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

H. Stephan Goedee MD, PhD1 | Ingrid J. T. Herraets MD1,2 | Leo H. Visser MD, PhD2 | Hessel Franssen MD, PhD1 | Jan-Thies H. van Asseldonk MD, PhD2 | W. Ludo van der Pol MD, PhD1 | Leonard H. van den Berg MD, PhD1

1Brain Centre Rudolf Magnus, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht, The Netherlands
2Department of Neurology and Clinical Neurophysiology, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands

Correspondence
Stephan Goedee, UMC Utrecht, Department of Neurology and Neurosurgery, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.
Email: h.s.goedee-2@umcutrecht.nl

Funding information
Prinses Beatrix Spierfonds, Grant/Award Number: W.OR14-08

Abstract

Introduction: We 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. 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: Nerve conduction studies 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.

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

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, EMG, multifocal motor neuropathy, nerve enlargement, nerve ultrasound

1 | 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 probability 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 MRI, albumino-cytological dissociation in cerebrospinal fluid, or the titre of anti-GM1 immunoglobulin (Ig) M antibodies (only for MMN), are abnormal.\(^3\) However, treatment response rates in such cases are relatively low. Other diagnostic strategies are required 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.

### TABLE 1 Patient characteristics

| Patient | Sex | Age, y | Disease duration, mo | First symptoms | Clinical findings | Clinical phenotype | Improvement after treatment |
|---------|-----|--------|----------------------|----------------|------------------|-------------------|-----------------------------|
| 1       | W   | 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 |
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.

2.2 | 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.

3 | 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 1, and results from ancillary investigations are presented in Table 2 (see Table S1): 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 patient 6, respectively) 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 required 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 criteria1,2 in patient 6 but not in the other patients (1-5). Sonography results are presented in Table 3 (see Figure S1). High-resolution ultrasound was performed on the same day as the 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 1, Table S2).

4 | 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 LMN 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

| TABLE 2 | Summary routine ancillary investigations |
|---|---|---|---|---|---|
| Patient | NCS(EFNS/PNS criteria are not fulfilled) | MRI(brachial plexus) | CSF protein content, mg/dL | Supportive criteria EFNS/PNSa | Diagnostic criteria EFNS/PNS |
| 1 | CMAP1: median bilateral, right tibial + left fibular nerves | Normal | 37 | 1 (treatment) | Not compatible |
| 2 | CMAP1 of left and absent on right fibular nerve | Normal | 103 | 2 (CSF, treatment) | Not compatible |
| 3 | SNAP1: right median, both sural nerves | Normalb | ... | 1 (treatment) | Not compatible |
| 4 | DML1 and SNAP1: of right median nerve (CTS), CMAP1 fibular and tibial nerves, SNAP1: 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 | SNAP1: 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 |

Abbreviations: ... data not available; CMAP, compound muscle action potential; CSF, cerebrospinal fluid (elevated protein content was defined as ≥40 mg/dL, indicated in bold type); CTS, carpal tunnel syndrome; DML, distal motor latency; EFNS/PNS, European Federation of Neurological Societies and the Peripheral Nerve Society; NCS, nerve conduction study; SNAP, sensory nerve action potential.

aAbnormal 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.
bAdditionally diagnosed with non-Hodgkin lymphoma.
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 result 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.

### CONFLICT OF INTEREST

The authors report no conflicts of interest relevant to the study reported here.

### REFERENCES

1. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. *J Peripher Nerv Syst.* 2010;15(4):295-301.

2. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—First Revision. *J Peripher Nerv Syst.* 2010;15(1):1-9.

3. Cats EA, van der Pol WL, Piepers S, et al. Correlates of outcome and response to IVIg in 88 patients with multifocal motor neuropathy. *Neurology.* 2010;75(9):818-825.

4. Goedee HS, van der Pol WL, van Asseldonk JH, et al. Diagnostic value of sonography in treatment-naive chronic inflammatory neuropathies. *Neurology.* 2010;75(9):818-825.

5. Gasparotti R, Lucchetta M, Cacciavillani M, et al. Neuroimaging in diagnosis of atypical polyradiculoneuropathies: report of three cases and review of the literature. *J Neurol.* 2015;262(7):1714-1723.

6. Pitarokoili K, Gold R, Yoon MS. Nerve ultrasound in a case of multifocal motor neuropathy without conduction block. *Muscle Nerve.* 2015;52(2):294-299.

7. Hobson-Webb LD, Donahue SN, Bey RD. Multifocal motor neuropathy: 30 years from onset to diagnosis. *Muscle Nerve.* 2016;53(3):490-491.

8. Lucke IM, Adrichem ME, Wieske L, et al. Intravenous immunoglobulins in patients with clinically suspected chronic immune-mediated neuropathy. *J Neurol Sci.* 2019;397:141-145.

9. Van Asseldonk JT, Van den Berg LH, Kalmijn S, Wokke JH, Franssen H. Criteria for demyelination based on the maximum slowing due to...
axonal degeneration, determined after warming in water at 37 degrees C: diagnostic yield in chronic inflammatory demyelinating polyneuropathy. Brain. 2005;128(Pt 4):880–891.
10. Van Asseldonk JT, Van den Berg LH, Wienieke GH, Wokke JH, Franssen H. Criteria for conduction block based on computer simulation studies of nerve conduction with human data obtained in the forearm segment of the median nerve. Brain. 2006;129(Pt 9): 2447–2460.
11. Bromberg MB, Franssen H. Practical rules for electrodiagnosis in suspected multifocal motor neuropathy. J Clin Neuromuscul Dis. 2015;16(3):141–152.
12. Draak TH, Gorson KC, Vanhoutte EK, et al. Does ability to walk reflect general functionality in inflammatory neuropathies? J Peripher Nerv Syst. 2016;21(2):74–81.
13. Merkies IS, Schmitz PI, Samijn JP, Meche FG, Toyka KV, van Doorn PA. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. Muscle Nerve. 2000;22(9):1393–1401.
14. Simon NG, Ayer G, Lomen-Hoerth C. Is IVIg therapy warranted in progressive lower motor neuron syndromes without conduction block? Neurology. 2013;81(24):2116–2120.
15. Beekman R, van den Berg LH, Franssen H, Visser LH, van Asseldonk JT, Wokke JH. Ultrasonography shows extensive nerve enlargements in multifocal motor neuropathy. Neurology. 2005;65(2):305–307.
16. Kerasnoudis A, Pitarokoili K, Behrendt V, Gold R, Yoon M. Correlation of nerve ultrasound, electrophysiological and clinical findings in chronic inflammatory demyelinating polyneuropathy. J Neuroimaging. 2015;25(2):207–216.
17. Goedee HS, van der Pol WL, Herraets UT, et al. Functional and morphological consequences of cellular and humoral responses in treatment-naive chronic inflammatory demyelinating polyneuropathy: a combined sonographic and nerve conduction study. In: Proceedings of the 2017 Peripheral Nerve Society Meeting; July 8–12, 2017; Sitges, Barcelona. Spain. J Periphr Nerv Syst. 2017;22(3):226–414.
18. Goedee HS, van der Pol WL, Hendrikse J, van den Berg LH. Nerve ultrasound and magnetic resonance imaging in the diagnosis of neuropathy. Curr Opin Neurol. 2018;31(5):526–533.
19. Beekman R, Schoemaker MC, Van Der Plas JP, et al. Diagnostic value of high-resolution sonography in ulnar neuropathy at the elbow. Neurology. 2004;62(5):767–773.
20. Visser LH, Smidt MH, Lee ML. High-resolution sonography versus EMG in the diagnosis of carpal tunnel syndrome. J Neurol Neurosurg Psychiatry. 2008;79(1):63–67.
21. Visser LH, Hens V, Soethout M, De Deugd-Maria V, Pijnenburg J, Brekelmans GJ. Diagnostic value of high-resolution sonography in common fibular neuropathy at the fibular head. Muscle Nerve. 2013;48(2):171–178.
22. Van Rosmalen M, Lieba-Samal D, Pillen S, van Alfen N. Ultrasound of peripheral nerves in neuralgic amyotrophy. Muscle Nerve. 2019;59(1): 55–59.
23. van Alfen N, Doorduin J, van Rosmalen MHJ, et al. Phrenic neuropathy and diaphragm dysfunction in neuralgic amyotrophy. Neurology. 2018;91(9):e843–e849.
24. Zaidman CM, Pestronk A. Nerve size in chronic inflammatory demyelinating neuropathy varies with disease activity and therapy response over time: a retrospective ultrasound study. Muscle Nerve. 2014;50(5):733–738.
25. Rattay TW, Winter N, Decard BF, et al. Nerve ultrasound as follow-up tool in treated multifocal motor neuropathy. Eur J Neurol. 2017;24(9):1125–1134.
26. Grimm A, Oertl H, Auffenberg E, et al. Differentiation between Guillain-Barre syndrome and acute-onset chronic inflammatory demyelinating polyradiculoneuropathy: a prospective follow-up study using ultrasound and neurophysiological measurements. Neurotherapeutics. In press.
27. Kerasnoudis A, Pitarokoili K, Gold R, Yoon MS. Nerve ultrasound and electrophysiology for therapy monitoring in chronic inflammatory demyelinating polyneuropathy. J Neuroimaging. 2015;25(6):931–939.
28. Hartig F, Ross M, Dammeier NM, et al. Nerve ultrasound predicts treatment response in chronic inflammatory demyelinating polyradiculoneuropathy-a prospective follow-up. Neurotherapeutics. 2018;15(2):439–451.

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

How to cite this article: Goedee HS, Herraets UT, Visser LH; et al. Nerve ultrasound can identify treatment-responsive chronic neuropathies without electrodiagnostic features of demyelination. Muscle Nerve. 2019;60:415–419. https://doi.org/10.1002/mus.26629

Limb-girdle muscular dystrophy: A perspective from adult patients on what matters most

Michael Hunter MD1 | Chad Heatwole MD, MS-CI2 | Matthew Wicklund MD3 | Conrad C. Weihl MD, PhD4 | Tahseen Mozaffar MD5 | Jeffrey M. Statland MD6 | Nicholas E. Johnson MD7

Abbreviations: LGMD, limb-girdle muscular dystrophy.