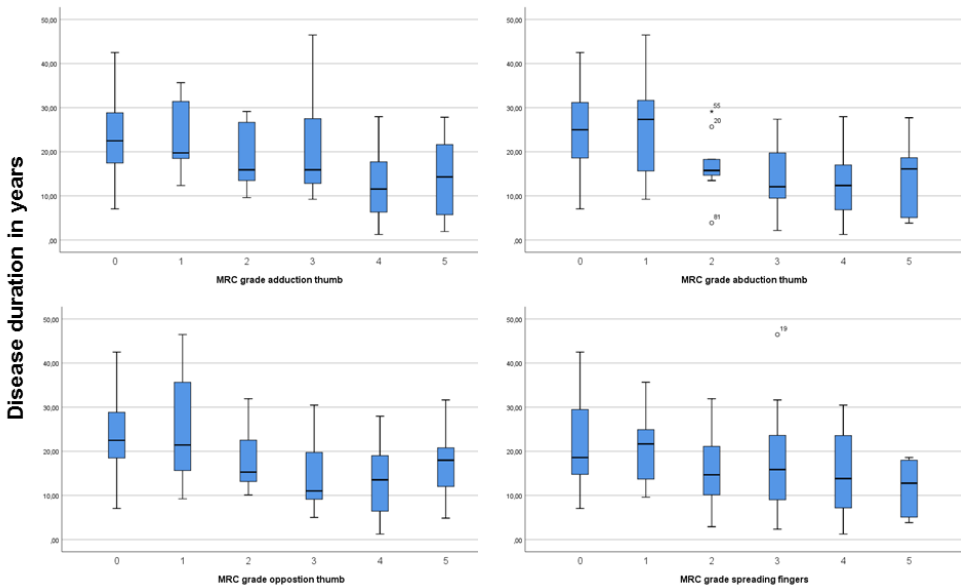
Figure 9.3 Correlation of MRC grade and disease duration per muscle group

The boxplots provide the variability in disease duration per MRC grade (0-5).

MRC grade = Medical Research Council grade of weakest side

Nerve conduction studies and laboratory investigations

One or more definite conduction blocks were detected in 74 patients (74.0%), a probable conduction block only in 19 patients (19.0%) and no conduction block in 7 patients (7.0%).[7] Of the 7 patients without conduction block, 4 patients (57.1%) had elevated anti-GM1 IgM antibodies titers, 2 patients (28.6%) had mildly increased CSF protein, 3 patients (42.9%) had an abnormal MRI of the brachial plexus and all showed response to immunoglobulin therapy. Axonal damage was found in 44 patients (44.0%) and presence of anti-GM1 IgM antibodies in 55/90 patients (61.1%).

Disability questionnaires

Results of the disability questionnaires are shown in **Supplemental Table 9.3**. Median ODSS of the arms was 2 (range 0-4), of the legs 1 (range 0-5) and of arms and legs combined 3 (range 0-8). Twelve patients (12.1%) reported no disability of the arms and 34 patients (34.7%) did not experience disability of the legs.

Correlates of outcome

Results from multiple linear regression analysis are summarized in **Table 9.2**. Lower MRC sum score correlated with longer disease duration without treatment, presence of anti-GM1 IgM antibodies and lower age at onset of symptoms ($p=0.024$, $p=0.046$ and $p=0.006$).

Outcome measures over time

Mean differences between visit 1 (2007) and visit 2 (2015-2016) of different outcome measures are shown in **Table 9.3**. Except for ODSS, FSS and vigorimetry of the left hand, all outcome measures deteriorated over time (all $p<0.01$).

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Table 9.2 Multiple linear regression analysis for determinants of weakness

Variable	Model 1		Model 2		Model 3		Model 4		Model 5		
	RC	SE	RC	SE	RC	SE	RC	SE	RC	SE	95% CI
Anti-GM1 antibodies	-10.87	5.27[b]	-10.68	5.17[b]	-10.81	5.18[b]	-11.10	5.20[b]	-10.65	5.24[b]	[-21.2,-0.21]
Sex	7.29	6.19	7.12	6.10							
Symptom onset leg	-8.52	6.32	-8.51	6.28	-8.98	6.28	-9.75	6.28			
Age at onset of Symptoms	0.44	0.34	0.45	0.34	0.51	0.33	0.67	0.31[b]	0.832	0.30[c]	[0.24,1.42]
Months untreated[a]	-4.65	2.53	-4.55	2.47	-4.85	2.46	-5.09	2.47[b]	-5.69	2.46[b]	[-10.6,-0.79]
Duration of treatment[a]	-4.55	2.98	-4.49	2.94	-3.68	2.87					
FSS	-0.04	0.17									
Adjusted R^2	0.21		0.22		0.22		0.21		0.19		

The results of multiple linear regression analyses to predict the MRC sum score 2015-2016 based on anti-GM1 IgM antibodies (presence=1, absence=0), sex (male=0, female=1), symptom onset in a leg (arm=0, leg=1), age at symptom onset in years, months untreated (log-transformed), duration of treatment in months (log-transformed) and FSS (0-63).

The models show the different steps of the backward selection. In model 1 all independent factors were included and in model 5 only the independent factors that were significantly associated with a lower MRC sum score.

[a] log transformed variable, [b] $p < 0.05$, [c] $p < 0.01$

FSS = Fatigue Severity Scale, RC = regression coefficient, SE = standard error, 95% CI =95% confidence interval

Table 9.3 Outcome measures over time

	Mean difference per year	**95% CI**	*p*-value
ODSS	-0.004	[0.03, -0.04]	0.81
MRC sum score	-1.361	[-0.97, -1.75]	<0.01
SES	0.352	[0.54, 0.16]	<0.01
FSS	-0.94	[-0.25, -1.63]	<0.01
Vibration sense	0.121	[0.15, 0.09]	<0.01
Reflexes arm	-0.055	[-0.02,-0.09]	<0.01
Reflexes leg	-0.072	[-0.03, -0.11]	<0.01
Reflexes sumscore	-0.121	[-0.06, -0.18]	<0.01
Grip strength right	-1.127	[-0.39, -1.87]	<0.01
Grip strength left	-0.770	[0.04, -1.58]	0.06

Mean difference per year was calculated as the difference between visit 1 (2007) and visit 2 (2015-2016) divided by the follow-up duration.

FSS = Fatigue Severity Scale, MRC = Medical Research Council, ODSS = Overall Disability Sum Score, SES = Self-Evaluation Scale, 95% CI = 95% confidence interval

Predictors of progression

Multiple linear regression showed that faster progression, i.e. a larger difference of the MRC sum score of visit 1 (2007) and visit 2 (2015-2016) per year correlated with the reflexes sum score (i.e. absent reflexes) and a lower MRC sum score in 2007 (*p*=0.016 and *p*=0.007)(**Table 9.4**).

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Table 9.4 Predictors of progression

Variable	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		
	RC	SE	RC	SE	RC	SE	RC	SE	RC	SE	RC	SE	95% CI
Anti-GM1 antibodies	0.18	0.34											
Sex	-0.52	0.37	-0.51	0.36	-0.47	0.36	-0.52	0.35	-0.50	0.35			
Symptom onset leg	-0.33	0.38	-0.33	0.37	-0.36	0.37	-0.32	0.36					
Months untreated[a]	-0.11	0.17	-0.11	0.17									
Reflexes sum score 2007	-0.17	0.08[b]	-0.17	0.07[b]	-0.16	0.07[b]	-0.16	0.07[b]	-0.17	0.07[b]	-0.18	0.07[b]	[-0.32,-0.03]
MRC sum score 2007	-0.03	0.02	-0.03	0.02	-0.03	0.02	-0.04	0.01[b]	-0.03	0.01[b]	-0.03	0.01[c]	[-0.06,-0.01]
ODSS 2007	0.15	0.16	0.16	0.16	0.15	0.16							
Age at symptom onset	-0.03	0.02	-0.03	0.02	-0.04	0.02	-0.04	0.02	-0.03	0.02	-0.03	0.02	
Adjusted R²	0.42		0.43		0.43		0.43		0.44		0.43		

Multiple linear regression analysis to predict the difference of the MRC sum score between visit 1 (2007) and visit 2 (2015-2016) per year based on anti-GM1 IgM antibodies (presence=1, absence=0), sex (male=0, female=1), symptom onset in leg (arm=0, leg=1), months untreated (log-transformed), age at onset of symptoms in years, sum score of reflexes (0-8), MRC sum score (0-180) and ODSS (0-8). The last three variables were analysed with data of the first visit (2007). The models show the different steps of the backward selection. In model 1 all independent factors were included and in model 6 only the independent factors that were significantly associated with the difference of the MRC sum score between visit 1 (2007) and visit 2 (2015-2016) per year.

[a]log transformed variable, [b] $p<0.05$, [c] $p<0.01$

MRC = Medical Research Council, ODSS = Overall Disability Sum Score, RC = regression coefficient, 95% CI =95% confidence interval, SE = standard error

DISCUSSION

This study aimed to document natural history of patients with MMN and identify predictors of disease progression. We combined cross-sectional data with longitudinal data with a mean duration between visits of eight years. Our clinical observations confirmed that MMN is a progressive disorder in the large majority of patients even when they receive immunoglobulin maintenance treatment. Virtually all selected outcome measures significantly deteriorated over time. Factors with prognostic value of a progressive disease course were absence of reflexes and a lower MRC sum score at baseline.

In a previous study the natural history of 38 treatment-naive patients with MMN was retrospectively described. Patients with longer disease duration (n=10) had significantly lower MRC sum scores and a higher number of affected regions. None of the patients experienced spontaneous improvement or a relapsing remitting course.[12] Taylor et al longitudinally assessed 18 patients with MMN and found a slowly worsening of muscle weakness i.e. a change in neurological impairment score (NIS) of 1.3 points/per year.[13] We performed multiple linear regression analysis to determine predictors of a progressive disease course and found that absence of at least one reflex and a lower MRC sum score at baseline were associated with a larger decrease of the MRC sum score over time. This amounted to a difference of 1.36 MRC point decrease of the MRC sum score per year in patients with generalized areflexia compared to those with normal reflexes. These findings can help to identify patients with a more progressive disease course. Until the development of more effective treatment strategies for MMN, the identification of patients at greater risk may ultimately help to tailor the dosing or frequency of immunoglobulin treatment in the future.

We used two approaches to analyze cross sectional data. First, we compared patients with a diagnosis before and after 2007, and thereby with longer and shorter disease duration. The distribution pattern of muscle weakness in patients with shorter and longer disease duration was similar but the severity of weakness of hand and lower leg/foot muscles was significantly increased in the latter. This finding supports the longitudinal data and also shows that proximal muscle groups are relatively spared. The second approach consisted of multiple linear regression analysis to determine factors that were associated with more severe weakness. Previous studies showed that axonal damage is highly associated with muscle weakness and therefore we performed the analysis without axonal damage as an independent factor.[4,14] We found that presence of anti-GM1 IgM antibodies and "years untreated" were associated with more severe weakness, which is similar to findings of smaller previous studies.[24-26] These data imply that to prevent permanent weakness, reducing time to diagnosis and providing earlier treatment are crucial. Increased awareness of MMN and possibly the extension of reliable diagnostic tools, such as nerve ultrasound might serve this goal. We think that MMN should also be actively excluded in older patients or those with asymmetric weakness in a leg.

The follow-up data showed that almost all outcome measures significantly deteriorated over time. However, there were some exceptions, most notably vigorimetry of the left hand. Although

we cannot explain this finding, we previously observed that weakness is more common in the dominant hand.[4] This has also been reported for other inflammatory asymmetric syndromes such as neuralgic amyotrophy.[27] Moreover, fatigue seemed to improve over time. Fatigue is a common symptom of chronic immune-mediated disorders but without intervention, at best remains stable but often deteriorates over time.[4,28,29] A possible explanation for the improvement of fatigue in MMN could be that patients get used to the feeling of fatigue or adapted by changing frequency or intensity of their daily activities (e.g. change or quit their jobs, improve their lifestyles).

Median age at onset of symptoms and age of diagnosis significantly increased over time. The higher median age at diagnosis could be explained by an already increased awareness of MMN, resulting in more frequent clinical suspicion in older patients presenting with asymmetric weakness. Moreover, the addition of novel diagnostic techniques other than nerve conduction studies such as nerve ultrasound or the more frequent use of immunoglobulin trials to assess response to treatment could also have led to the higher median age at diagnosis.[1 6,7,30] The cause of the increase of age at onset is unknown although it is not unique for MMN. Similar trends have been observed in other disorders such as multiple sclerosis and amyotrophic lateral sclerosis (ALS) (unpublished data of ALS cohort of 2900 patients in The Netherlands).[31,32]

Despite the fact that MMN is considered a pure motor neuropathy, we found vibration sense abnormalities in 57% of the patients. These deficits were confined to the feet in 97% of the patients and in general occurred in patients with longer disease duration. Vibration sense also significantly deteriorated over time, which is similar to previous studies that showed reduced sensory nerve action potentials years after MMN onset.[33,34]

Our study has some limitations. Neurological examination at both study visits was performed by different investigators. However, the authors who performed neurological examination were trained prior to the second tier of the study to minimize differences in performance, evaluation and interpretation of the MRC and Rydell-Seiffer scales. The large majority of patients received immunoglobulin maintenance treatment, which will have attenuated the true progression of MMN.

Our study shows that MMN is a progressive disorder in the large majority of patients despite immunoglobulin maintenance treatment. Diagnostic delays are more common in older patients or with onset of weakness in one of the legs. Absence of reflexes and lower MRC sum score at baseline predict a more progressive disease course. Whether these patients would benefit from more aggressive treatment approaches with immunoglobulins needs to be established.

SUPPLEMENTAL MATERIAL

Supplemental Table 9.1 Specification of neurological examination and questionnaires

Modality	Description
MRC score	Bilateral measurement of motor function of:
	Abduction of the arm
	Flexion and extension of the
	forearm wrist, and fingers
	Spreading of the fingers
	Abduction, adduction and opposition of the thumb
	Flexion of the hip
	Flexion and extension of the knee and foot
	Extension and flexion of the toes
	MRC sum score: 0-180 points
Vibration sense	Bilateral assessment of sensory function using Rydell-Seiffer tuning fork
	Normal (grade 0)
	Abnormal hallux valgus (grade 1)
	Abnormal ankle (grade 2)
	Abnormal knee (grade 3)
	Abnormal at the acromioclavicular joint or anterior superior iliac spine (grade 4)
Vigorimetry	Bilateral measurement of grip strength in Kilopascals (kPa) with the Martin Vigorimeter (Martin Medizintechnik, Tuttlingen, Germany)

FSS = Fatigue Severity Scale, MRC = Medical Research Council, ODSS = Overall Disability Sum Scale, SES = Self-Evaluation Scale

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Supplemental Table 9.2 Mean MRC grade per muscle group

	Total cohort (n=100)	Disease duration < 180.6 months (n=50)	Disease duration ≥ 180.6 months (n=50)	*p*-value
Proximal arm				
Elbow extension	4.7	4.7	4.6	0.33
Elbow flexion	4.4	4.5	4.3	0.63
Shoulder abduction	4.5	4.5	4.5	0.38
Wrist flexion	4.4	4.5	4.3	0.63
Wrist extension	3.9	4.1	3.6	0.20
Hand				
Flexion fingers	4.5	4.7	4.3	0.01
Extension fingers	3.3	3.7	3.0	0.03
Adduction thumb	3.4	3.9	2.9	0.01
Opposition thumb	3.2	3.7	2.7	0.03
Spreading fingers	3.1	3.5	2.7	0.03
Abduction thumb	3.0	3.6	2.4	0.01
Upper Leg				
Hip flexion	4.9	4.8	4.9	0.33
Knee flexion	4.9	4.9	4.9	0.73
Knee extension	4.9	5.0	4.9	0.38
Lower leg/foot				
Foot plantar flexion	4.3	4.8	3.9	0.03
Flexion toes	4.2	4.7	3.7	0.03
Foot dorsal flexion	3.4	4.2	2.6	0.01
Extension toes	3.5	4.1	2.9	0.04

MRC = Medical Research Council grade of the weakest side

Supplemental Table 9.3 Outcome measures

	All inclusions (n=100)
MRC sum score	165 (69-180)
Vibration sense	
Abnormal in at least one limb	57 (58)
Normal	42 (42)
Reflexes	
At least one reflex abnormal	63 (64)
Areflexia	16 (16)
Normal	20 (20)
ODSS	
Arms	2 (0-4)
Legs	1 (0-5)
Total	3 (0-8)
SES	10 (1-25)
FSS	37 (9-61)

Data are shown in median (range) or in number of patients (%).

FSS = Fatigue Severity Scale, MRC = Medical Research Council, ODSS = Overall Disability Sum Scale, SES = Self-Evaluation Scale

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CHAPTER 10

Prognostic value of nerve ultrasound: a prospective multicenter study on the natural history of polyneuropathy

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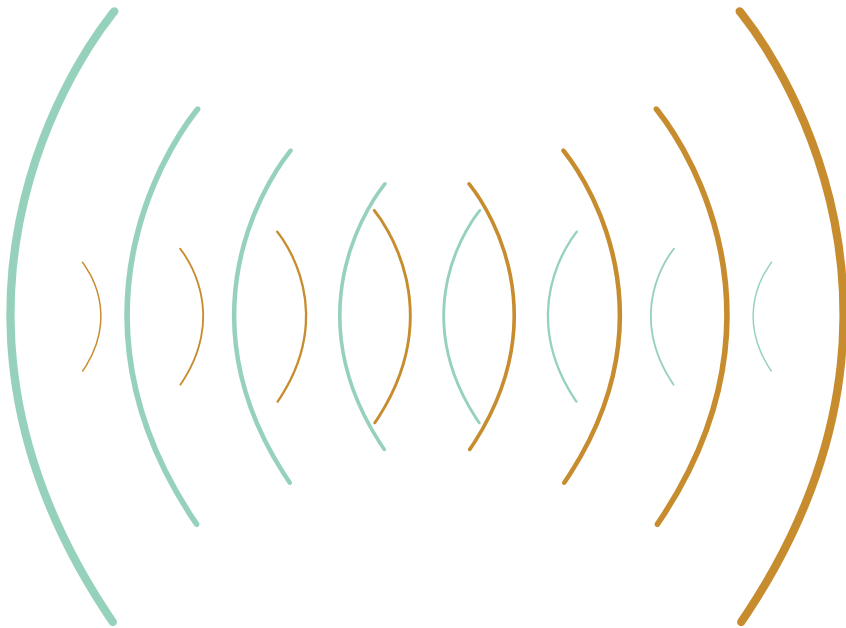
ABSTRACT

Objective

To determine prognostic value of sonographic nerve size development in chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN).

Methods

In this prospective multicenter cohort study (n=237), we enrolled patients with CIDP (typical n=52, atypical n=74), and MMN (n=72), of which 71 were treatment-naive. Patients with chronic idiopathic axonal polyneuropathy (CIAP, n=35) were considered as disease controls. Standardized neurological examination (including grip strength), questionnaires and nerve ultrasound were obtained at baseline and one-year follow-up. Nerve size development over time and correlation between nerve size and clinical outcome measures, were determined using linear mixed effects models.

Results

Nerve size development over time was heterogeneous in both CIDP and MMN. In MMN, there was a negative correlation between the size of the C5 nerve root and grip strength (-1.3 kPa/mm^2 (95%-CI -2.3 – -0.2 kPa/mm^2). No other significant correlations between nerve size and clinical outcome measures were found. Presence of nerve enlargement at inclusion predicted development of grip strength in MMN (an increase of 27.6 kPa in 1 year in patients without enlargement compared to 10.0 kPa with enlargement), and patients with MMN with enlargement confined to the brachial plexus seemed to have more favorable outcome. No other predictive effects of sonographic nerve size were found.

Conclusions

Prognostic value of nerve ultrasound is limited. It generally does not predict treatment response. In MMN, degree and distribution of nerve enlargement found during the diagnostic phase may have some prognostic value. Currently, performance of nerve ultrasound after the diagnostic phase should not be encouraged.

INTRODUCTION

Nerve ultrasound is emerging as a low-cost, widely available tool for the investigation of peripheral nerves. Its diagnostic value has been established for mononeuropathies, and more recently to distinguish inflammatory and potentially treatment-responsive polyneuropathies from more common forms.[1-5] We found that nerve ultrasound had low interobserver variability and can be used in a multicenter setting even if different types of sonographic devices are used.[6]

The prognostic value of nerve ultrasound, i.e. its value in predicting disease course or the effects of immune-modulatory treatment in inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), has been suggested but not been investigated in larger populations or in detail.[7-11] In CIDP and MMN only few predictors of treatment-response have been identified, including axonal damage, presence of conduction blocks and prolonged disease duration before start of treatment.[12-15] New and sensitive prognostic tools would be helpful to predict disease course, treatment efficacy and particularly remission, since patients with CIDP and MMN often require long term and expensive treatment with immunoglobulins. We performed a prospective multicenter cohort study in both treatment-naive and treated patients with CIDP, and MMN. Patients with chronic idiopathic axonal polyneuropathy (CIAP) were included as a control group, as we hypothesized that this disease generally shows no nerve enlargement and that nerves would therefore not alter over time. We determined nerve size development and its potential prognostic value over time in these diseases.

METHODS

Standard protocol approvals, registrations and patient consents

This international prospective longitudinal multicenter cohort study was conducted between May 2015 and May 2018 at the Neurology outpatient clinics of two tertiary referral centers in The Netherlands, i.e. the University Medical Center Utrecht and the Amsterdam University Medical Center, a large general teaching hospital in The Netherlands, i.e. the Elisabeth-Tweesteden Hospital in Tilburg and a tertiary referral center in Austria, i.e. the Allgemeines Krankenhaus in Vienna. The study was approved by the Brabant Regional Ethics Committee (NL50375.028.14) and the boards of all participating hospitals. All participants gave written informed consent.

In- and exclusion criteria

Consecutive newly diagnosed incident and earlier diagnosed prevalent patients with CIDP and MMN were eligible for inclusion, as well as CIAP patients.

Inclusion criteria were:
1) age ≥18

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2a) a diagnosis of possible, probable or definite CIDP or MMN according to the EFNS/PNS criteria,[16, 17] or

2b) a strong suspicion of CIDP or MMN based on previously described diagnostic criteria (i.e. patients with a clinical phenotype of CIDP or MMN according to the EFNS/PNS criteria (typical/ atypical), nerve ultrasound results compatible with a diagnosis of CIDP or MMN and objective treatment effect, but without characteristic nerve conduction abnormalities),[3,5] or

2c) a diagnosis of CIAP according to previously published clinical criteria, nerve conduction studies (NCS) results and laboratory testing.[18]

Exclusion criteria for this study were:

1) prior history of polyneuropathy other than CIDP, MMN, and CIAP.

2) physical inability to undergo nerve ultrasound.

Study Design

We obtained standardized neurological examination, questionnaires, and nerve ultrasound at inclusion and after 1 year of follow-up (**Figure 10.1**). An extra follow-up visit at 6 months could be performed in treatment-naive CIDP and MMN in order to document potential early nerve size changes after start of treatment. Neurological examination consisted of testing of muscle strength and sensory functions. Muscle strength of 14 muscle groups was graded bilaterally with the Medical Research Council (MRC) scale,[5] and grip strength was determined in kilopascal (kPa) with Martin Vigorimetry (Martin Medizintechnik, Tuttlingen, Germany). Sensory functions were tested bilaterally with the modified INCAT Sensory Sum score (mISS). In addition, the INCAT Overall Disability Sum Score (ODSS), Rasch-built Overall Disability Scale (RODS; for CIDP),[19] and Modified Rankin Score (MRS; for CIAP) were obtained.

Nerve ultrasound was performed by investigators with ≥1 year of experience with nerve ultrasound, who were blinded for results of previous ultrasound investigations. Ultrasound was performed with a Philips EPIQ7 (Philips Medical Instruments, Bothell, WA) at the UMC Utrecht, an Esaote MyLabTwice (Esaote, Genoa, Italy) at the Amsterdam UMC, a Toshiba Xario XG (Toshiba, Tokyo, Japan) at the ETZ Tilburg, and a GE Logiq E9 Platform (GE Healthcare, Chicago, USA) at the Algemeine Krankenhaus in Vienna. All investigators used a high-frequency probe (5-18 MHz). Nerve cross-sectional area (CSA) was measured bilaterally within the hyperechoic rim at standardized sites in upper extremity nerves: the median nerve (at wrist, forearm, and upper arm), ulnar nerve (at wrist, forearm, distal to the ulnar sulcus, at the ulnar sulcus (at the medial epicondyle), proximal to the ulnar sulcus, and at the upper arm), and the brachial plexus (C5 and C6 nerve roots).

In incident patients with CIDP, MMN, and CIAP, nerve conduction studies (NCS) were performed following the centers' standardized protocols and graded according to the criteria of the EFNS/ PNS.[16, 17] In all centers NCS included at least investigation of median, ulnar, fibular, tibial, and sural nerves. NCS were evaluated for presence of axonal loss (present if distal compound muscle action potential (CMAP) was: <3.5 mV for the median nerve (abductor pollicis brevis

muscle), <2.8 mV for the ulnar nerve (adductor digiti minimi muscle), <2.5 mV for the fibular nerve (extensor digitorum brevis muscle), or <2.9 mV for the tibial nerve (abductor hallucis muscle)), and presence of possible or definite conduction blocks in the median nerve (stimulated up to Erb's point).
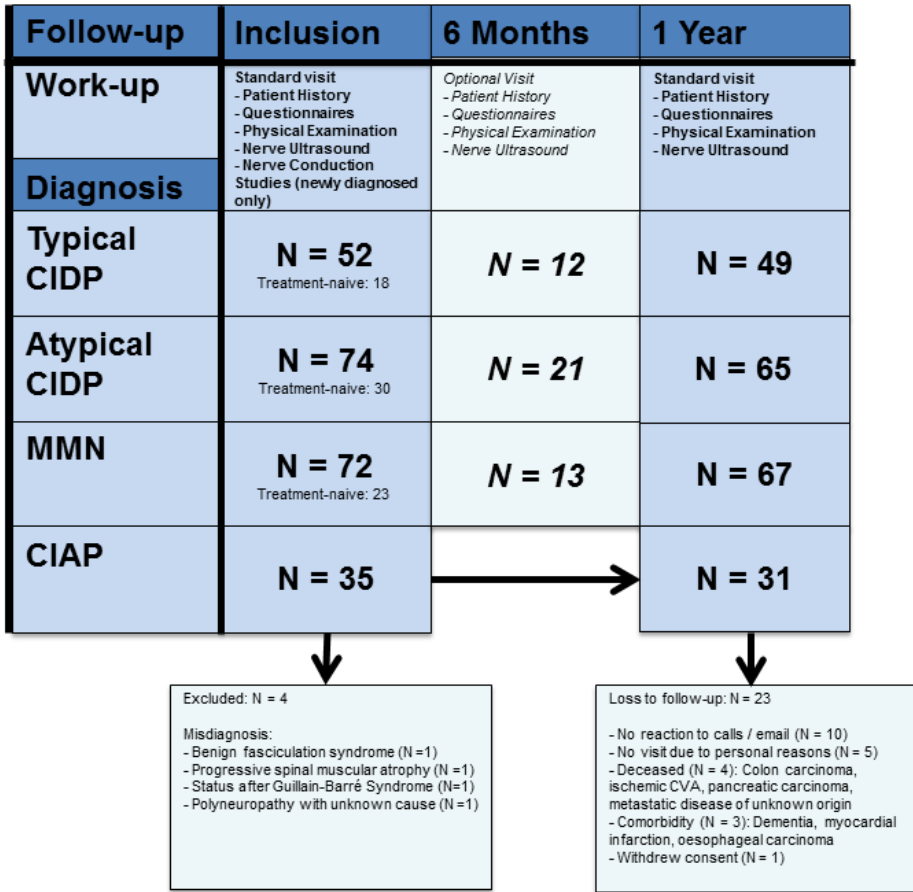
Follow-up	Inclusion	6 Months	1 Year
Work-up **Diagnosis**	Standard visit - Patient History - Questionnaires - Physical Examination - Nerve Ultrasound - Nerve Conduction Studies (newly diagnosed only)	Optional Visit - Patient History - Questionnaires - Physical Examination - Nerve Ultrasound	Standard visit - Patient History - Questionnaires - Physical Examination - Nerve Ultrasound
Typical CIDP	N = 52 Treatment-naive: 18	N = 12	N = 49
Atypical CIDP	N = 74 Treatment-naive: 30	N = 21	N = 65
MMN	N = 72 Treatment-naive: 23	N = 13	N = 67
CIAP	N = 35	→	N = 31

Excluded: N = 4

Misdiagnosis:
- Benign fasciculation syndrome (N =1)
- Progressive spinal muscular atrophy (N =1)
- Status after Guillain-Barré Syndrome (N =1)
- Polyneuropathy with unknown cause (N =1)

Loss to follow-up: N = 23

- No reaction to calls / email (N = 10)
- No visit due to personal reasons (N = 5)
- Deceased (N = 4): Colon carcinoma, ischemic CVA, pancreatic carcinoma, metastatic disease of unknown origin
- Comorbidity (N = 3): Dementia, myocardial infarction, oesophageal carcinoma
- Withdrew consent (N = 1)

Figure 10.1 Flowchart study

The standardized work-up applied in this study, including optional pre-study visits (patients already under treatment that underwent nerve ultrasound in diagnostic work-up prior to study inclusion) and optional 6 month follow-up visit for newly diagnosed patients with CIDP and MMN. The figure additionally shows the number of in- and excluded patients, and loss to follow-up.

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy

Statistics

We used SPSS version 25 (SPSS Inc., Chicago IL, USA) for statistical analysis. Data were analyzed for four different disease groups: typical CIDP (according to the clinical criteria of the EFNS/PNS), atypical CIDP (according to the clinical criteria of the EFNS/PNS, including pure motor CIDP, pure sensory CIDP, asymmetrical variants of CIDP, and distal predominant CIDP), MMN, and CIAP. Distinction between typical and atypical CIDP was made because we hypothesized that patients with typical CIDP have distinct clinical symptoms and therefore could have a more uniform pathophysiological mechanism underlying nerve enlargement as they show similar complaints, whilst in atypical CIDP symptoms may vary considerably. Treatment-naive CIDP and MMN were also analyzed separately. Data were summarized per disease group as mean (standard deviation (SD)) for normally distributed variables, median (range) for non-normal distributed variables, and n (%) for categorical variables. We compared mean nerve CSA at all investigated nerve sites between disease groups with Kruskal-Wallis test and post-hoc Mann-Whitney U test based on non-normal distribution of the data. The average nerve CSA of the right and left side was used in all analyses.

We used CSA of the median nerve at the forearm, upper arm and the C5 nerve root for additional analyses as these sites show relatively low inter-observer variability.[5,6] We studied associations between these nerves sites and vigorimetry (as primary outcome), ODSS (for all disease groups), RODS CIDP (for typical and atypical CIDP), MRS (for CIAP) and mISS (for typical and atypical CIDP and CIAP). The MRC-sum score was omitted from these analyses because of extreme skewness of the data. This relationship between clinical outcome measures and nerve CSA was assessed using linear mixed effects models (LME). Each model contained a random intercept per individual and nerve CSA of the investigated nerve site as fixed effect. Models were fitted with restricted maximum likelihood (REML) based on an unstructured covariance matrix.

To determine nerve size development over time, a similar approach was used, in which LMEs were fitted where nerve CSA served as outcome measure, and study duration (in months) as fixed effect. The random part contained a random intercept and slope (for study duration) per individual in order to correct for variability in nerve size development due to individual patient characteristics.

To determine the prognostic value of nerve ultrasound each patient was assigned a code of either enlargement (1) or no enlargement (0) for the investigated non-entrapment nerve site (i.e. median nerve at forearm, upper arm and C5 nerve root) at the inclusion visit.[5, 20] These results were entered in an LME as fixed effect. Study duration (in months), and the interaction between study duration and presence of enlargement at inclusion were also entered as fixed effects to determine whether the development over time depended on the presence of nerve enlargement. A random intercept and slope for study duration were entered for patients to correct for variability due to individual patient characteristics.

To evaluate presence of other potential prognostic factors in CIDP and MMN, patients were dichotomized as either having decreased or increased (i.e. change larger than 0) in vigorimetry or ODSS at 1 year of follow-up. Differences in clinical, NCS, and sonographic parameters between

these groups were tested using the independent t-test (continuous, normal), Mann-Whitney U test (continuous, non-normal), chi-square test (categorical) or Fishers' exact test (categorical, small sample size).

RESULTS

Study population
A total of 237 patients were included in this study (**Figure 10.1**): 126 patients with CIDP (52 typical and 74 atypical), 72 with MMN, and 35 with CIAP; 4 patients were excluded from the final analysis because of a changed diagnosis during follow-up. Of the patients with chronic inflammatory neuropathy, 71 were treatment-naive at inclusion (18 typical CIDP, 30 atypical CIDP, 23 MMN). Baseline characteristics of 233 patients are shown in **Table 10.1**.

The one-year follow-up visit was completed by 210 patients (90.1%) and 23 patients were lost to follow-up (9.9%). There were no significant differences in age, sex, disease type, disease duration, or treatment status between the groups that completed 1 year of follow-up or were lost to follow-up, although mean age was 5.3 years higher and median disease duration 17.6 months shorter in patients lost to follow-up.

Correlation between nerve size and clinical outcome measures
No correlation between nerve size and grip strength in (a)typical CIDP and CIAP was found (**Table 10.2**). We observed a negative correlation between grip strength and CSA of the C5 nerve root (slope -1.3 kPa (95%-CI -2.3 – -0.2 kPa), p=0.02) in patients with MMN. This indicates that grip strength decreases with 1.3 kPa for each mm^2 increase in CSA at the C5 nerve root. This negative correlation was also present at the median nerve at the upper arm, although not significant (p=0.10). The negative correlation with the C5 nerve root size was more pronounced (slope -3.8 kPa (95%-CI -6.7 – -0.9 kPa), (p=0.10). The negative correlation with the C5 nerve root size was more pronounced (slope -3.8 kPa (95%-CI -6.7 – -0.9 kPa), p=0.01) in treatment-naive patients with MMN. Additionally, in patients with pure motor CIDP this correlation was observed as well (n=11, slope -4.8 kPa (95%-CI -8.3 – -1.4 kPa), p=0.01). There was no significant correlation of nerve CSA with other outcome measures (ODSS, RODS, MRS and mISS).

Nerve size development over time
Nerve CSA of the median nerve at the forearm, upper arm and at the C5 nerve root was significantly higher in CIDP and MMN than in CIAP, both at inclusion and at 1 year follow-up (**Figure 10.2**). We observed a decrease in nerve size over time of the median nerve at the forearm in atypical CIDP (slope – 0.067 mm^2/month; 95%-CI -0.121 – -0.013 mm^2/month) and MMN (slope -0.056 mm^2/ month; 95%-CI -0.099 – -0.013 mm^2/month). This corresponds with an average decrease of

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Table 10.1 Baseline characteristics

	CIDP typical (n=52)	CIDP atypical (n=74)	MMN (n=72)	CIAP (n=35)
Hospitals				
AMC Amsterdam	12 (23)	6 (8)	6 (8)	0 (0)
ETZ Tilburg	8 (15)	12 (16)	4 (6)	19 (54)
UMC Utrecht	31 (60)	53 (72)	61 (85)	16 (46)
AKW Vienna	1 (2)	3 (4)	1 (1)	0 (0)
Age (years), mean (SD)	60.3 ±14.0	59.0 ±13.0	53.6 ±10.7	63.5 ±8.9
Sex (male)	35 (67)	52 (70)	57 (79)	20 (57)
Disease duration (months), median (range)	29 (1-360)	50 (2-312)	72 (3-550)	60 (10-240)
Treatment-naive	18 (35)	30 (41)	23 (32)	-
EFNS/PNS criteria				
Definite	39 (75)	64 (86)	44 (61)	-
Probable	3 (6)	2 (3)	12 (17)	-
Possible	1 (2)	0 (0)	16 (22)	-
Not fulfilled	9 (17)	8 (11)	0 (0)	-
Follow-up 1 year completed	47 (89)	65 (88)	67 (93)	31 (89)
Treatment received (during 1 year follow-up period)				
IVIg	22 (47)	40 (62)	66 (99)	-
Corticosteriods	5 (11)	5 (8)	-	-
IVIg + corticosteroids	10 (21)	9 (14)	-	-
Plasmaferesis	1 (2)	3 (5)	0 (0)	-
No treatment: in remission	6 (13)	10 (15)	1 (1)	-
No treatment: no remission	4 (9)	1 (2)	0 (0)	-
In remission at 1 year of follow-up	12 (26)	16 (25)	2 (3)	-

The baseline characteristics of 233 included patients per disease group. In addition, details on the treatment received by patients completing 1 year follow-up during this year are shown. Data are shown as number of patients (%) unless stated otherwise.

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, IVIg = intravenous immunoglobulins, MMN = multifocal motor neuropathy

Table 10.2 Correlation of vigorimetry and nerve size

	Nerve Site	Mean grip strength (kPa)	Correlation of grip strength and nerve size in kPa/mm2 (95%-CI)	P-value of correlation
CIDP Typical	MFA	70.2	-0.4 (-1.6 – 0.9)	0.57
	MUA	66.6	0.0 (-0.9 – 0.9)	0.99
	C5	70.8	-0.5 (-1.5 – 0.6)	0.38
CIDP Atypical	MFA	60.1	0.4 (-0.5 – 1.4)	0.35
	MUA	57.1	0.4 (-0.1 – 1.0)	0.10
	C5	65.2	-0.1 (-0.8 – 0.7)	0.87
MMN	MFA	74.9	-0.1 (-1.6 – 1.4)	0.92
	MUA	86.2	-0.8 (-1.9 – 0.2)	0.10
	C5	**85.0**	**-1.3 (-2.3 – -0.2)**	**0.02**
CIAP	MFA	81.4	-0.1 (-2.8 – 2.7)	0.95
	MUA	52.9	2.9 (-0.6 – 6.4)	0.10
	C5	83.2	-0.5 (-4.1 – 3.1)	0.79

The correlation of grip strength and nerve size of the median nerve at forearm and upper arm and the C5 nerve root (in mm^2) per disease group. Results obtained by the fitted LME's are shown, including the mean grip strength (intercept) and average increase/decrease in grip strength per mm^2 in nerve size (slope) including a 95%-CI and p-value of the slope.

CIDP = chronic inflammatory demyelinating polyneuropathy, kPa = Kilopascal, LME = linear mixed model, MFA = median nerve at the forearm, MMN = multifocal motor neuropathy, MUA = median nerve at the upper arm, 95%-CI = 95%-confidence interval

nerve CSA of 0.804 mm^2 and 0.672 mm^2 per year at these sites (-7.8% and -7.7% of the baseline mean nerve size per year, respectively). Nerves size in patients with typical CIDP and CIAP did not change over time (**Figure 10.3**). Further analysis of patients with atypical CIDP showed that the decrease of nerve size over time was attributable to distal predominant CIDP (n=35, slope -0.107 mm^2/month; 95%-CI -0.195 – -0.018 mm^2/month) but not to pure motor CIDP (n=11), pure sensory CIDP (n=11) and asymmetrical variants of CIDP (n=21). Among treatment naive patients, a reduction in size of the median nerve at the forearm was observed only in MMN (slope -0.114 mm^2/month; 95%-CI -0.178 – -0.054 mm^2). Patients that did not use maintenance therapy with immunoglobulins after 1 year of follow-up (n=30; 12 typical CIDP, 16 atypical CIDP, 2 MMN) also showed large heterogeneity in nerve size development, and no significant change of nerve size was observed in this group of patients.

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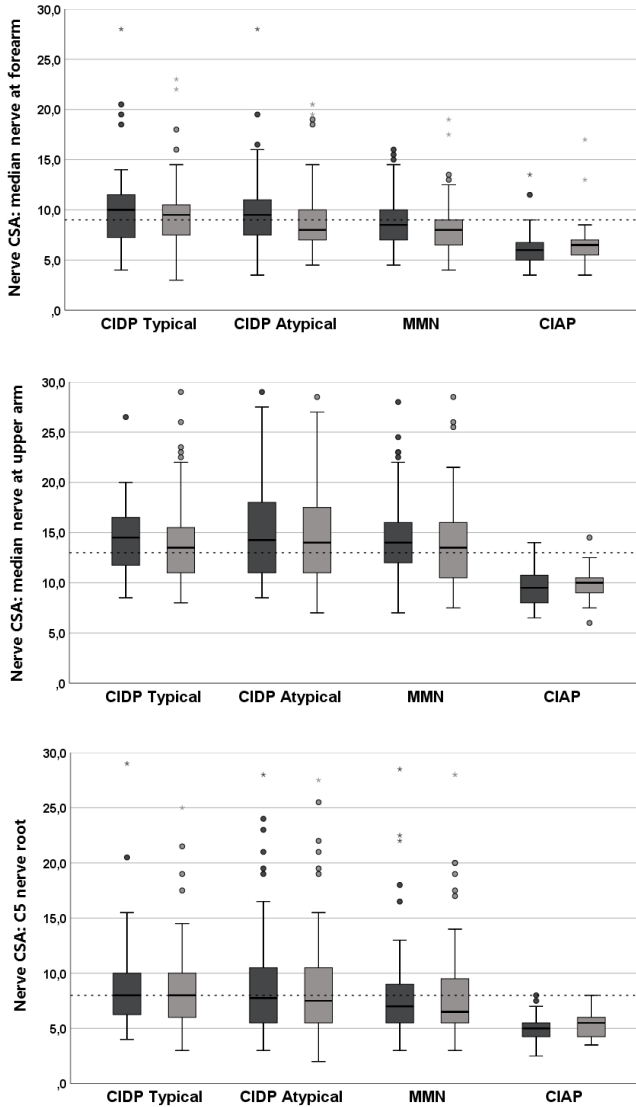
Figure 10.2 Nerve size at inclusion and follow-up

Boxplots of median nerve at forearm and upper arm and C5 nerve size in mm[2] per disease group at inclusion and 1 year of follow-up. Nerve size at inclusion is shown in light grey, nerve size at 1 year of follow-up in dark grey. The dotted lines represent the cut-off value for demyelination established in our previously published diagnostic cohort study.[20]

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN =multifocal motor neuropathy
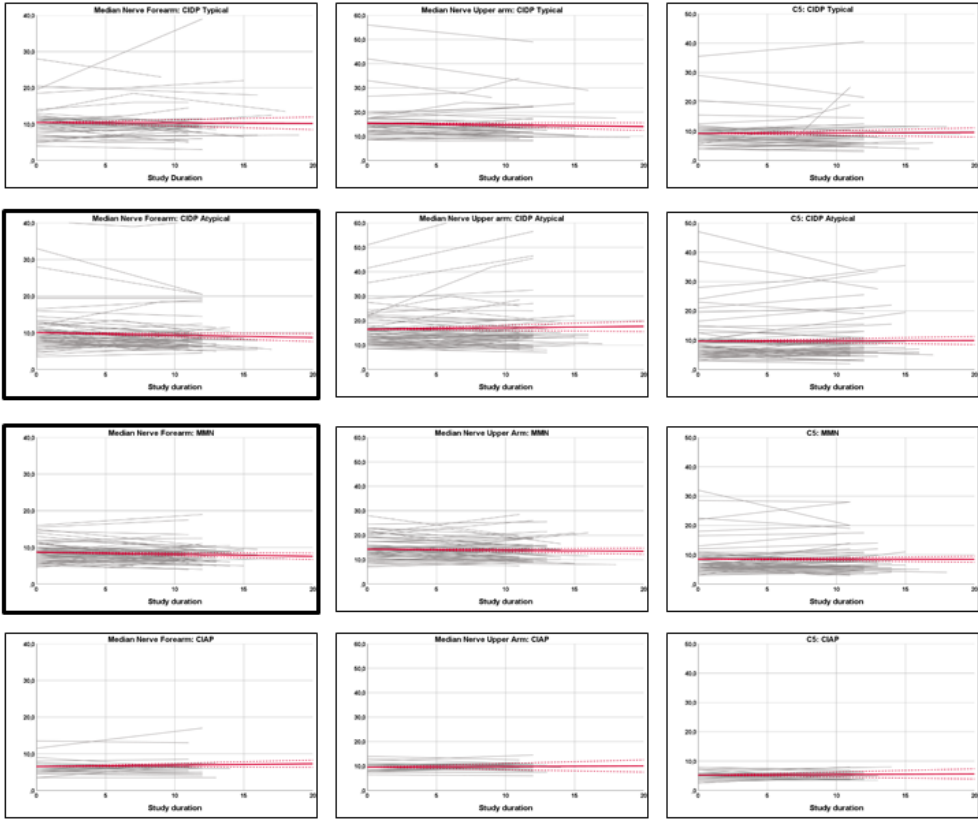
Figure 10.3 Development of nerve size over time in individual patients

Development of nerve size of the median nerve (at forearm level and arm level) and the C5 nerve root over time in CIDP (typical), CIDP (atypical), MMN, and CIAP for individual patients and an estimated overall nerve size development. After mixed model analysis, no significant correlation between time and nerve size was found, except for the median nerve at the forearm in atypical CIDP (slope – 0.067 mm^2/month; 95%-CI -0.121 – -0.013 mm^2/month) and MMN (slope -0.056 mm^2/month; 95%-CI -0.099 – -0.013 mm^2). Grey lines represent individual patients, red lines represent overall nerve size development over time, red dotted lines represent 95%-confidence interval of the nerve size development over time.

CIAP = chronic idiopathic axonal polyneuropathy, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy, 95%-CI = 95% confidence interval

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Prognostic value of nerve CSA on development of clinical outcome measures

Presence of enlargement of the median nerve at the upper arm predicted deterioration of grip strength in patients with typical CIDP and MMN (**Table 10.3**). This predictive effect was more pronounced in treatment-naive patients with MMN: without enlargement slope 1.13 kPa/month (95%-CI 0.13 – 2.13

kPa/month) versus with enlargement -0.82 kPa/month (95%-CI -1.67 – 0.03 kPa/month), p=0.006. This indicates that patients without nerve enlargement of the median nerve at the upper arm have higher grip strength after 1 year of follow-up than patients with nerve enlargement (an increase of 13.56 kPa/year compared to a decrease of 9.84 kPa/year). No significant effect of the presence of nerve enlargement on grip strength was observed at other nerve sites (**Figure 10.4**).

Presence of enlargement of the C5 nerve root at inclusion predicted a significantly improved ODSS over time in treatment-naive patients with MMN; without enlargement slope 0.00 points per month (95%-CI -0.06 – 0.06 per month) versus with enlargement -0.12 points per month (95%-CI -0.19 – -0.04 per month), p=0.02. It also predicted significantly better RODS over time in typical CIDP: without enlargement slope 0.28% (95%-CI -0.23 – 0.79%) versus with enlargement 1.03% (95%-CI 0.52 – 1.55%), p=0.04. This positive effect of presence of enlargement at the C5 nerve root was also observed for vigorimetry, ODSS and mISS in typical CIDP, and for vigorimetry and ODSS in the entire group of patients with MMN, though these results were not significant (**Table 10.4**).

Additional analyses showed that patients with MMN with nerve enlargement confined to the brachial plexus had a more favorable outcome (i.e. improvement of grip strength) than patients with MMN with more generalized enlargement.

CIAP was excluded from these analyses due to the limited number of patients with nerve enlargement (median nerve at the forearm n=2, 5.7%; median nerve at the upper arm n=1, 2.9%; C5 nerve root n = 0, 0.0%).

Table 10.3 Prognostic value of nerve enlargement on development of grip strength

	Nerve site	No nerve enlargement at inclusion	Nerve enlargement at inclusion	P-value
		Slope (95%-CI) in kPa/month	Slope (95%-CI) in kPa/month	
CIDP Typical	MFA	1.39 (016 – 2.61)	1.23 (0.42 – 2.05)	0.84
	MUA	2.30 (1.12 – 3.47)	0.85 (0.06 – 163)	0.04
	C5	1.04 (0.08 – 1.99)	1.57 (0.65 – 2.49)	0.43
CIPD Atypical	MFA	0.04 (-0.57 – 0.65)	0.16 (-0.45 – 0.77)	0.79
	MUA	-0.23 (-0.89 – 0.43)	0.33 (-0.23 – 0.88)	0.21
	C5	0.21 (-0.39 – 0.81)	0.00 (-0.62 – 0.61)	0.63
MMN	MFA	0.00 (-0.43 – 0.44)	-0.21 (-0.75 – 0.32)	0.52
	MUA	0.33 (0.18 – 0.84)	-0.37 (-0.079 – 0.06)	0.04
	C5	-0.16 (-0.56 – 0.24)	0.10 (-0.52 – 0.72)	0.50

The effect of presence of nerve enlargement at inclusion on development of grip strength over time (in kPa/month).

CIDP = chronic inflammatory demyelinating polyneuropathy, MFA = median nerve at forearm, MMN = multifocal motor neuropathy, MUA = median nerve at upper arm
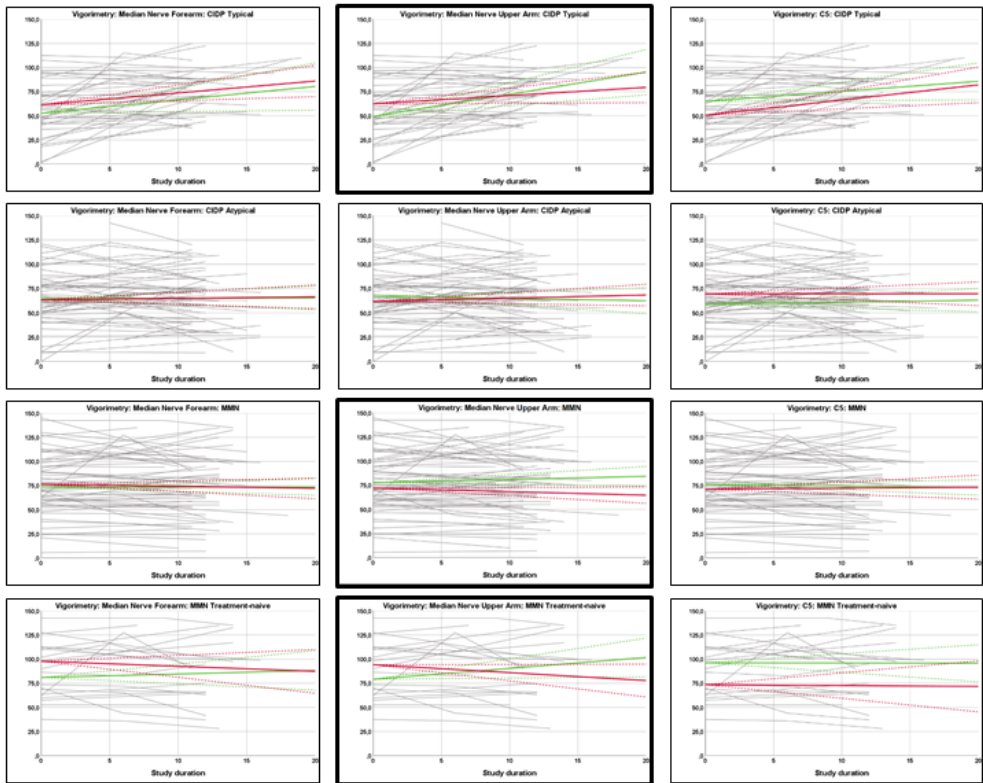
Figure 10.4 Prognostic value of nerve enlargement on development of vigorimetry

The effect of presence of nerve enlargement at inclusion at given sites (i.e. median nerve at forearm and arm, and C5 nerve root) on the development of vigorimetry over time in typical CIDP, atypical CIDP, and MMN. Estimated slopes obtained from LME's for patients without enlargement (green) and with enlargement (red) are shown with 95%-CI (dotted lines). Grey lines represent individual patients. Only a significant effect for the median nerve at arm level in typical CIDP (slope 2.30 kPa/month (95% CI 1.12 – 3.47 kPa/month) without enlargement versus 0.85 kPa / month (95% CI 0.06 – 1.63 kPa/month) with enlargement, p=0.04), and MMN (slope 0.33 kPa/month (95%-CI -0.18 – 0.84 kPa/month) without enlargement versus -0.37 kPa/month (95%-CI -0.79 – 0.06 kPa/month) with enlargement, p=0.04). The lowest box shows plots for treatment-naive patients with MMN, though only significant at upper arm (slope 1.13 kPa/month (95%-CI 0.13 – 2.13 kPa/month) without enlargement versus -0.82 kPa/month (95%-CI -1.67 – 0.03 kPa/month) with enlargement, p=0.02), increase in grip strength also tended to be lower in case of enlargement at the forearm or C5 nerve root, though not significant.

CIDP = chronic inflammatory demyelinating polyneuropathy, kPa = Kilopascal, LME = linear mixed model, MMN = multifocal motor neuropathy, 95%-CI = 95% confidence interval

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Table 10.4 Effect of presence of nerve enlargement on outcome measures

	Nerve Site	Vigorimetry	ODSS	RODS	mISS
CIDP Typical	MFA	-3.3%	0.0%	+5.9%	-16.1%
	MUA	**-30.1%**	-17.5%	+0.8%	+4.6%
	C5	+11.0%	-11.7%	**+15.3%**	-8.0%
MMN	MFA	-3.4%	0.0%		
	MUA	**-11.3%**	0.0%		
	C5	+4.2%	-16.2%		
MMN treatment-naive	MFA	-12.0%	-8.8%		
	MUA	**-26.6%**	-8.8%		
	C5	-0.8%	**-52.6%**		

The estimated effects of presence of enlargement of the median nerve at forearm and upper arm and C5 nerve root at inclusion on several outcome measures. Dark red indicates significant worsening of an outcome measure in case of enlargement, dark green significant improvement. Light red and green also indicate worsening/improvement, though results of the LME were not significant in that case. A percentual difference in change per year between patients with and without enlargement at inclusion is shown, in which the mean value of the outcome measure, obtained with LME, is used as starting value.

CIDP = chronic inflammatory demyelinating polyneuropathy, LME = linear mixed model, MFA = median nerve at the forearm, mISS = modified INCAT Sensory Sum score, MMN = multifocal motor neuropathy, MUA = median nerve at the upper arm, ODSS = Overall Disability Sum Score, R-ODS = Rasch-Built Overall Disability Scale.

Other prognostic factors in CIDP and MMN

Prognostic effects of previously identified clinical and NCS factors were tested in our multicenter cohort.[12-15] Shorter disease duration to treatment, a subacute start of complaints (nadir ≤6 weeks), lower age, absence of conduction block in the median nerve, and absence of axonal loss were all associated with improved vigorimetry and/or ODSS in both typical CIDP and MMN (p-value all <0.05).

DISCUSSION

This large prospective study with low loss to follow-up showed that nerve ultrasound has limited prognostic value in patients with inflammatory neuropathies. MMN is a possible exception, since larger nerve size at inclusion was associated with lower grip strength after 1 year follow-up. Moreover, patients with MMN who had brachial plexus enlargement fared better than patients with more generalized nerve enlargement. Nevertheless, sonographic nerve abnormalities were very heterogeneous, which limits its prognostic value in individual patients.

Previous studies on the prognostic value of nerve ultrasound showed promising results by suggesting a correlation between decreasing nerve size and better outcome. In the study of Zaidman et al improved grip strength was associated with normalization of nerve size in a cohort of 23 patients with CIDP.[11] In other studies a decrease in a sonographic score for nerve enlargement (UPSS) and in intra-nerve variability ratio was associated with an improved clinical outcome.[7-9] However, we could not replicate these findings that were obtained in studies mostly retrospective in design, with small sample size and with predominantly treated patients included. It is less likely that this prospective study including a large group of untreated patients suffers from comparable inclusion bias.

Nerve size development in CIDP and MMN was strikingly heterogeneous. This heterogeneity may be explained by the assumption that despite the fact that nerve enlargement is the final common pathway of pathophysiological processes underlying CIDP and MMN, its reversal is not crucial for nerve function improvement. Onion bulb formation, inflammatory cell infiltrates and endoneurial edema, interstitial accumulation of amorphous substances or fibrosis can all cause nerve enlargement, but their relation with the development of clinical symptoms may differ.[21-23] It remains to be shown whether other nerve ultrasound parameters than CSA are better predictors of outcome. Some small studies found that differences in echogenicity correlated with clinical outcome in patient with CIDP, with patients showing hyperechoic nerves having a worse outcome.[8,21,24] The value of additional sonographic parameters may thus deserve further attention.[8,21,24-27]

Despite the limited level of correlation of nerve size with clinical outcome measures, a few of our observations may be helpful in clinical practice. Patients with MMN showing only nerve enlargement of the brachial plexus on average had a better therapeutic prognosis than patients with more generalized peripheral nerve enlargement. This pattern of distribution may therefore have some prognostic value. Differences in patterns may reflect variation in underlying pathophysiological processes or represent different stages in the disease. Although additional studies are needed, involvement of the brachial plexus only may be a prognostically beneficial factor in addition to previously identified clinical and NCS prognostic factors.[12-15] A previous study on prognostic value of MRI of the brachial plexus in MMN did not find any value, but this study did not investigate coinciding peripheral nerve involvement.[28] Further studies combining MRI and ultrasound assessments of peripheral nervous system may thus shed additional light on these topics.

This study had some limitations. First, the follow-up duration of one year was relatively short, and though we included a large group of patients with CIDP, subgroups of patients with clinical subtypes of CIDP were small. Another limitation is that we only included data on nerve size in the analyses. It was not possible to perform reliable post-hoc classification of nerves based on nerve echogenicity, among other things, due to the use of different sonographic devices in this multicenter study. In our study, follow-up visits were planned irrespective of the time interval between the last course of immunoglobulins. As clinical complaints may vary markedly, this may have affected results on correlation between nerve size and clinical outcome measures, though

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the results on the prognostic value of nerve enlargement at inclusion are likely less biased, as these represent long term effects. Treatment of inflammatory neuropathies is often required for longer periods of time. To ensure that we will not miss prognostic effects after one-year follow up, this study will continue another year.

Nerve ultrasound becomes increasingly important for the diagnosis of CIDP and MMN. A short ultrasound protocol allows reliable identification of these patients.[3-5] In this study we show that initial sonographic abnormalities remain present over time, which suggests that nerve ultrasound is a useful diagnostic tool even in case of diagnostic delay. The usefulness of nerve ultrasound as a follow-up tool seems, based on the results of this study, relatively limited. Only in MMN some prognostic value of nerve ultrasound is suggested. Overall, nerve ultrasound does not detect changes in nerve sizes that reflect treatment efficacy, remission or exacerbations, and its use after the initial diagnostic phase should not be encouraged.

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CHAPTER 11

Human Immune Globuline 10% with Recombinant Human Hyaluronidase in Multifocal Motor Neuropathy

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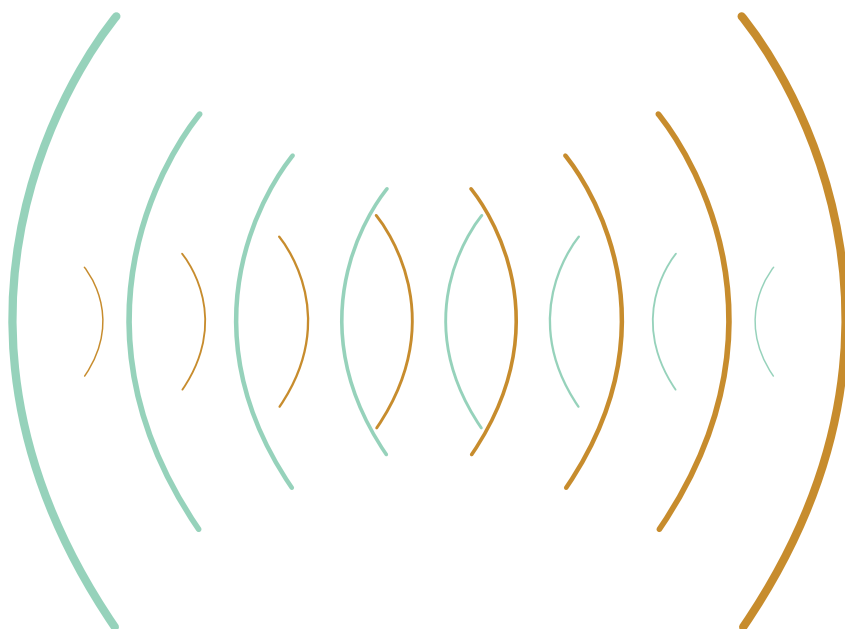
ABSTRACT

Objective

The primary aim was to determine the safety of treatment with Human Immune Globulin 10% with Recombinant Human Hyaluronidase (fSCIg) compared to intravenous immunoglobulin (IVIg) in a prospective open-label study in patients with multifocal motor neuropathy (MMN).

Methods

Our study consisted of two phases: the *IVIg phase* (visits 1-3; 12 weeks), in which patients remained on IVIg treatment, and the *fSCIg phase* (visits 4-7; 36 weeks), in which patients received fSCIg treatment. After visit 3, IVIg was switched to an equivalent dose and frequency of fSCIg. Outcome measures were safety, muscle strength, disability and treatment satisfaction.

Results

Eighteen patients were enrolled in this study. Switching to fSCIg reduced the number of systemic adverse events (IVIg 11.6 *vs.* fSCIg 5.0 adverse events/per person-year, $p<0.02$), and increased the number of local reactions at the injection site (IVIg 0 *vs.* fSCIg 3.3 local reactions/per person-year, $p<0.01$). Overall, no significant differences in muscle strength and disability between fSCIg and IVIg were found. Treatment with fSCIg was perceived as optimal treatment option by eight of the 17 patients (47.1%) and they continued with fSCIg after study closure because of improved independence and flexibility to administer treatment.

Conclusions

Treatment with fSCIg can be considered a safe alternative for patients with MMN on IVIg treatment. fSCIg could be a favorable option in patients who prefer self-treatment and more independency, and in patients who experience systemic adverse events on IVIg or have difficult intravenous access.

INTRODUCTION

Multifocal motor neuropathy (MMN) is an immune-mediated demyelinating neuropathy characterized by asymmetric muscle weakness, predominantly of the upper limbs.[1-3] Men are more commonly affected as woman with a ratio of 2.6:1.[1,2] In most patients the first symptoms occur between age 20 and 50 years.[1] Various trials have shown a beneficial effect of intravenous immunoglobulins (IVIg) on muscle strength in MMN and a comparable effect of subcutaneous immunoglobulins (SCIg).[4-7]

Although a large number of studies have demonstrated that IVIg treatment is well tolerated, various systemic adverse events have been reported: the majority, such as headache, malaise and chills, are transient and relatively mild, but some rare adverse events, such as anaphylactic and skin reactions, are serious.[4] Moreover, repeated venous access and administration in hospital or at home, in the presence of a nurse, is a burden for the patient. SCIg treatment is considered a good alternative as it can be administered by the patient or informal caregiver and produces fewer systemic adverse reactions.[5,8] However, limitations of subcutaneous infusion volumes and reduced bioavailability require more frequent infusion and an increase in dose in approximately 50% of the patients.[5]

A relatively new treatment that overcomes the disadvantages of the conventional SCIg is Human Immune Globulin 10% with Recombinant Human Hyaluronidase (fSCIg). Subcutaneous administration of hyaluronidase increases SCIg dispersion and absorption and therefore provides higher doses of SCIg with less frequent infusion and with the benefit of a higher bio-availability.[9-11] Treatment with fSCIg has been approved by the Food and Drug Administration (FDA) for primary immunodeficiency (PID), but not for inflammatory neuropathies including MMN. This study explores the safety and treatment satisfaction of fSCIg compared to IVIg in patients with MMN.

METHODS

Study design and patients

This prospective, open-label study was performed between November 2016 and February 2018 in the UMC Utrecht, a tertiary referral center for neuromuscular disorders. Patients with the diagnosis of MMN according to the EFNS/PNS criteria, who had been stable on IVIg therapy for ≥ 1 year, were eligible for inclusion in this study. Exclusion criteria for this study were: 1) treatment with other immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, cyclosporine) in the 6 months preceding the study, 2) age <18, and 3) female patient pregnant or breast-feeding. The study protocol was approved by the local medical ethics committee Utrecht (METC Utrecht; file ID NL52642.041.15). All patients gave written informed consent.

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Outcome measures

This study consisted of two successive phases: the *IVIg phase* lasting 12 weeks and the *fSCIg phase* of 36 weeks (**Figure 11.1**). During the *IVIg phase*, patients visited the outpatient clinic every six weeks (visit 1-3). In the *fSCIg phase*, patients visited the outpatient clinic on weeks 18 (visit 4), 24 (visit 5), 36 (visit 6) and 48 (visit 7). At each visit all outcome measures were collected, except for hand-held dynamometry (HHD) (visits 1-4-7) and laboratory tests (visits 3-5-7) (**Figure 11.2**).
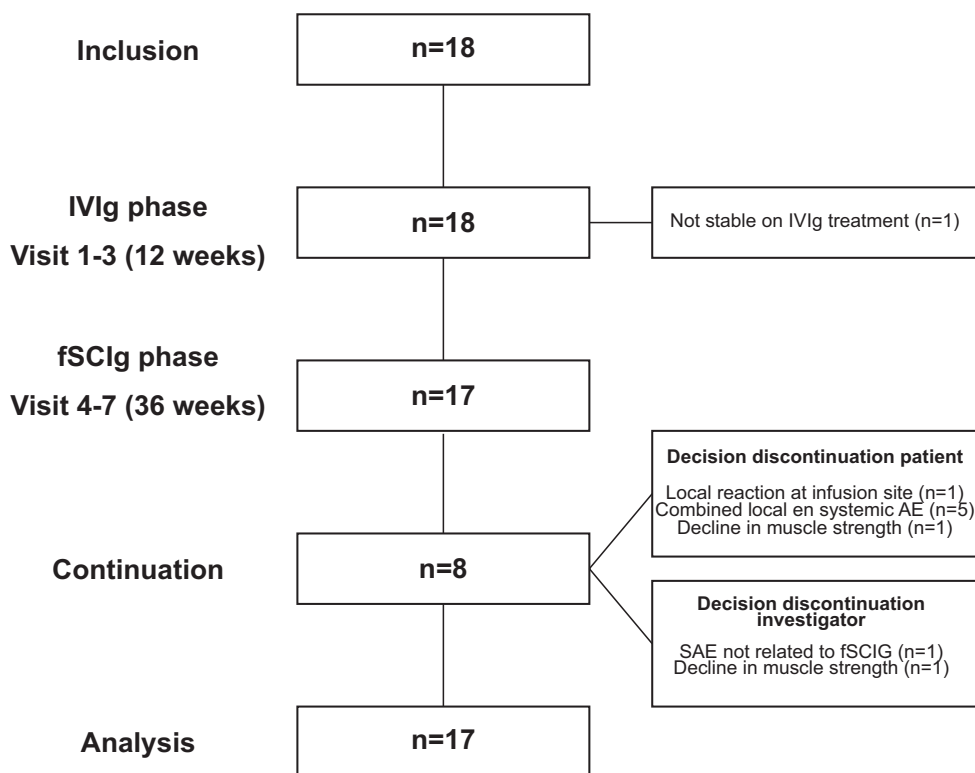
Figure 11.1 Flowchart study

AE = adverse event, fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, IVIg = intravenous immunoglobulins, SAE = serious adverse event
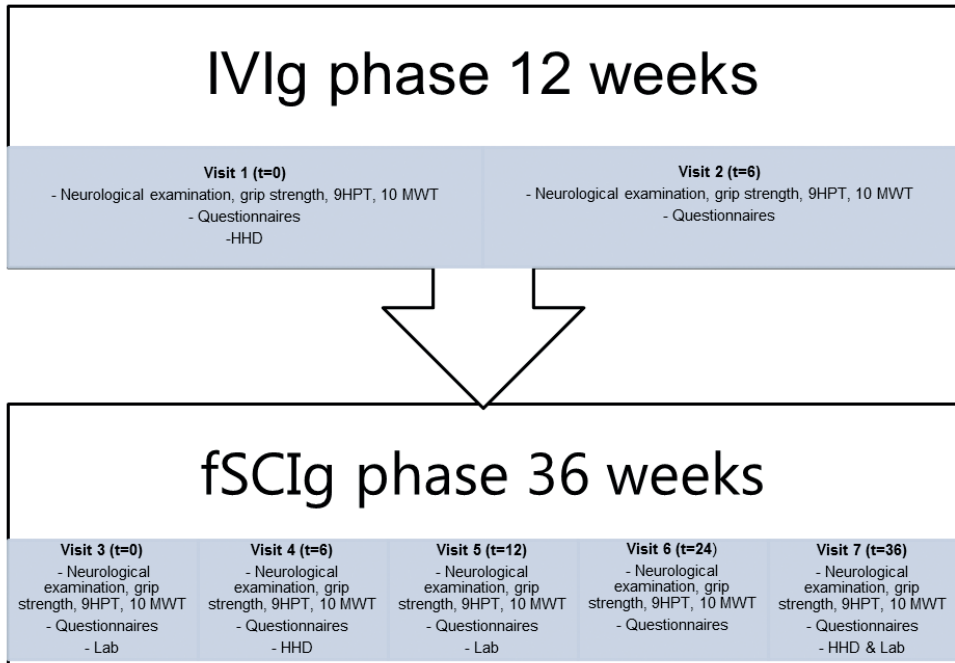
Figure 11.2 Outcome measures collected per visit

Questionnaires consisted of a standardized questionnaire for adverse events, treatment satisfaction rated on a 0-10 VAS scale, Guy's Neurological Disability Scale and Self-Evaluation Scale.

fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, HHD = Hand-held dynamometry, IVIg = intravenous immunoglobulins, Lab = laboratory tests, t= time in weeks, 9 HPT = 9-Hole Peg Test, 10 MWT = 10-Meter Walk Test

The primary aim was to assess the safety of fSCIg treatment. During the study we documented safety using a standardized questionnaire that included a number of adverse events and laboratory tests, including hemoglobin, hematocrit, haptoglobin, reticulocytes, lactate dehydrogenase, bilirubin, and direct Coombs test to exclude hemolytic anemia due to fSCIg. In addition, blood samples were obtained to explore a possible association between rHuPH20-binding antibody positivity and adverse events. In case of a serious adverse event related to fSCIg, the study treatment had to be discontinued. If a patient experienced an adverse event, the investigator or the patient him/herself could decide to discontinue the study treatment and resume regular IVIg treatment.

The second aim of this study was to measure muscle strength. All patients underwent a standardized neurological examination, and motor function of 18 muscle groups (abduction

of the arm, flexion and extension of the forearm, wrist and fingers, spreading of the fingers, abduction, adduction and opposition of the thumb, flexion of the hip, flexion and extension of the knee, and flexion and extension of the foot and toes) was graded bilaterally using the Medical Research Council (MRC) scale to calculate the MRC-sum score. Grip strength was determined bilaterally with the Martin-Balloon-Vigorimeter (Firma Gebrüder Martin, Tuttlingen, Germany) and measured in Kilopascals (kPa). Hand-held dynamometry (HHD) was performed bilaterally in nine muscle groups (abduction of the arm, flexion of the forearm, extension of the wrist and fingers, spreading of the fingers, abduction of the thumb, flexion of the hip, and extension of the foot and big toes) by a physiotherapist using the microFET2 (Hoggan health industries, Draper, UT, USA). Muscle strength with HHD was measured in Newton (N).

In addition, disability was determined with the Guy's Neurological Disability Scale and Self-Evaluation Scale (SES). To measure hand function and finger dexterity, the 9-Hole Peg Test (9-HPT) was performed with the most affected hand and the mean duration (in seconds) of five subsequent trials was calculated. Walking was evaluated with the 10-Meter Walk Test (10 MWT), for which the mean duration (in seconds) and number of steps of three repeats was calculated. Finally, patients were asked to rate their treatment satisfaction on a 0-10 point VAS-scale.

Treatment protocol

During the *IVIg phase*, patients remained on their regular IVIg maintenance therapy regimen to determine their current neurological functioning on therapy. After completion of the *IVIg phase*, patients switched to fSCIg treatment at a dose and frequency equivalent to the IVIg dose and frequency. Both Human Immune Globuline 10% and Recombinant Human Hyaluronidase were infused using a Micrel Rythmic pump. Personalized titration schedules were devised to increase the dose of fSCIg slowly and thus allow patients to get used to the presence of fluid in their abdominal wall. In general, patients received a dose of 25% of fSCIg in week 1, of 50% in week 2 and their total dose of fSCIg in week 3. IVIg treatment was discontinued when the total dose of fSCIg was administered. Treatment with fSCIg was administered in the patients' home setting. Specialized nurses were present during the first six infusions to teach patients how to administer fSCIg and to monitor and treat potential adverse events. After the first six infusions, patients were allowed to self-administer fSCIg at home.

If patients developed a decline in muscle strength during fSCIg treatment, investigators could increase the dose of fSCIg, provided there was no increase in adverse events. This decline in muscle strength was defined as a worsening of ≥1 of the outcome measures: Guy's Neurological Disability Scale (increase ≥1 in either the upper or lower limb score), SES (an increase of ≥1 at ≥2 motor activities) and HHD (a decrease of 50% in ≥2 clinically affected muscles groups). If patients showed no improvement after increasing fSCIg dose, or if adverse events occurred, fSCIg maintenance treatment was discontinued and IVIg treatment resumed.

Statistical analysis

All data were summarized using the median and range for continuous variables and number and percentage for categorical variables. Clinical characteristics between patients that continued with fSCIg or discontinued were compared using the Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The absolute frequency of adverse events with IVIg and fSCIg were compared using Fisher's exact test. For each patient we determined whether he or she switched back to IVIg, and, if so, the time spent on fSCIg. This time-to-event variable was visualized using Kaplan-Meier curves. Subsequently, we assessed which baseline factors affected the time spent on fSCIg using a Cox proportional hazards model. The mean difference of the HHD measurement was calculated as the difference between first evaluation under fSCIg (visit 4) and baseline (visit 1) and analysed using a paired t-test. The longitudinal outcome measures were analysed using linear mixed effect models (LMMs). The dependency in the data due to the repeated measures was accounted for by a random intercept per individual. The fixed effects part contained a term for treatment (IVIg or fSCIg) and a term for time (in months). Significance of both factors was determined using the likelihood ratio test. Due to the exploratory nature of this study, we did not adjust for multiple testing and results were considered significant when the *p*-value was lower than 0.05. All analysis were conducted in SPSS 22 (SPSS Inc., Chicago IL, USA) except for the LMMs that were fitted using the lmer function in the R package lme4 (version 1.1-12).[12]

RESULTS

Patients

The MMN database of the UMC Utrecht was screened (n=130) and all patients fulfilling the inclusion criteria were invited for participation (n=102). Of these, 54 patients did not respond or could not be reached, and 30 patients declined participation. In total, 18 patients, all treated with IVIg in home setting, were enrolled in this study between November 2016 and May 2017. Clinical characteristics of participants (n=18) and non-participants (n=30) were not significantly different, except for disease duration (6.7 years versus 16.9 years). One patient appeared to be unstable on IVIg treatment during the *IVIg phase* and was excluded from the study. The baseline characteristics of the remaining 17 patients are provided in **Table 11.1**. Two patients were lost to follow-up, both at visit 4 after discontinuation of fSCIg. In one patient, visit 4 was missing because of surgery for a hernia. According to the protocol, an increase of dose was required in one patient on IVIg treatment and in three patients on fSCIg treatment.

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Table 11.1 Baseline characteristics

	Total cohort (n = 17)	Continuation fSCIg (n=8)	Discontinuation fSCIg (n=9)	*P*-value
Age at inclusion (years)	57.7 (36.5-69.5)	61.6 (36.5-69.5)	50.2 (46.2-68.9)	0.16
Sex (male)	14 (82.4)	7 (87.5)	7 (77.8)	>.99
Symptom duration (years)	6.9 (2.0-29.9)	6.6 (2.0-29.9)	10.2 (4.9-23.9)	0.67
Duration of IVIg therapy (years)	4.9 (1.2-23.8)	4.3 (1.2-23.8)	4.9 (1.2-13.5)	0.88
Dosage IVIg (g/kg)	0.5 (0.3-2.2)	0.4 (0.3-2.2)	0.6 (0.4-0.6)	0.37
Interval IVIg (days)	21 (7.0-35.0)	21.0 (7.0-28.0)	21.0 (7.0-35.0)	0.37
Abnormal CSF protein	5/6 (83.3)	3/4 (75.0)	2/2 (100.0)	>.99
Abnormal MRI brachial plexus	6/10 (60.0)	2/5 (40.0)	4/5 (80.0)	0.52
Presence of anti-GM1 autoantibodies	11/16 (68.8)	7/8 (87.5)	4/8 (50.0)	0.28

Data are shown for the total cohort (n=17) and for patients that continued with fSCIg (n=8) and discontinued with fSCIg (n=9). Data are in median (range) or n (%).

CSF = cerebrospinal fluid, fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, g/kg = grams per kilogram, IVIg = intravenous immunoglobulins

Reasons and determinants of discontinuation

Nine patients (52.9%) discontinued fSCIg during the treatment phase after an average number of infusions of 4.7 (SD: 4.6). Baseline characteristics of patients that continued with fSCIg (n=8) and discontinued (n=9) were not significantly different (**Table 11.1**). Six participants decided to discontinue because of adverse events (local reactions at the injection site (n=6), nausea (n=1), cramps (n=1), general malaise (n=2) and headache (n=1)). One patient showed a decline in muscle strength but refused to increase the dose of fSCIg and chose to switch back to IVIg. The investigators withdrew two participants because of an unrelated serious adverse event (ischemic stroke, n=1) and decline in muscle strength despite increasing the dose of the fSCIg (n=1) (**Figure 11.1**).

We evaluated which outcome measures were associated with treatment discontinuation (i.e. treatment satisfaction, Guy's Neurological Disability score, SES, 10 MWT and 9-HPT).

Interestingly, treatment satisfaction was the only baseline factor associated with continuation of fSCIg: a higher satisfaction during the *IVIg phase* of the trial was associated with the continuation of fSCIg (HR 0.31 95% CI 0.12 – 0.83, p=0.007). To exemplify: after six months, 78% of the patients, whose satisfaction with IVIg treatment was initially ≥8, remained on fSCIg, compared to 25% of patients with a satisfaction rate <8 (**Supplemental Figure 11.1**).

Safety

Frequencies of adverse events, adverse events per year and adverse events per patient are shown for IVIg and fSCIg in **Table 11.2**. The frequency of systemic adverse events was lower in

fSCIg (n=87 on IVIg vs. n=35 on fSCIg, p=0.04); headache and general malaise occurred less often in fSCIg (*p*<0.01; *p*<0.01), while cramps and local reactions at the injection site occurred more often (*p*=0.03; p<0.01). None of the patients developed hemolytic anemia, nor did any develop rHuPH20-binding antibodies after initiation of fSCIg treatment.

During the study, three serious adverse events (coronary artery disease, ischemic stroke and diabetes mellitus) occurred in two patients (**Table 11.2**). Thrombosis is a rare adverse event of immunoglobulin treatment. However, all serious adverse events were considered unrelated to fSCIg treatment. The first patient reported angina pectoris at visit 4, during fSCIg treatment, but, in retrospect, this complaint had already been present three months before the start of the study (during treatment with IVIg), and had not been reported at visits 1-3. After cardiological evaluation, coronary artery disease was diagnosed. The cardiovascular risk profile of this patient consisted of hypertension, hypercholesterolemia, recurrent transient ischemic attacks (TIAs) treated with carotid endarterectomy and smoking. Between visits 6 and 7 (during IVIg treatment), the same patient had been admitted to hospital because of new onset diabetes mellitus. The second patient reported headache and visual complaints; i.e. spots in the left visual field, after only one low dose of fSCIg (10 gram) combined with a regular high dose of IVIg (40 gram). MRI cerebrum showed a small occipital lobe infarction. After extensive work-up performed by a neurovascular specialist, a combination of cardiovascular risk factors (hypercholesterolemia, hypertension and smoking) was deemed to be the most likely cause. During follow-up, this patient made a full recovery. Recovery of the visual field was confirmed by a normal perimetry examination performed by an ophthalmologist.

Muscle strength and disability

Overall, there were no significant differences between fSCIg and IVIg expressed in vigorimetry, 9-HPT, MRC sum score or HHD total score (**Table 11.3 and Table 11.4**). Interestingly, there was a strong improvement over time in the 10-meter walk test (both in time taken and number of steps, *p*-values <0.001). This observation may suggest a learning effect over time. Despite the adjustment for time this learning effect might obscure accurate estimation of the difference between fSCIg and IVIg in the 10-meter walk test. The SES increased by 0.6 points (95% CI 0.1 – 1.2, p=0.021) when switching to fSCIg. The deterioration in SES is temporary and improvable as it is most likely caused by a decline in muscle strength of one patient at visit 5, with a normalisation of the score when the dose of fSCIg was increased. Excluding this patient results in an increase in SES of 0.4 points (95% CI -0.1 – 0.8, p=0.097).

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Table 11.2 Safety profile of IVIg and fSCIg

	IVIg		fSCIg		
	Frequency	*Rate*	*Frequency*	*Rate*	*P-value*
Any systemic adverse event	81(14)	11.6	35 (11)	5.0	0.02
Skin reactions	12 (5)	1.6	6 (4)	0.9	0.79
Dizziness	4 (2)	0.5	2 (2)	0.3	1.00
Headache	26 (6)	3.5	6 (3)	0.9	<0.01
General malaise	17 (6)	2.3	2 (2)	0.3	<0.01
Fatigue	18 (5)	2.4	8 (3)	1.1	0.36
Increased hunger sensation	4 (1)	0.5	3 (1)	0.4	0.43
Cramps	1 (1)	0.1	5 (4)	0.7	0.03
Diarrhea	0 (0)	0.0	1 (1)	0.1	0.39
Dry mouth	0 (0)	0.0	1 (1)	0.1	0.39
Nausea	0 (0)	0.0	1 (1)	0.1	0.39
Lumbago	1 (1)	0.1	0 (0)	0.0	>0.99
Palpitations	1 (1)	0.1	0 (0)	0.0	>0.99
Hypertension	3 (2)	0.4	0 (0)	0.0	0.28
Local reactions at injection site	0 (0)	0.0	23 (11)	3.3	<0.01
Serious adverse event	3 (2)	0.1	0 (0)	0.0	0.29

Frequency = absolute frequency of adverse events, in brackets are the unique patients, fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, IVIg= intravenous immunoglobulins, P-value = comparison of absolute frequency of adverse events with IVIg and fSCIg, Rate = number of adverse events/per person-year

Treatment satisfaction and reasons for continuation

Overall, treatment satisfaction remained unchanged. The average treatment satisfaction with regard to IVIg and fSCIg was 7.9 (95% CI 7.3 to 8.5) and 7.5 (95% CI 6.8 to 8.1), respectively. Main reasons for continuation of fSCIg were independence to administer treatment (n=8) and decrease in presence of adverse events (general malaise (n=1), skin reaction (n=1)).

Table 11.3 Longitudinal outcome measures

Endpoint	Intercept	Treatment (IVIg vs. fSCIg)			Time (Months)		
		Coefficient	95% CI	P-value	Coefficient	95% CI	P-value
Vigorimetry, *kPa*	131.2	-2.9	-12.2 – 6.4	0.540	0.5	-0.7 – 1.6	0.410
MRC sum (0-180)	163.4	-0.8	-2.2 – 0.7	0.300	0.2	0.0 – 0.3	0.051
SES	11.4	0.6	0.1 – 1.2	0.021	0.0	0.0 – 0.1	0.360
10-meter walk, *steps*	14.0	0.3	0.1 – 0.6	0.020	-0.1	-0.1 – 0.0	< 0.001
10-meter walk, *seconds*	8.4	0.3	0.0 – 0.5	0.040	-0.1	-0.1 – -0.1	< 0.001
9-hole peg, *seconds*	32.3	2.5	0.0 – 5.1	0.051	-0.2	-0.6 – 0.1	0.120
Treatment satisfaction	7.9	-0.5	-1.0 – 0.0	0.067	0.0	-0.1 – 0.1	0.820

Results are given per mixed model with a fixed effect for treatment and a random intercept per individual (n = 17), adjusted for time to account for potential disease progression during study follow-up. The treatment estimate is the mean difference between treatment arms.

fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, IVIg = intravenous immunoglobulins, kPa = Kilopascals, MRC = Medical Research Council, SES = Self-Evaluation Scale, 95% CI = 95% confidence interval

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Table 11.4 Mean difference in Hand-held dynamometry

Endpoint	Mean difference (Post – Pre)	95% CI	*P*-value
Dynamometry, *Newton*			
Total	-21.3	-75.8 – 33.3	0.42
Shoulder abduction	-11.4	-33.0 – 10.2	0.28
Biceps flexion	-1.1	-11.5 – 9.2	0.82
Wrist extension	1.5	-7.2 – 10.2	0.72
Finger extension	2.5	-4.5 – 9.5	0.46
Finger spreading	2.5	0.0 – 5.0	0.049
Thumb abduction	-1.8	-4.5 – 0.9	0.18
Hip flexion	-4.8	-16.3 – 6.7	0.38
Ankle flexion	-7.5	-24.8 – 9.8	0.37
Toe extension	-1.2	-9.9 – 7.6	0.78

Two patients were excluded due to missing data of fSCIg. The mean difference was calculated as the difference between first evaluation under fSCIg (visit 4) and baseline (visit 1).

95% CI = 95% confidence interval

DISCUSSION

In the present study, we showed that the safety of fSCIg, a new mode of treatment, is comparable to IVIg, with the advantages of higher doses and less frequent infusion compared to conventional SCIg. In The Netherlands, approximately 90% of the patients with MMN are treated in a home care program, in contrast to countries where IVIg treatment is only given in a hospital setting. For this reason, the satisfaction rate for IVIg treatment is high, as there is no burden of travelling to hospital. Nevertheless, fSCIg was preferred compared to IVIg treatment by almost half of the patients, and they continued with fSCIg after study closure, in particular because of independence and flexibility to administer treatment and a decrease in systemic adverse events. A significant number of patients remained on IVIg treatment, probably because the benefits of fSCIg (i.e. more independence and flexibility of administration and a decrease in systemic adverse events) did not outweigh the well-facilitated IVIg home program due to the local reactions at fSCIg injection site. Moreover, in countries which do not offer the option of IVIg treatment in home setting, fSCIg could be an even more favorable option.

Regarding safety of fSCIg, we found similar results compared to previous publications on SCIg in MMN or to fSCIg in primary immunodeficiencies, and to a recently published study that compared fSCIf with conventional SCIg in 20 patients with MMN.[5-7,9,11,13-16] We reported local reactions at the injection sites in 64.7% of the patients, which is in accordance with previous studies that described local adverse reactions of fSCIg in 44-100% of the patients. [5-7,16,17] A systematic review and meta-analysis reported a significant reduction of 28% in the relative risk ratio of systemic

adverse events of SCIg compared to IVIg; this is comparable to a significant reduction in systemic adverse events of fSCIg versus IVIg in our study.[15] Overall, similar to previous studies, muscle strength, disability and treatment satisfaction in our study remained stable, showing equal muscle strength and disability and unchanged or improved quality of life and treatment satisfaction for SCIg compared to IVIg in patients with MMN.[5-7,13,14,16] Therefore, fSCIg could be a favorable alternative to IVIg treatment in MMN, as systemic adverse events may decrease, muscle strength, disability and treatment satisfaction remains stable, and there is the advantage of independence and flexibility of administration. Moreover, professional supervision of administration is not necessary for fSCIg treatment and could therefore reduce medical costs.[17-19]

An advantage of treatment with fSCIg is the reduced number of infusions compared to SCIg. This is relevant since we have previously found that patients in The Netherlands preferred IVIg in home setting to SCIg because of the high number of infusions of SCIg (unpublished data). This is in accordance with the results of a randomized single blinded cross-over trial and follow-up study by Harbo et al, investigating SCIg versus IVIg.[6,20] In this study, 4/9 patients preferred IVIg to SCIg especially because of the significantly lower number of infusions. Additionally, fSCIg allows self-administration of loading doses if necessary, as opposed to SCIg treatment, which requires IVIg loading doses and hence loss of independence and flexibility of administration.[7,21]

No clinical outcomes were associated with an increased risk of discontinuing fSCIg. Remarkably, the only prognostic factor for continuation of fSCIg was a higher (≥8) satisfaction in the *IVIg phase* of the study. These findings may be explained by the expectation level of patients regarding treatment with fSCIg. Patients who were less satisfied with IVIg treatment may have had higher expectations of fSCIg treatment, but as muscle strength, disability and treatment satisfaction were comparable to IVIg, these expectations may not have been met, causing patients to discontinue fSCIg earlier. Interestingly, in this study, patients who continued with fSCIg after study closure were more satisfied compared to their previous IVIg treatment because of the independence and flexibility of administration.

Study limitations include the relatively small number of patients, a common challenge in studies on rare disorders such as MMN. We were able to contact 48 patients with MMN of whom 18 (38%) participated. Furthermore, the study design was a prospective cohort and not a randomized controlled blinded trial. However, the route of administration of fSCIg did not allow a blinded study design, and as IVIg is standard of care this would limit the possibility withholding patients from immunoglobulin treatment. Moreover, we believe this study design was adequate for our aim to explore whether fSCIg could replace IVIg in individual patients, and whether it could serve as an alternative route of administration in a relatively rare disorder.

In conclusion, our study shows that safety of fSCIg is comparable to IVIg. Overall muscle strength, disability and treatment satisfaction remained unchanged after switch to fSCIg. Therefore fSCIg could be a favorable option in patients who prefer self-treatment and more independency, and in patients who experience systemic adverse events on IVIg or have difficult intravenous access.

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SUPPLEMENTAL MATERIAL
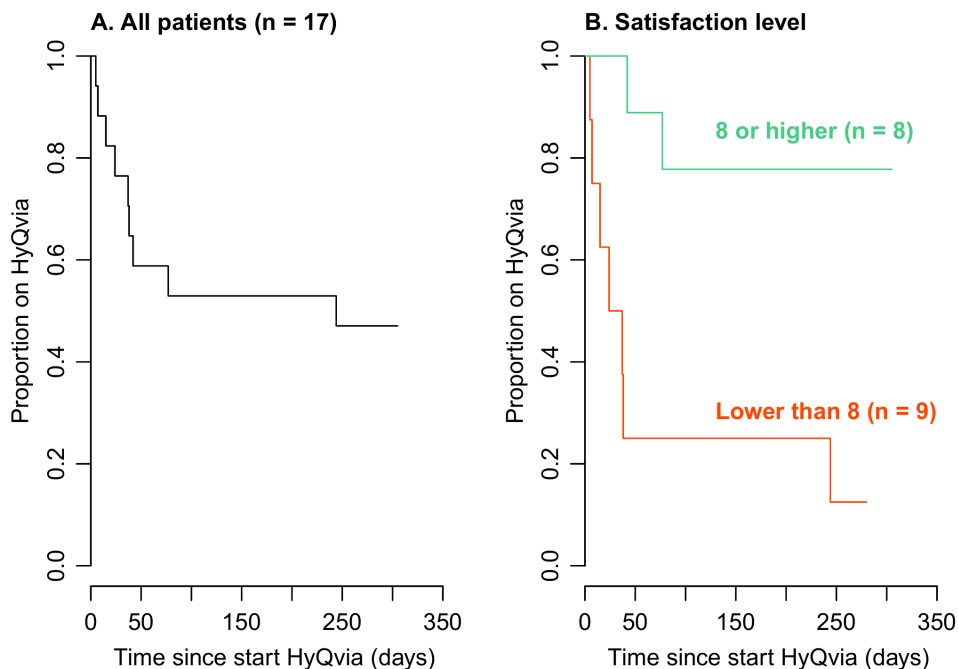
Supplemental Figure 11.1 Proportion of patients remaining on fSCIg treatment

(A) Kaplan-Meier curve of the proportion of patients on fSCIg treatment, the median time on fSCIg treatment was 244 days (n=17); for patients that continued with fSCIg 267 days and patients that discontinued with fSCIg 37 days. (B) For each patient, the average treatment satisfaction score on IVIg was calculated during phase 1 (visit 1-3) and assessed in a Cox proportional hazards models (HR 0.31 95% CI 0.12 – 0.83, p=0.007). To visualize its effects, we created two subgroups (green line; higher satisfaction level on IVIg and red line; lower satisfaction level on IVIg) based on the median of this satisfaction level.

fSCIg = Human Immune Globulin 10% with Recombinant Human Hyaluronidase, IVIg = intravenous immunoglobulins

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CHAPTER 12

General discussion
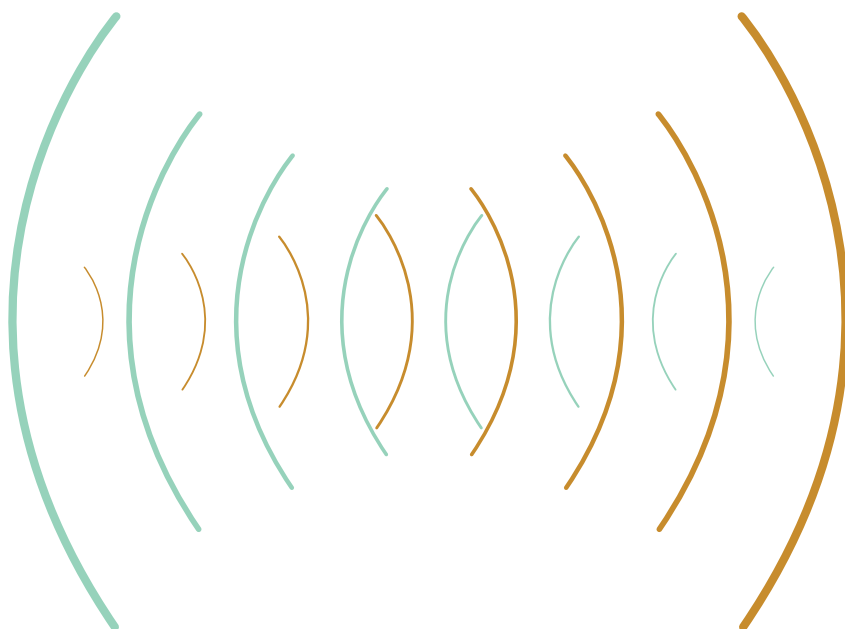
GENERAL DISCUSSION

Polyneuropathies are common disorders in neurological practice.[1-3] The discrimination of chronic inflammatory neuropathies including chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and Lewis Sumner syndrome (LSS), from the more common axonal forms is relevant, as treatment with immunoglobulins, corticosteroids or plasmapheresis can improve outcome.[4-8] Currently, the diagnosis of chronic inflammatory neuropathies is facilitated by consensus criteria in which nerve conduction studies (NCS) play a key role.[9-11] However, even after extensive NCS and other ancillary investigations, diagnosing chronic inflammatory neuropathies can be challenging and patients with treatable chronic inflammatory neuropathies may still be missed.[12-17] Therefore, new diagnostic tools are necessary to improve diagnostic yield. An important aim of this thesis was to investigate the value of the most promising new diagnostic tool: nerve ultrasound. This technique has the advantages of relatively low cost, low burden for patients, and its bedside feasibility.

Interobserver variability of nerve ultrasound

Previous studies that examined interobserver variability of nerve ultrasound had several limitations, e.g. single center design, data acquisition in only healthy controls and assessment of only a limited number of nerves.[17-19] Therefore, we investigated the interobserver variability in a multicenter setting (**chapter 2**). Nerve ultrasound was performed on different sonographic devices by different investigators. We enrolled both patients with different polyneuropathies and healthy controls and investigated nerve size at multiple nerve sites. Our results are therefore representative for both mono- and polyneuropathies. Various aspects that might contribute to interobserver variability were analyzed. Taken together, we found variability between investigators primarily in leg nerves and C6 and C7 nerve roots. The multilevel mixed model showed that different devices and different hospitals had no influence on interobserver variability. These findings indicate that nerve ultrasound of arm nerves and the C5 root can be reliably used in clinical practice and that in multicenter studies after proper training data can be pooled between centers. Inclusion of leg nerves and C6 and C7 nerve roots should preferably be avoided as interobserver variability of these sites is high. Interobserver variability of other sonographic parameters such as vascularization and echogenicity has not been studied, which can be potentially informative and may be addressed in future studies.

Pathophysiology

Both cellular and humoral responses play an important role in the pathophysiology of chronic inflammatory neuropathies, but the exact mechanisms still remain to be elucidated.[4, 20-24] CIDP, LSS and MMN are probably different diseases. Imaging techniques could contribute to our understanding of pathophysiology. An important piece of missing information is whether nerve ultrasound and nerve conduction studies yield similar or different information regarding function and morphology of peripheral nerves. We therefore systematically examined NCS features

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of demyelination and sonographic nerve enlargement in the different subtypes of chronic inflammatory neuropathies (**chapter 4, 5**).

a) Electrophysiological patterns

We found characteristic patterns of electrophysiological abnormalities (e.g. a lower occurrence of demyelinating features in sensory subtypes of CIDP and less frequent and more focal loss of sensory and motor axons in LSS) in the different subtypes of chronic inflammatory neuropathies, which support the hypothesis of distinct disease entities (**chapter 4**). An exception to this rule is the overlap between MMN and the pure motor subtype of CIDP; these disorders have different clinical phenotypes but show electrophysiological (preservation of sensory conduction combined with less slowing and more conduction block) and immunological (i.e. presence of anti-GM1 IgM antibodies) similarities.

b) Different findings in nerve ultrasound and NCS

We found no correlation between NCS features of demyelination and sonographic nerve enlargement, i.e. nerve enlargement was distributed randomly among nerves and segments with and without demyelination or axon loss (**chapter 4**). This discrepancy in function and morphology has previously been described in neurological disorders such as MS lesions and silent stroke. Moreover, it suggests that nerve ultrasound and NCS detect distinctive pathophysiological mechanisms (i.e. edema, inflammation, dysmyelination versus nodal and axonal dysfunction).

c) Distinct sonographic patterns in Charcot-Marie-Tooth type 1a (CMT1a) and chronic inflammatory neuropathies

In **chapter 5** we visualized the entire tract of both the median and ulnar nerve to complement previous findings at specific nerve sites. An important additional goal was comparison of CIDP and CMT1a as experience from previous studies suggests that the distinction of these disorder remains challenging.[17] The sonographic pattern in CMT1a differed from that in CIDP with significantly larger mean nerve CSA along the entire tract of the ulnar nerve and along a substantial part of the tract of the median nerve. This implies that nerve ultrasound is able to discriminate CIDP from CTM1a, although observations in larger patient groups (in particular CMT1a) are needed.

In chronic inflammatory neuropathies nerve enlargement of both the median nerve (proximal segments) and ulnar nerve (proximal and distal segments) was found, but more pronounced in CIDP and LSS than in MMN, and more focal in LSS compared to CIDP. These different sonographic patterns in chronic inflammatory neuropathies suggest that CIDP, MMN and LSS have unique pathophysiological mechanisms.

Taken together assessment of sonographic patterns seems to be of additional diagnostic value and supports the hypothesis of different disease entities of CIDP, MMN and LSS. However, we included a relatively small number of patients per disease group and future studies with a larger number of patients should be performed to replicate these findings. Other sonographic

parameters and investigations should also be addressed, e.g. echogenicity, fascicle size, MRI or excitability testing to further elucidate pathophysiology or to improve diagnostic yield.[25-28] Moreover, currently high frequency probes >70mhz are being developed, which could improve visualization of nerves; i.e. enable visualization of microstructural nerve architecture which could also improve the diagnostic possibilities of nerve ultrasound.[29]

d) Sonographic patterns in other conditions

In **chapter 3** we examined the sonographic pattern in Wartenberg's migrant sensory neuritis (WMSN), a rare patchy sensory neuropathy in which an auto-immune etiology has been suggested.[30-33] In this disease NCS may show a decrease of sensory nerve action potentials (SNAPs) in clinically affected nerves, but without characteristics features of demyelination.[30,32] We found mild multifocal enlargement in clinically affected and non-affected nerves at entrapment sites but also at non-entrapment sites and with involvement of the brachial plexus. This pattern shares characteristics with the pattern of both chronic inflammatory neuropathies and vasculitic neuropathy, which supports a possible inflammatory etiology of WMSN.[34,35] However, the pattern in WMSN is different, as in vasculitic neuropathy the brachial plexus is spared and in chronic inflammatory neuropathies enlargement in proximal nerve segments is more severe. Therefore, this pattern could be useful to establish a diagnosis of WMSN in patients with pure sensory complaints.

These data complement previously reported patterns of nerve enlargement detected by nerve ultrasound. In sarcoid neuropathy nerve enlargement predominates in the lower limbs.[36] In POEMS syndrome enlargement of both entrapment and non-entrapment sites has been described.[37-39] Currently, studies that examine sonographic patterns in other inflammatory conditions, i.e. celiac neuropathy, or Sjögren syndrome are lacking.

Diagnostic value of nerve ultrasound in chronic inflammatory neuropathies

In a previous study, our study group developed a short sonographic protocol that consisted of a limited number of nerve sites, i.e. the median nerve in the forearm, upper arm and the brachial plexus, using ROC curve analyses.[35] In **chapter 8** we validated this short sonographic protocol in patients with a clinical suspicion of a chronic inflammatory neuropathy in a multicenter setting. With a slightly modified version (i.e. with exclusion of nerve root C6 and C7 for which the interobserver variability is high) the sensitivity remained high, although specificity decreased to a moderate level.[40] This is the first sonographic protocol validated in a multicenter setting. It consists of only three nerve sites with low interobserver variability, rendering it a useful tool for clinical practice compared to previously described extensive sonographic protocols.[41-43]

In **chapter 6** we describe six patients who had nerve enlargement of the specific nerve sites of our short protocol, without NCS results that suggest demyelinating features according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS), but with objective response on treatment. These results suggest that nerve ultrasound is able to improve

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the identification of patients who can benefit from treatment that could postpone permanent deficits. These findings are supported by the results from a prospective single center study in patients with a clinical suspicion of chronic inflammatory neuropathy (**chapter 7**). The main hurdle in this study was defining the proper reference test for the index test, i.e. nerve ultrasound. The EFNS/PNS diagnostic consensus criteria were not useful, since NCS are a key element of these diagnostic criteria and we already knew that nerve ultrasound could detect treatment-responsive patients without the characteristics demyelination features on NCS.[12-17] Therefore, we decided to use a combination of the EFNS/PNS diagnostic consensus criteria and nerve ultrasound abnormalities. When patients met the EFNS/PNS diagnostic consensus criteria a diagnosis of chronic inflammatory neuropathy was established. On the other hand, when patients did not meet these consensus criteria, but had nerve ultrasound abnormalities fitting chronic inflammatory neuropathy, a diagnosis of chronic inflammatory neuropathy could be established if there was treatment response according to predefined criteria. In **chapter 7** we identified eight patients without characteristic demyelinating features according to the EFNS/PNS NCS criteria, but with abnormal nerve ultrasound and a response on treatment. The additional value to identify treatment-responsive patients with chronic inflammatory neuropathy was therefore 21% (8/38). In the multicenter validation study (**chapter 8**) we found a comparable added value of nerve ultrasound of 20-27% among centers. A consistent percentage between centers, making physician or hospital-bias less likely. The specificity of nerve ultrasound was much lower than the specificity of NCS. This can partly be explained by the fact that in case of nerve ultrasound abnormalities, treatment response was required, but treatment response rates vary between 70-90% in chronic inflammatory neuropathies.[5,44-46] This indicates that in patients with nerve ultrasound abnormalities but without treatment response a diagnosis of chronic inflammatory neuropathy could still be possible.

In our studies, compared to NCS, sensitivity of nerve ultrasound was higher and specificity much lower. Therefore, these investigations are complementary rather than comparable techniques. The test characteristics suggest that nerve ultrasound is able to exclude CIDP, MMN or LSS and that NCS can confirm these diagnoses. Replacement of one technique by the other seems not preferable, but diagnostic strategies in which both investigations are combined need to be developed. Based on the results of our study (**chapter 7**) we have designed two diagnostic strategies (**Figure 12.1**; A and B) to identify all patients who respond to therapy. As sensitivity of nerve ultrasound is high, strategy B - in which nerve ultrasound serves as screening tool - is most favorable, as this reduces the number of cumbersome NCS by 56%. In our study the treatment response rate was 63%, a bit lower compared to previous studies probably due to the predefined stringent criteria for treatment response. Therefore, in both strategies A and B, patients with nerve ultrasound or NCS abnormalities fitting CIDP or MMN, but without
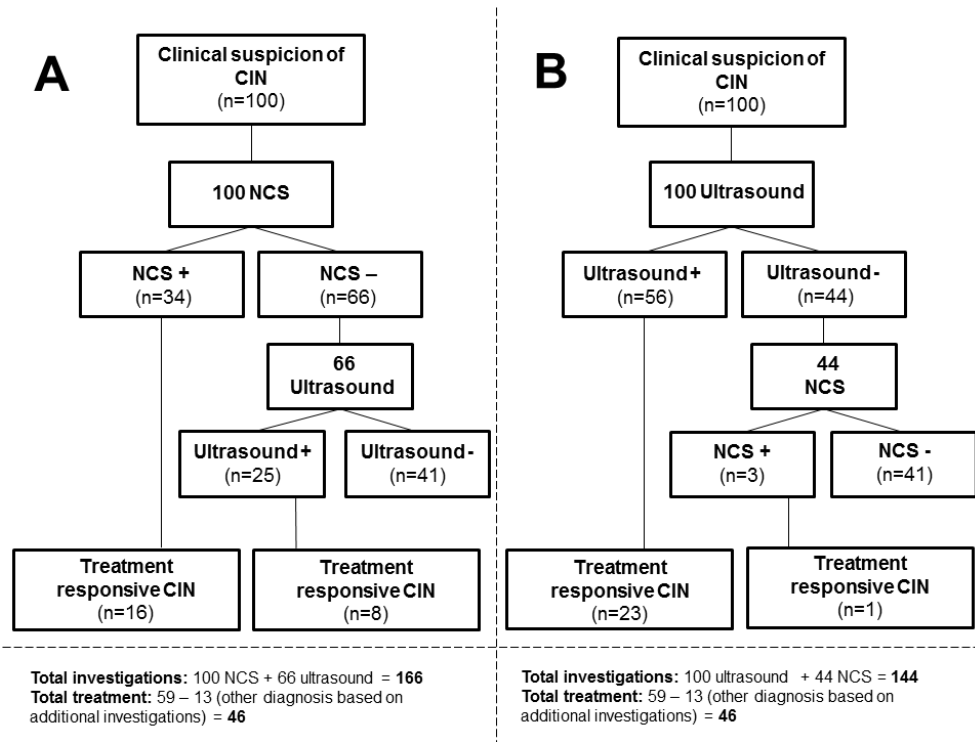
Figure 12.1 Diagnostic strategies A and B

Possible diagnostic strategies based on a subset of patients with documented treatment response.
Strategy 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

treatment response were not diagnosed as MMN or CIDP. This raises the question if a reduction in number of conducted NCS by 56% - with the aim to detect only patients who may benefit from treatment - outweighs diagnosing of chronic inflammatory neuropathy in only 63% of the patients. Therefore, we have also developed two other diagnostic strategies (**Figure 12.2**; C and D) in which "all" patients with a diagnosis of chronic inflammatory neuropathy were identified, independent of their response to treatment. Strategy D, seems to be the favorable strategy, in total 11 additional diagnostic investigations have to be performed compared to strategy C, but the number of NCS is reduced by 33%, and the number of treated patients remained stable. In strategy D, the first step in the diagnostic work-up will also be nerve ultrasound. Patients with nerve ultrasound abnormalities fitting chronic inflammatory neuropathy will receive treatment and in case of treatment response a diagnosis of chronic inflammatory neuropathy is established. In

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case of no response on treatment or in patients without abnormalities on nerve ultrasound, NCS will be performed to confirm a diagnosis of chronic inflammatory neuropathy. Taken together, both strategy B and D, starting with nerve ultrasound in the diagnostic work-up seem to be favorable, as these reduce the number of NCS.
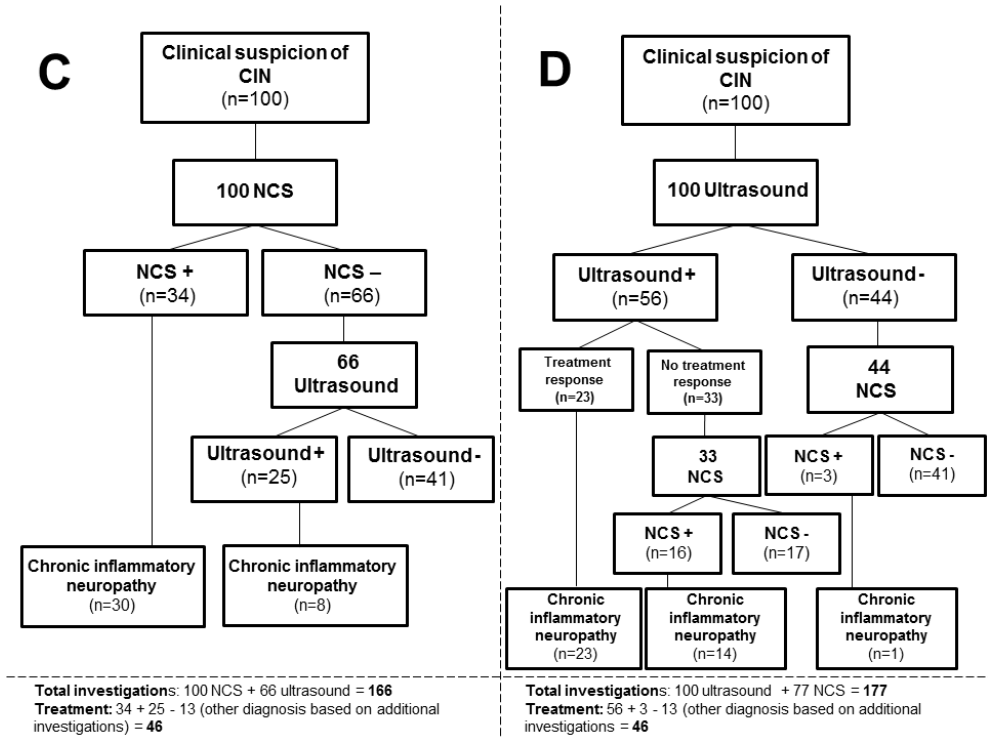

Figure 12.2 Diagnostic strategies C and D

Possible diagnostic strategies to identify "all" patients with a chronic inflammatory neuropathy independent of response on treatment.
Strategy C: NCS as primary investigation
Strategy D: 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

Although these approaches will reduce the number of NCS and thereby burden to patients, they will increase costs, since IVIg or SCIg trials need to be used to confirm the diagnosis. This will not be a completely new approach, since the EFNS/PNS diagnostic criteria suggest the use of trial treatment in case NCS results are not completely compatible with MMN or CIDP. Some may argue that the use of nerve ultrasound through its false positive results will lead to overtreatment.

We think that the availability of techniques and considerations of cost-effectiveness will shape diagnostic approaches in the future.

Proposal of new guidelines, practical implementation and future directions
Diagnostic consensus criteria such as the EFNS/PNS criteria are developed to provide evidence-based guidance on the definition, investigation and treatment of CIDP and MMN.[10,11] As nerve ultrasound and NCS have shown complementary test characteristics, nerve ultrasound should be implemented in future revisions of these criteria. A proposal for the revision of future diagnostic criteria based on the combination of nerve ultrasound and NCS, in which nerve ultrasound serves as screening tool, is shown in **Figure 12.3** and **Table 12.1**.
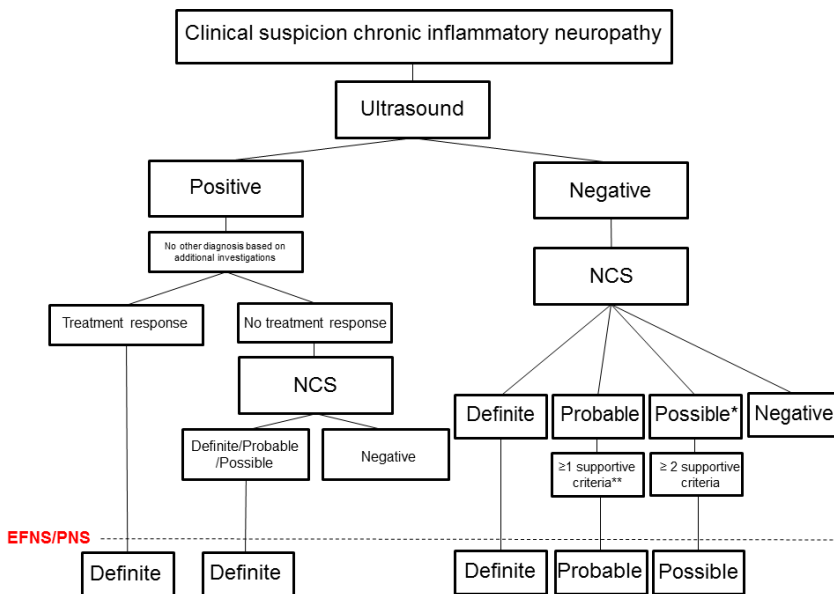
Figure 12.3 Summary of proposal of diagnostic criteria of chronic inflammatory neuropathies with nerve ultrasound as screening tool

NCS = nerve conduction studies

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Table 12.1 Summary of proposal of diagnostic criteria of chronic inflammatory neuropathies with nerve ultrasound as screening tool

CIDP

	1. Clinical criteria	2. Ultrasound	3. NCS	4. Supportive criteria				
				MRI brachial/ lumbosacral plexus	CSF protein	Treatment	NCS	Biopsy
	Key symptoms - Chronic (progressive, stepwise, recurrent) - Symmetric - Proximal & distal - Arms & legs - Absence or reduced reflexes Supportive symptoms - Tremor - Ataxia - Cranial nerve involvement	≥1 nerve sites with enlargement: - Median nerve forearm > 10 mm^2 - Median nerve upper arm > 13 mm^2 - C5 nerve root > 8 mm^2	Definite ≥1 features of demyelination in ≥ 2 nerves - DML ↑ - MCV ↓ - F-waves ↑ - Absence of F-wave - Temporal dispersion ↑ - Conduction block (area >50% ↓) - Distal CMAP duration ↑ Probable - Conduction block (area >30% ↓) Possible Features of demyelination as in definite but only in 1 nerve	Brachial/ lumbosacral plexus or spinal roots Hypertrophy or gadolinium enhancement	↑	Objective response	Abnormal sensory electrophysiology in ≥ 1 nerve	Demyelination and/or remyelination
Definite	+	+	Not performed	+		Treatment response		
	+	-	Definite	-		Not necessary		
	+	+	Definite/probable/ possible	+		No treatment response; other supportive criteria not necessary		
Probable	+	-	Probable	≥1 supportive criteria				
Possible	+	-	Possible	≥2 supportive criteria				

MMN

1. Clinical criteria	2. Ultrasound	3. NCS	4. Supportive criteria			
			MRI brachial plexus	CSF protein	Treatment	Lab
Key symptoms - Chronic progressive - Focal asymmetric - Weakness ≥ 2 nerve - No sensory symptoms Supportive symptoms -Predominant upper limb - Decrease or absent reflexes - No cranial nerve involvement - Cramps - Fasciculations	≥1 nerve sites with enlargement: - Median nerve forearm > 10 mm² - Median nerve upper arm > 13 mm² - C5 nerve root > 8 mm²	Definite - Conduction block (area >50% ↓) - Increase negative peak CMAP duration ≤ 30 % - Normal sensory nerve conduction upper limbs with conduction block Probable - Conduction block (area >30% ↓) - Increase negative peak CMAP duration ≤ 30 % or - Conduction block (area >50% ↓) - Increase negative peak CMAP duration >30% and - Normal sensory nerve conduction upper limbs with conduction block	Brachial roots Increased signal intensity on T2-weighted imaging	↑	Objective response	Anti-GM1 IgM antibodies ↑

Definite			
+	+	Not performed	Treatment response
+	-	Definite	Not necessary
+	+	Definite/probable/possible	No treatment response; other supportive criteria not necessary

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Table 12.1 continued

Probable	+	-	Probable ≥ 2 nerves	≥1 supportive criteria
	+	-	Probable ≥ 1 nerves	≥2 supportive criteria
Possible	Only 1 nerve weakness	-	Definite or probable ≥ 2 nerves	Not necessary
	Only 1 nerve weakness	-	Probable ≥ 1 nerves	≥2 supportive criteria
	Only 1 nerve weakness	+	Not performed	Treatment response + 1 supportive criteria

CIDP = chronic inflammatory demyelinating polyneuropathy, CMAP = compound muscle action potential, CSF = cerebrospinal fluid, DML = distal motor latency, MCV = motor conduction velocity, MMN = multifocal motor neuropathy, NCS = nerve conduction studies

Nerve ultrasound was initially performed in only a few specialized hospitals in The Netherlands, but the transition to a tool with additional diagnostic value in mononeuropathies has already led to the implementation of nerve ultrasound in many hospitals.[47-50] Moreover, our results (**chapter 6, 7, 8**) support further implementation of nerve ultrasound and they contributed to the inclusion of nerve ultrasound in the Dutch guideline for polyneuropathies. To facilitate the implementation of nerve ultrasound several changes are required, as hospitals need to create budget to finance equipment and training to adequately perform this test in polyneuropathies. As nerve ultrasound could replace a substantial number of the expensive and time-consuming NCS, this may reduce costs and therewith budget can become available for the implementation of nerve ultrasound.

A relatively new sonographic technique is 3D-ultrasound, which is already used in gynecology and cardiology. This technique has been sparsely investigated in peripheral nerve diseases.[51-54] The technique of 3D-nerve ultrasound could have several advantages compared to the conventional 2D technique; i.e. volumetric measurement could be performed which could improve follow-up of nerve abnormalities and could possibly decrease interobserver variability. The capability of scanning and storage of an entire nerve tract could be useful for the follow-up of specific patterns of nerve enlargement or tumors. Therefore, 3D nerve ultrasound seems promising, although future studies are needed that systematically assess a potential additional value compared to 2D nerve ultrasound. For chronic inflammatory neuropathies, the additional value seems limited as the 2D short nerve ultrasound protocol has high diagnostic accuracy and the additional value of follow-up on nerve size has to be examined (**chapter 10**).

Prognosis of chronic inflammatory neuropathies

Prediction of treatment response and disease course are important as this could select patients who may benefit from treatment and select patients who need more aggressive treatment. In **chapter 10** we explored the prognostic value of nerve ultrasound. We systematically assessed the correlation between nerve enlargement and clinical outcome measures, nerve size development over time and whether nerve size could predict clinical deterioration. We found that nerve ultrasound has limited prognostic value. Only in MMN, larger nerve CSA at baseline was associated with lower grip strength and involvement limited to the brachial plexus predicted a better outcome. However, overall, distribution and development over time of nerve enlargement in chronic inflammatory neuropathies was very heterogeneous. Our findings are in contrast to previous studies, in which a potential prognostic value of nerve ultrasound to predict disease course based on degree of nerve enlargement was described.[55-59] However, these studies had several shortcomings such as small sample sizes or a retrospective design. Based on our prospective study in a large sample of patients, nerve ultrasound has less of a value as a biomarker for disease progression. Repeated performance should not be encouraged and therefore nerve ultrasound can not replace the old-fashioned, systematic clinical follow-up of patients.

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Currently, we only analyzed the one-year follow-up data. The two years data will be further examined to ensure that potential long-term prognostic value will not be missed. Also, the group of patients with atypical variants of CIDP (e.g. pure sensory or pure motor variants) was relatively small. Therefore in these subgroups nerve ultrasound could also be useful as follow-up tool and future studies with a larger sample size are required. Other sonographic parameters e.g. echogenicity or vascularization should be examined in future to identify potential prognostic value in chronic inflammatory neuropathies. An example is quantification of intra-neural blood flow, already described in leprosy and patients with end-stage kidney disease, in which disappearance of intra-neural blood flow was associated with positive treatment response.[60,61] A new technique, which allows standardized assessments of intra-neural vascularization, is Superb Micro-Vascular Ultrasound Imaging (SMI), but the usefulness and whether this application is feasible in clinical practice should be further explored.

In **chapter 9** we performed a combined cross-sectional cohort and longitudinal study to explore the natural history of MMN patients. We found that almost all clinical outcome measures significantly deteriorated over time despite the fact that 87% of the patients were treated. This confirms that MMN is a progressive disorder and that studies are needed to investigate new and more aggressive treatment strategies.

Longer disease duration before treatment, presence of anti-GM1 IgM antibodies and younger age at onset of symptoms were associated with more severe weakness. Therefore, early recognition and treatment of MMN is important and new diagnostic tools such as nerve ultrasound could also serve this goal. The longitudinal follow-up data showed that lower MRC sum score and absence of reflexes at baseline were associated with a more progressive disease course.

Currently, the only effective treatment option is immunoglobulin therapy.[5,7,62,63] In The Netherlands almost all patients are treated with intravenous immunoglobulins (IVIg) at home. Disadvantages of IVIg are systemic adverse events i.e. skin reactions, headache and thromboembolic events.[8] Moreover, IVIg needs to be administered by a nurse. Therefore, new immunoglobulin therapies that can be administered independently and have fewer systemic adverse events could be an attractive alternative. Human immune globuline 10% with recombinant human hyaluronidase (fSCIg; HyQvia) is a new immunoglobulin treatment, already proven effective and registered in primary immunodeficiencies.[64-66] fSCIg overcomes the disadvantages of IVIg, as it can be administered by the patient or caregiver and has fewer systemic side effects. The main advantage compared to the conventional subcutaneous immunoglobulins is that a larger amount of infusion can be administered - due to the addition of hyaluronidase – which allows less frequent injections at fewer sites. In **chapter 11** we investigated fSCIg in MMN and found comparable safety, efficacy and treatment satisfaction to IVIg. Eight out of the 17 patients preferred fSCIg and continued after study closure. As many patients still await new treatment options in MMN this new therapy could decrease disease burden in individual patients, e.g. patients with many systemic adverse events or patients who aim for independence.

Conclusions

The main aim of this thesis was to determine the diagnostic value of nerve ultrasound in chronic inflammatory neuropathies. We found that nerve ultrasound could be reliably implemented in clinical practice and that addition of nerve ultrasound to routine diagnostic work-up improves identification of patients who may benefit from treatment by approximately 25%. Therefore, our results indicate that nerve ultrasound deserves a prominent place in future revisions of diagnostic consensus criteria and that this promising diagnostic tool should be implemented in general neurologic practices.

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ADDENDUM

Nederlandse samenvatting

Dankwoord

List of publications

About the author

NEDERLANDSE SAMENVATTING

Dit proefschrift is een verzameling van studies naar zeldzame maar vaak behandelbare ziekten van de perifere zenuwen en naar de waarde van zenuwechografie om dat soort ziekten op te sporen. Perifere zenuwen brengen de aansturende signalen vanuit de hersenen bij de spieren en informeren de hersenen en het ruggenmerg via de gevoelszenuwen over de stand van gewrichten en de relatie met de omgeving. Perifere zenuwen zijn onmisbaar bij beweging van vrijwel iedere spier en beschermen ons ook tegen schade door bijvoorbeeld scherpe voorwerpen, hitte en extreme koude. Een belangrijk bestanddeel van perifere zenuwen zijn zenuwcellen. In perifere zenuwen vormt een groot aantal zenuwcellen bundels. Deze bundels worden omhuld door een gelaagde en vetrijke structuur die myeline wordt genoemd. Myeline wordt gemaakt door het tweede belangrijke bestanddeel van perifere zenuwen, de zogenaamde Schwann cellen.

Het niet goed functioneren van perifere zenuwen of schade aan zenuwen geeft symptomen zoals krachtsverlies, gevoelsverandering, pijn, trillen (tremor) en onhandig bewegen (ataxie). Een aandoening van de zenuwen die dit soort klachten veroorzaakt noemen we 'polyneuropathie'.

Polyneuropathie is een veelvoorkomende aandoening binnen de neurologie. Neurologen onderscheiden vormen van polyneuropathie waarbij vooral de zenuwcel aangedaan lijkt (axonale polyneuropathie) en vormen waarbij het myeline of Schwann cellen betrokken zijn (demyeliniserende polyneuropathie). Er zijn veel verschillende oorzaken van beide vormen van polyneuropathie. De meest voorkomende oorzaken van axonale polyneuropathie zijn aandoeningen die kwetsbare zenuwcellen blootstellen aan stoffen die schadelijk zijn als ze een zekere drempelwaarde overschrijden, zoals bij diabetes mellitus (suikerziekte), nierfunctiestoornissen, vitamine tekorten of overmatig alcoholgebruik. Oorzaken van demyeliniserende polyneuropathie zijn 'fouten' in het DNA (de erfelijke varianten van polyneuropathie) of ontstekingsziekten die als groep worden aangeduid als 'chronisch inflammatoire polyneuropathieën'. Chronisch inflammatoire polyneuropathieën zijn zeldzaam, maar een juiste diagnose is belangrijk omdat ze – anders dan de meeste axonale polyneuropathieën – behandelbaar zijn.

De belangrijkste chronische inflammatoire polyneuropathieën zijn multifocale motorische neuropathie (MMN) en chronische inflammatoire demyeliniserende polyneuropathie (CIDP). Het belangrijkste kenmerk van MMN is in de loop van jaren toenemende asymmetrische spierzwakte van handen en onderbenen. CIDP veroorzaakt naast symmetrische spierzwakte van benen en in mindere mate de armen vaak ook gevoelsstoornissen en soms ataxie. Het Lewis Sumner syndroom (LSS) is een soort tussenvorm, met asymmetrische gevoelsstoornissen en spierzwakte. Momenteel wordt een diagnose van CIDP, MMN of LSS gesteld aan de hand van diagnostische consensus criteria waarbij de criteria van de European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) de belangrijkste zijn. Binnen deze diagnostische criteria speelt het EMG, maar vooral geleidingsonderzoek een centrale rol. Bij

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geleidingsonderzoek wordt onderzocht hoe snel en in welke mate zenuwen elektrische prikkels door kunnen geven. Dit onderzoek duurt lang, is vaak onplezierig en de interpretatie ervan vereist veel expertise die beslist niet in ieder ziekenhuis aanwezig is. Andere vormen van onderzoek die kunnen bijdragen aan de diagnostiek van chronisch inflammatoire polyneuropathieën zijn MRI onderzoek van de plexus brachialis (vlechtwerk van zenuwen in de hals), onderzoek van het vocht dat het ruggenmerg en de perifere zenuwen omringt (liquor), dat kan worden verkregen via een ruggenprik, bloedonderzoek naar de aanwezigheid van antistoffen die de zenuw kunnen beschadigen en een proefbehandeling met een infuus (intraveneuze immuunglobulines; IVIg) waarbij een positieve reactie als bewijs gezien wordt voor de diagnose. IVIg behandeling is zeer kostbaar en heeft ook bijwerkingen. Er is dus behoefte aan betere en goedkope methoden voor de diagnostiek van chronische inflammatoire polyneuropathieën.

Een relatief nieuw diagnostisch middel is zenuwechografie. Echografie maakt gebruik van geluidsgolven die niet schadelijk zijn. Dit onderzoek wordt al langere tijd in de gynaecologie en cardiologie gebruikt. Binnen de neurologie is gebleken dat (oppervlakkige) zenuwen goed kunnen worden afgebeeld met echografie, waarbij de zenuw er op een dwarse (transversale) doorsnede uitziet als een ronde/ovale honingraat structuur. Zenuwechografie is anders dan EMG pijnloos, relatief gemakkelijk uitvoerbaar en het duurt korter. De bruikbaarheid van zenuwechografie is met name onderzocht voor de zogenaamde mononeuropathieën, aandoeningen waarbij slechts 1 zenuw is aangedaan, meestal ten gevolge van compressie. Voorbeelden hiervan zijn het carpale tunnel syndroom (CTS) in de pols of de ulnaropathie in de elleboog. Voor deze aandoeningen is zenuwechografie al langer een belangrijk onderdeel van de diagnostiek zoals beschreven in de Nederlandse richtlijn van de Vereniging voor Neurologie voor CTS en ulnaropathie.

Tot een aantal jaar geleden was er minder bekend over de waarde van zenuwechografie voor polyneuropathieën. Een groeiend aantal studies laat echter zien dat ook bij deze aandoeningen de zenuwoppervlakte op een dwarsopname vaak vergroot is. De aanwezigheid of het specifieke patroon van deze verdikkingen is wellicht karakteristiek voor een specifieke oorzaak van de polyneuropathie. Hoewel deze bevindingen veelbelovend zijn was de kwaliteit van deze eerste onderzoeken nog niet goed genoeg om zenuwechografie voor polyneuropathie dezelfde plaats te geven als voor mononeuropathie. De onderzoeken waren namelijk voornamelijk retrospectief, waarmee bedoeld wordt dat al eerder verzamelde data werden gebruikt, wat kan leiden tot verkeerde of overdreven conclusies. Daarnaast werden in deze studies patiënten die al behandeld werden naast onbehandelde patiënten beschreven. Onderzoekers gebruikten ook verschillende onderzoeksprotocollen, wat betekent dat niet altijd dezelfde zenuwen op dezelfde manier werden onderzocht en het was ook niet bekend of de onderzoeksprotocollen in de handen van verschillende onderzoekers bij dezelfde patiënt ook dezelfde resultaten zouden opleveren. Deze zogenaamde reproduceerbaarheid is belangrijk om zeker te zijn van de betrouwbaarheid van een onderzoekstechniek. Om deze redenen is een aantal jaren geleden door samenwerkende Utrechtse en Tilburgse onderzoekers een relatief grote studie uitgevoerd

waarbij met zenuwechografie onder andere de zenuwdikte in een groep patiënten met CIDP, MMN en LSS en als controlegroep patiënten met vergelijkbare symptomen zoals de spierziekte ALS of een axonale polyneuropathie, is gemeten. Vervolgens kon worden vastgesteld welke zenuwdikte alleen bij ziekten als MMN en CIDP wordt gezien. Met deze gegevens is vervolgens een echoprotocol ontwikkeld dat een zeer hoge diagnostische waarde lijkt te hebben om chronische inflammatoire polyneuropathieën te onderscheiden van de andere ziektebeelden met vergelijkbare symptomen. Dit echoprotocol is makkelijk uitvoerbaar, kost weinig tijd en kan na een korte training worden toegepast. Het bestaat uit meting van de dwarsdoorsnede van de nervus medianus in de onderarm en bovenarm in combinatie met zenuwwortels C5, C6 en C7. De waarde van dit echoprotocol is vervolgens getest in een aantal van de hoofdstukken in dit proefschrift.

Zoals hierboven al genoemd moet een nieuw diagnostisch middel dat ingezet gaat worden in de dagelijkse diagnostiek een hoge reproduceerbaarheid hebben, dat wil zeggen dat onderzoekers die na elkaar hetzelfde onderzoek uitvoeren bij dezelfde patiënt dezelfde bevindingen rapporteren. In **hoofdstuk 2** hebben we in drie verschillende ziekenhuizen voor het eerst de reproduceerbaarheid van zenuwechografie onderzocht in een groep patiënten met verschillende aandoeningen van perifere zenuwen. We vonden geen grote systematische verschillen in uitslagen verkregen met zenuwecho door verschillende onderzoekers, in verschillende centra of met verschillende echo-apparaten. Deze resultaten laten zien dat zenuwechografie betrouwbaar is en kan worden ingezet als instrument voor de diagnostiek.

Hoofdstuk 3 beschrijft de waarde van zenuwecho bij de diagnostiek van een zeer zeldzame aandoening waarbij alleen gevoelszenuwen zijn aangedaan, het syndroom van Wartenberg ('Wartenberg's migrant sensory neuritis (WMSN). WMSN is een polyneuropathie waarvan de oorzaak niet geheel duidelijk is maar waarbij mogelijk gedacht wordt aan een auto-immuun ziekte of aan ontsteking van de bloedvaatjes die de zenuwen omhullen. Patiënten hebben gevoelsklachten die optreden in kleine gedeeltes van de romp, het gelaat, armen of benen. De diagnose WMSN wordt gesteld op basis van deze specifieke symptomen. Het EMG kan aanwijzingen tonen voor lichte axonale schade (schade aan de binnenlaag) van alleen de aangedane gevoelszenuwen maar dit is geen specifiek kenmerk. Met zenuwechografie hebben we voor het eerst acht patiënten met WMSN onderzocht en deze vergeleken met een controlegroep. We vonden lichte verdikkingen op compressieplekken maar ook buiten deze plekken. Dit is een patroon wat lijkt op het patroon van zenuwverdikkingen beschreven bij patiënten met chronisch inflammatoire polyneuropathieën. Dit ondersteunt de hypothese dat WMSN wordt veroorzaakt door een ontstekingsproces. Zenuwecho kan in de toekomst bijdragen aan de diagnostiek van deze zeldzame aandoening.

Of zenuwecho en EMG onderzoek vergelijkbare resultaten opleveren en of zenuwen die er op een echobeeld verdikt uitzien ook afwijkend zijn bij EMG onderzoek hebben we onderzocht in

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hoofdstuk 4. In deze studie is een groep van 140 patiënten met een chronisch inflammatoire polyneuropathie geïncludeerd. Het bleek dat er geen duidelijke samenhang was tussen EMG parameters die samenhangen met demyelinisatie en de zenuwdikte. Zenuwverdikkingen konden gevonden worden in zenuwen met en zonder EMG afwijkingen. Een discrepantie tussen functie en anatomie/structuur is niet ongewoon in de neurologie. EMG en zenuwechografie leggen waarschijnlijk verschillende aspecten van de ziektemechanismen van chronisch inflammatoire polyneuropathieën vast. Het betekent mogelijk ook dat de technieken elkaar in de diagnostiek kunnen aanvullen (zie **hoofdstuk 6 en 7**).

Het gaat niet alleen maar om hoe dik zenuwen zijn, maar ook om het specifieke patroon van zenuwverdikkingen. Een patroon is soms ziekte specifiek. **Hoofdstuk 5** beschrijft hoe we door middel van zeer gedetailleerde metingen ("inching", wat betekent dat we de zenuwdikte elke 2 cm wordt gemeten) over de volledige lengte van twee zenuwen deze patronen in nog meer detail hebben onderzocht. We vonden dat zenuwverdikkingen in chronisch inflammatoire polyneuropathieën het meest uitgesproken zijn in de bovenarm. De mate van verdikkingen verschilde echter tussen de chronisch inflammatoire polyneuropathieën; bij CIDP en LSS was de zenuwdikte gemiddeld groter dan bij MMN. Daarnaast is bij CIDP en LSS de nervus ulnaris en nervus medianus ter hoogte van de bovenarm verdikt en bij MMN lijkt dit alleen bij de nervus medianus het geval te zijn. Deze patronen zouden een toegevoegde waarde kunnen hebben voor het onderscheiden van CIDP, MMN en LSS indien de klinische symptomen niet geheel specifiek zijn.

In **hoofdstuk 6** hebben we zes patiënten beschreven die *geen* EMG afwijkingen hadden die wijzen op een chronische inflammatoire polyneuropathie, maar *wel* verdikkingen op de zenuwecho passend bij CIPD, MMN en LSS én een positieve reactie op behandeling. Deze studie laat zien dat er een toegevoegde waarde van zenuwechografie is in de detectie van behandelbare patiënten met CIDP, MMN en LSS. Hoe groot deze toegevoegde waarde is bleek uit de eerste 'prospectieve' studie (**hoofdstuk 7**) naar de waarde van zenuwechografie. We gebruikten zenuwechografie en EMG naast elkaar bij 100 patiënten die voor het eerst de polikliniek bezochten en bij wie er een verdenking was op CIDP, MMN of LSS. In totaal kon bij 38 patiënten een chronisch inflammatoire neuropathie worden gediagnosticeerd, waarvan bij 30 patiënten de diagnose met EMG kon worden gesteld. Door de toevoeging van echo konden er dus 8/38 (21%) extra patiënten worden geïdentificeerd. De sensitiviteit (een maat voor de gevoeligheid van een test) van zenuwechografie was dus duidelijk hoger. Deze hogere gevoeligheid betekende echter ook dat er met echo meer patiënten werden gevonden met verdikkingen die uiteindelijk geen chronische inflammatoire polyneuropathie bleken te hebben. De 'specificiteit' (bepaalt hoe specifiek een test is) van het EMG was duidelijker hoger. Dit geeft aan dat EMG en zenuwecho een complementaire diagnostische waarde hebben. Op basis van deze bevindingen hebben we een diagnostische strategie geformuleerd, waarin zenuwechografie dient als eerste test en EMG kan dienen ter bevestiging. Dit zorgt voor een daling van het aantal te verrichte EMG's van

56%. Echter deze strategie zal wel een stijging geven van de kosten omdat behandeling met immunoglobulines zal moeten worden ingezet om een diagnose te bevestigen. In de toekomst zal dan ook een kosteneffectiviteitsstudie moeten worden uitgevoerd waaruit zal blijken wat de meest optimale diagnostische strategie zal zijn.

Waar in **hoofdstuk 7** de waarde van zenuwecho bij de diagnostiek in slechts één ziekenhuis werd onderzocht, deden we dit in **hoofdstuk 8** met hetzelfde korte echoprotocol op vergelijkbare wijze bij 100 patiënten met een klinische verdenking op een chronisch inflammatoire polyneuropathie in 3 andere ziekenhuizen. Het bleek dat met een protocol van drie zenuwpunten (nervus medianus in de onderarm, bovenarm en wortel C5) de diagnostische betrouwbaarheid van zenuwechografie hoog bleef. De resultaten uit **hoofdstuk 7** werden volledig bevestigd in deze studie. Ook in deze studie bleek de sensitiviteit van zenuwechografie hoger dan die van het EMG en was dit voor de specificiteit omgekeerd. Het onderzoek bevestigde dat het gebruik van zenuwechografie als screeningstool leidt tot een daling van het aantal aangevraagde EMG's met 53%. Opnieuw vonden we 25% meer patiënten met een chronisch inflammatoire neuropathie die positief op behandeling reageerden. Concluderend blijkt uit **hoofdstuk 6, 7 en 8** dat zenuwechografie een belangrijk diagnostisch instrument is voor chronisch inflammatoire polyneuropathieën en dat bij de revisie van de huidige EFNS/PNS criteria zenuwechografie moet worden toegevoegd.

Of zenuwechografie ook kan worden gebruikt om het beloop van chronisch inflammatoire polyneuropathieën in de tijd of het effect van een kostbare therapie te meten is nooit systematisch in grote aantallen patiënten onderzocht. Kleine studies suggereerden dat indien een patiënt goed op therapie reageerde de zenuwdikte ook afnam. In **hoofdstuk 10** hebben we de prognostische waarde van zenuwechografie onderzocht in een multicenter studie met 230 patiënten met een chronische inflammatoire polyneuropathie of een axonale polyneuropathie. We hebben in deze studie patiënten één jaar lang vervolgd. Het blijkt dat zenuwechografie geen duidelijke prognostische waarde heeft in de periode van één jaar. Op basis van deze resultaten lijkt het dus niet zinvol om zenuwechografie te herhalen om het beloop of behandeleffect te meten.

De laatste hoofdstukken beschrijven studies naar het beloop en de behandeling van MMN. Over deze zeldzame aandoening is nog relatief weinig bekend. In **hoofdstuk 9** hebben we de resultaten van de studie naar het natuurlijk beloop van MMN beschreven. In deze studie werden 100 MMN patiënten geïncludeerd. Zestig van hen deden ook mee aan een studie die is uitgevoerd in 2007 in het UMC Utrecht. We konden in deze groep daarom onderzoeken hoe het beloop van de ziekte is in ongeveer 10 jaar. De resultaten van deze studie toonden dat MMN geen indolente aandoening is, maar een progressieve ziekte ondanks het feit dat een grote meerderheid van de patiënten behandeld werd. Zeven van de tien instrumenten die we gebruikten om de conditie van de zenuwen vast te leggen toonden een verslechterende functie. Afwezigheid van spierrekkingsreflexen en een lagere spierkracht uitgedrukt in de door neurologen dagelijks gebruikte classificatie voor spierkracht ('MRC score') zijn voorspellend

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voor een snellere progressie van de ziekte. Daarnaast lijkt de leeftijd van het ontstaan van de klachten en de leeftijd ten tijde van de diagnose in de afgelopen jaren te zijn gestegen, terwijl de tijd die dokters nodig hebben om de diagnose te stellen juist korter is geworden. Het stellen van een diagnose duurde het langst bij patiënten met klachten die in het been begonnen of bij oudere patiënten. Een verklaring hiervoor kan zijn dat deze klachten niet geheel typisch zijn voor MMN. Vanuit eerdere studies weten we dat hoe langer er geen behandeling wordt ingezet hoe slechter de uitkomst. Het verder afnemen van de tijd tot diagnose is dan ook van groot belang en hopelijk zal de toevoeging van zenuwechografie aan de diagnostiek hieraan gaan bijdragen.

Immunoglobulines spelen een belangrijke rol in de behandeling van chronisch inflammatoire polyneuropathieën. Het grootste deel van de patiënten in Nederland wordt met intraveneuze (via een infuus; IVIg) of subcutane (onder de huid, SCIg) immunoglobulines behandeld. Nadelen van deze behandeling zijn de bijwerkingen zoals hoofdpijn, huidreacties en algehele malaise maar daarnaast kunnen er ook zeldzame bijwerkingen optreden zoals een ernstige allergische reactie of de vorming van bloedstolsels (trombo-embolieën), die kunnen leiden tot bijvoorbeeld een longembolie of beroerte. Subcutane en intraveneuze immunoglobuline behandeling zijn beiden effectief. Voordelen van de subcutane behandeling zijn dat er voor toediening geen verpleegkundige nodig is maar dat patiënten dit zelfstandig kunnen uitvoeren en dat er minder bijwerkingen optreden. Nadelen van de subcutane immunoglobulines zijn echter dat er maar een kleine dosering per keer kan worden toegediend en patiënten dus vaak meerdere keren per maand moeten injecteren. Een nieuw medicijn, al geregistreerd voor primaire immuundeficiënties, is Human Immune Globuline 10% with Recombinant Human Hyaluronidase (HyQvia). HyQvia is een subcutane immunoglobuline gecombineerd met een enzym dat ervoor zorgt dat in de onderhuidse bindweefsellaag kortdurend een reservoir ontstaat waardoor een grote hoeveelheid immunoglobulines in één keer kan worden toegediend. In **hoofdstuk 11** hebben we de behandeling met HyQvia onderzocht bij 17 patiënten met MMN. HyQvia was veilig en daarnaast leek het even effectief te zijn als intraveneuze immunoglobulines. De helft van de patiënten was tevreden met de nieuwe behandeling en wilde na het beëindigen van de studie graag HyQvia blijven gebruiken.

De belangrijkste bevinding in dit proefschrift is dat zenuwechografie een betrouwbare en zeer gevoelige methode is om zeldzame maar op behandeling reagerende aandoeningen van perifere zenuwen op te sporen. Deze techniek kan idealiter naast geleidingsonderzoek worden gebruikt. Door de toevoeging van zenuwechografie aan de diagnostiek van chronisch inflammatoire polyneuropathieën verbetert de detectie van behandelbare patiënten met 25%. Om deze reden staat de titel in een **kwart**punt op de voorkant van dit proefschrift. Zenuwechografie als diagnosticum is inmiddels toegevoegd aan de Nederlandse richtlijn voor polyneuropathieën en hopelijk gebeurt dit ook bij de revisie van de internationale ENFS/PNS richtlijnen.

DANKWOORD

"Alone we can do so little; together we can do so much" – Helen Keller

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ABOUT THE AUTHOR

Ingrid Herraets was born on the 27th of December 1985 in Venray, The Netherlands. She graduated in 2004 from secondary school (Gymnasium, Raayland College Venray). After studying Health Sciences for one year, she switched to the study Medicine at Maastricht University. During her study she was involved in research projects at Kempenhaeghe Epilepsy Center in Heeze and at the department Human Biology at the University of Maastricht. After graduating in 2011 she worked as a medical doctor at the Neurology department at Medisch Spectrum Twente in Enschede. In 2013 she started her Neurology residency under supervision of dr. P.L.M. de Kort and currently under supervision of dr. J.T.H. van Asseldonk at Elisabeth-Tweesteden Ziekenhuis in Tilburg. In January 2016 she started her PhD programme on the diagnostic and prognostic value of nerve ultrasound in chronic inflammatory neuropathies under supervision of prof. dr. L.H. van den Berg and prof. dr. L.H. Visser at the UMC Utrecht. She lives together with Tim and their daughter Amber in Breda and they are expecting their second child in April 2020.

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