CLINICAL RESEARCH SHORT REPORT

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

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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,

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS/PNS, European Federation of Neurological Societies and the Peripheral Nerve Society; HRUS, high-resolution ultrasound; Ig, immunoglobulin; IVIg, intravenous Ig; LMN, lower motor neuron; MMN, multifocal motor neuropathy; MRC, medical research council; NCS, nerve conduction study; NHL, non-Hodgkin lymphoma; UMCU, University Medical Centre Utrecht.

W. L. van der Pol and L. H. van den Berg contributed equally to this work as joint last authors.

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.

2 | MATERIALS AND METHODS

2.1 | 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[4] because their NCS showed no electrodiagnostic features of demyelination.[2,9-11] They underwent extensive NCS according to a previously published standardized protocol after warming extremities in water at 37°C for 45 minutes[4,9] and routine ancillary investigations according to consensus diagnostic guidelines.[1,2] We used a previously published HRUS protocol of median nerves and brachial plexus trunks.[4] The physiotherapist and clinical neurophysiologist (H.F.) were blinded to the HRUS results. The treating physicians (W.L.P., L.B.) were blinded to the details of HRUS evaluations and were 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

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 criteria[1,2] 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/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

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.

[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.

TABLE 3 Summary sonographic nerve size median nerves and brachial plexus

		Cross-sectional area, mm^2									
		Right median nerve		Left median nerve		Right brachial plexus			Left brachial plexus		
Patient	Reference values	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 cutoff 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	**8.5**	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.

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.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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

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

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Abbreviations: LGMD, limb-girdle muscular dystrophy.