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Research

Nerve sonography to detect peripheral nerve involvement in vasculitis syndromes

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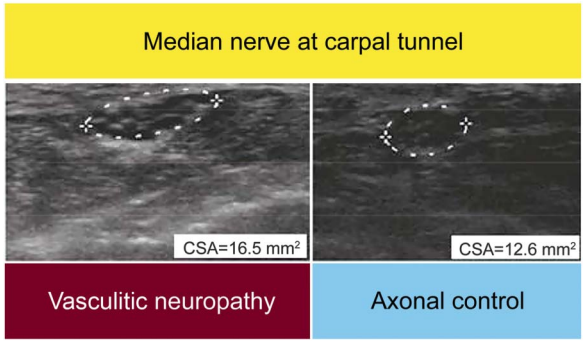
Abstract

Background: We sought to determine the usefulness of sonography in the detection of nerve involvement in patients with vasculitic neuropathy. **Methods:** We enrolled 16 consecutive patients with vasculitic neuropathy (11 systemic vasculitis and 5 single organ peripheral nerve vasculitis), who met the diagnostic criteria of the Peripheral Nerve Society, and 16 disease controls with noninflammatory axonal polyneuropathy (10 cryptogenic, 4 metabolic, 2 hereditary). Patients underwent standardized nerve conduction studies and assessment of muscle strength (Medical Research Council scale), in addition to sonography of large arm and leg nerves, and brachial plexus. Nerves were evaluated bilaterally at predetermined sites for nerve size (cross-sectional area) and presence of hypervascularization. **Results:** We found enlarged nerves at common sites of nerve compression in all vasculitic and control patients. Multifocal enlargement in arm nerves, proximal to common sites of nerve compression, was sensitive (94%) and specific (88%) for vasculitic neuropathy. Sonography showed nerve enlargement in 51% of clinically or electrodiagnostically unaffected nerves. Sonography of the brachial plexus was normal. We found hypervascularization in 3 patients with systemic vasculitis. **Conclusions:** Sonographic enlargement of arm nerves proximal to sites of nerve compression with sparing of the brachial plexus may indicate a pattern characteristic of patients with vasculitic neuropathy. Sonography may represent a sensitive and specific technique for the detection of inflammatory neuropathy. **Classification of evidence:** This study provides Class III evidence that sonographic enlargement of arm nerves proximal to sites of nerve compression accurately identifies patients with vasculitic neuropathy. ***Neurol Clin Pract* 2016;6:293-303**



Vasculitic neuropathy is characterized by an acute or subacute and painful onset of sensory and motor deficits of multiple nerves.[1–3] Peripheral nerve involvement may be a complication of large, medium-sized, or small vessel vasculitis syndromes, but may also be caused by so-called single organ peripheral nerve vasculitis or

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High-resolution ultrasound evaluation of the peripheral nerves is an emerging technique for the diagnosis of mononeuropathies and polyneuropathies.

nonsystemic vasculitic neuropathy that is confined to nerve-associated vessels.[1,2] Although clinical presentation is often typical, diagnosis of vasculitic neuropathy may not be straightforward even after extensive laboratory screening for systemic disease, nerve conduction studies (NCS), and nerve biopsy.[4–8] Immunosuppressive treatment is often required to prevent accumulation of nerve damage.[5,7,8]

Sensitive, specific, and preferably noninvasive tools for the diagnostic workup of vasculitic neuropathies to shorten time to diagnosis and to facilitate treatment decisions are needed. High-resolution ultrasound evaluation of the peripheral nerves is an emerging technique for the diagnosis of mononeuropathies and polyneuropathies.[9–13] A few published case reports have reported sonographic nerve enlargement in patients with vasculitic neuropathy,[14,15] but few studies have documented nerve size in multiple nerves.[16] Sonographic studies of patients with nonsystemic vasculitic neuropathy are lacking.[13,16]

In this study, we sought to determine the usefulness of sonography in the detection of nerve involvement in patients with vasculitic neuropathy. We assessed multiple sonographic parameters using an extensive protocol in 16 consecutive patients with systemic and nonsystemic vasculitic neuropathy and 16 disease controls with noninflammatory axonal polyneuropathy.

METHODS

Study population

Sixteen consecutive patients with vasculitic neuropathy were enrolled at the outpatient clinic for peripheral neuropathies at the University Medical Centre Utrecht, a tertiary center for neuromuscular disorders, between January 2013 and January 2015. The inclusion criterion was a diagnosis of pathologically definite, probable, or possible or clinically probable vasculitic neuropathy according to the diagnostic consensus criteria of the Peripheral Nerve Society (PNS), i.e., based on the combination of results from clinical history, clinical findings, NCS, laboratory screening for abnormalities associated with systemic vasculitis, and nerve biopsy.[7] We also enrolled 16 disease controls with noninflammatory axonal polyneuropathy (10 cryptogenic, 4 metabolic, and 2 hereditary axonal polyneuropathies).[17]

Standard protocol approvals, registrations, and patient consent

The local medical ethical committee approved the study protocol. Written and informed consent was obtained from all participants.

Clinical assessment

We evaluated patients with a predetermined set of clinical and ancillary investigations. One of the authors (H.S.G.) assessed muscle strength of 13 muscle groups bilaterally (finger flexors, extensors, interossei, wrist extensors and flexors, biceps and triceps, deltoid, iliopsoas, hamstrings and quadriceps, foot extensors and flexors) using the Medical Research Council (MRC) scale. MRC data were used to calculate an MRC sumscore (range 0–130) and sumscores of sets of 2 muscles per fibular, ulnar, and median nerve.

Nerve conduction studies

We performed NCS of the median, ulnar, radial, tibial, fibular, and sural nerves. A Nicolet VIKING IV EMG machine (CareFusion Japan, Tokyo, Japan) was deployed after warming

Table 1 Sonographic protocol and cutoff values for abnormal nerve size of corresponding anatomical sites

Nerve	Anatomical site	Abnormal if CSA value, mm²
Median	Carpal tunnel	>11
	Forearm (1/3 from carpal tunnel)	>9
	Upper arm (1/2 from humerus)	>9
Ulnar	Distal sulcus	>9
	Sulcus	>9
	Proximal sulcus	>9
	Upper arm (1/2 from humerus)	>9
Brachial plexus	Superior truncus	>8
	Median truncus	>8
	Inferior truncus	>8
Fibular	At level of knee	>9
	At level of fibular head	>11
Posterior tibial	At level of medial malleolus	>14
Sural	Between lateral and medial gastocnemic head (14 cm above lateral malleolus)	>3

Cutoff values of cross-sectional area (CSA) for each nerve and corresponding anatomical site, as measured on transverse images with ellipse tool inside the hyperechoic rim of the nerve.

arms and legs in water at 37°C for 45 minutes.[18] We assessed distal compound muscle action potentials (CMAP), distal motor latencies (DML), motor conduction velocities (MCV), and F-waves of median, ulnar, fibular, and tibial nerves unilaterally, sensory nerve action potentials (SNAP) of median, ulnar, and radial nerve on the same side as motor responses, and sural nerve bilaterally. Contralateral nerves were investigated if there were signs of weakness or sensory deficits. A decreased or absent distal CMAP or SNAP was considered electrodiagnostic proof of nerve involvement.

Ultrasound studies

A Philips iU22 (Philips Medical Instruments, Bothell, WA) with a 5–17 MHz linear array transducer was deployed to evaluate the peripheral nerves. Nerve size and vascularization were determined bilaterally of median nerve (carpal tunnel, forearm, upper arm), ulnar nerve (cubital sulcus, distal and proximal cubital sulcus, upper arm), fibular nerve (fibular head, popliteal fossa), tibial nerve (medial malleolus), and sural nerve (14 cm above lateral malleolus).[19,20] Nerve size of the trunks in the brachial plexus was also assessed bilaterally.[19,20] Nerve size was measured on transverse images with the ellipse tool defining the area within the hyperechoic rim of the nerve.[19] In order to evaluate nerve enlargement outside the predetermined sites, we also scanned median and ulnar nerve from axilla to wrist.[19] We used previously reported cutoff values for nerve enlargement (table 1).[19,20] Nerve enlargement was further categorized into (1) enlargement at common sites of nerve entrapment and (2) enlargement proximal to these sites: forearm and upper arm for median nerve, proximal and distal cubital sulcus, upper arm for ulnar nerve, brachial plexus, popliteal fossa for fibular nerve, tibial and sural nerve. Power Doppler was deployed to screen for presence of increased nerve vascularization at each site, with the exception of the brachial plexus.[19–21] The normal vascularization of nerves cannot be visualized with contemporary ultrasound machines; therefore any presence of vascularization on power Doppler was considered abnormal or increased vascularization.[19] Echogenicity of the nerve

Table 2 Characteristics of patients with vasculitic neuropathy and noninflammatory axonal polyneuropathy disease controls

	Vasculitic neuropathy (n = 16)	Noninflammatory axonal polyneuropathy (n = 16)
Type of vasculitis		
Sjögren	3	
Granulomatosis with polyangiitis	4 (2 biopsy)	
Microscopic polyangiitis	2	
Polyarthritis nodosa, myelodysplastic syndrome	1 (biopsy)	
Non-small-cell lung carcinoma	1	
Single organ peripheral nerve vasculitis	5 (3 biopsy)	
Age, y	65 (49-69)	57 (51-65)
Male/female	7/9	7/9
Disease duration, mo	4 (3-23)	47 (21-74)
Treatment		
No	10	
Yes, duration, mo	6 (9 [5-66])	
Antineutrophil cytoplasmic antibodies		
Negative	10	
Anti-MPO	3	
Anti-PR3	3	
MRC sumscore	123 (114-128)	129 (124-130)

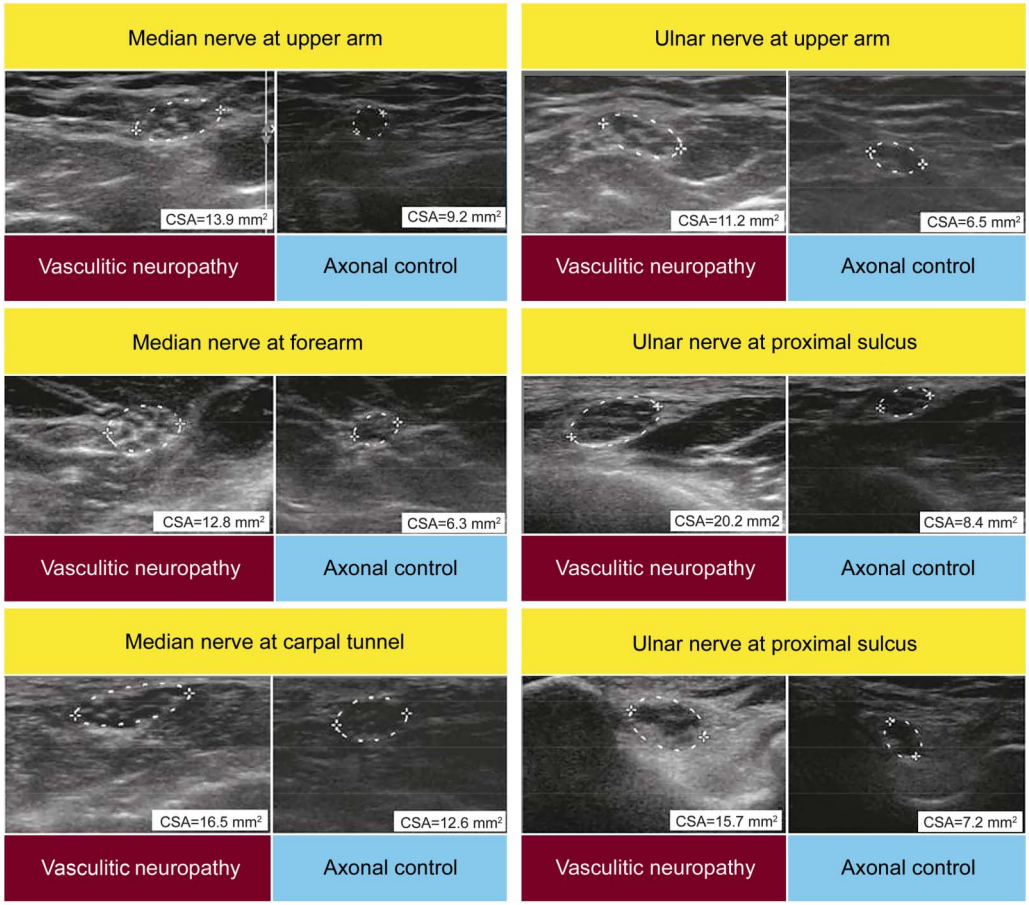
Characteristics of enrolled patients with vasculitic neuropathy and disease controls with noninflammatory axonal polyneuropathy. Age, disease duration, duration of treatment, Medical Research Council (MRC) sumscore, and number of enlarged nerves are expressed as median values (interquartile range). The MRC sumscore (range 0–130) is calculated from the muscle strength assessed in 13 muscle groups bilaterally (finger flexors, extensors, interossei, wrist extensors and flexors, biceps and triceps, deltoid, iliopsoas, hamstrings and quadriceps, foot extensors, and flexors).

was also measured at these sites; fascicle size was only assessed in median, ulnar, and fibular nerves. Nerve echogenicity and fascicle size were assessed quantitatively, using the ImageJ software (NIH, Bethesda, MD).[19] Nerve echogenicity was determined offline with automatic thresholding techniques, applying the MaxEntropy, RenyiEntropy, and Yen thresholding methods.[19,22] Blinded to the NCS and independent from the authors diagnosing vasculitic neuropathy (A.F.J.E.V., N.C.N., W.L.v.d.P., L.H.v.d.B.), one of the authors (H.S.G.) performed the sonographic examinations and successively a second author (L.H.V.) rated all sonographic measurements.

Statistical analysis

We used SPSS 22.0 software (SPSS, IBM, Armonk, NY) for statistical analysis. Nonparametric tests were deployed, Spearman rho for associations between variables (age, disease duration, MRC sumscore, number of enlarged nerves, nerve and fascicle size, echogenicity) and Mann-Whitney for comparing ordinal (sex, clinical presentation, any weakness in arm or leg, any sensory disturbance in arm or leg, clinical involvement of median and ulnar nerve, treatment at time of sonographic interrogation and hypervascularization, distal CMAP, DML, SNAP, MCV) with continuous variables. We used Benjamini-Hochberg correction for multiple testing where appropriate and set the level of significance at a p value of 0.05.

Figure 1 Sonography findings in a representative patient with vasculitic neuropathy and a noninflammatory axonal disease control



Nerve enlargement (i.e., cross-sectional area [CSA] >9) of median nerve and ulnar nerve at multiple sites outside common sites of nerve compression in the patient with vasculitic neuropathy (left panels), but only in the median nerve at the carpal tunnel in the noninflammatory axonal disease control (right panels), i.e., CSA >11 mm².

RESULTS

Clinical characteristics

We enrolled 16 patients with vasculitic neuropathy and 16 noninflammatory axonal polyneuropathy disease controls (table 2). Six patients underwent a sural nerve biopsy. Five fulfilled the PNS diagnostic criteria for pathologically definite, 1 pathologically probable, and the remaining 11 clinically probable vasculitic neuropathy (table e-1 at Neurology.org/cp).[7] Seven patients were already under treatment at the time of referral (and enrollment), with median treatment duration of 9 months (interquartile range 5–66). There was no difference in age, sex, disease duration, or MRC sumscore between treated and untreated patients in the vasculitic neuropathy group. There was no correlation between age, sex, or disease duration and MRC sumscore or weakness in median, ulnar, or fibular nerve innervated muscles.

Supplemental Data
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Sonographic studies

We detected nerve enlargement at multiple common sites of nerve compression (i.e., cubital sulcus, carpal tunnel, and fibular head) in all patients with vasculitic neuropathy and disease controls (figure 1, table 3). Multifocal enlargement of at least 1 arm nerve proximal to common sites of nerve compression was seen in 15 of 16 (94%) patients with vasculitic neuropathy and only in 2 of 16 (12%) disease controls (table 3, $p < 0.001$). Enlargement

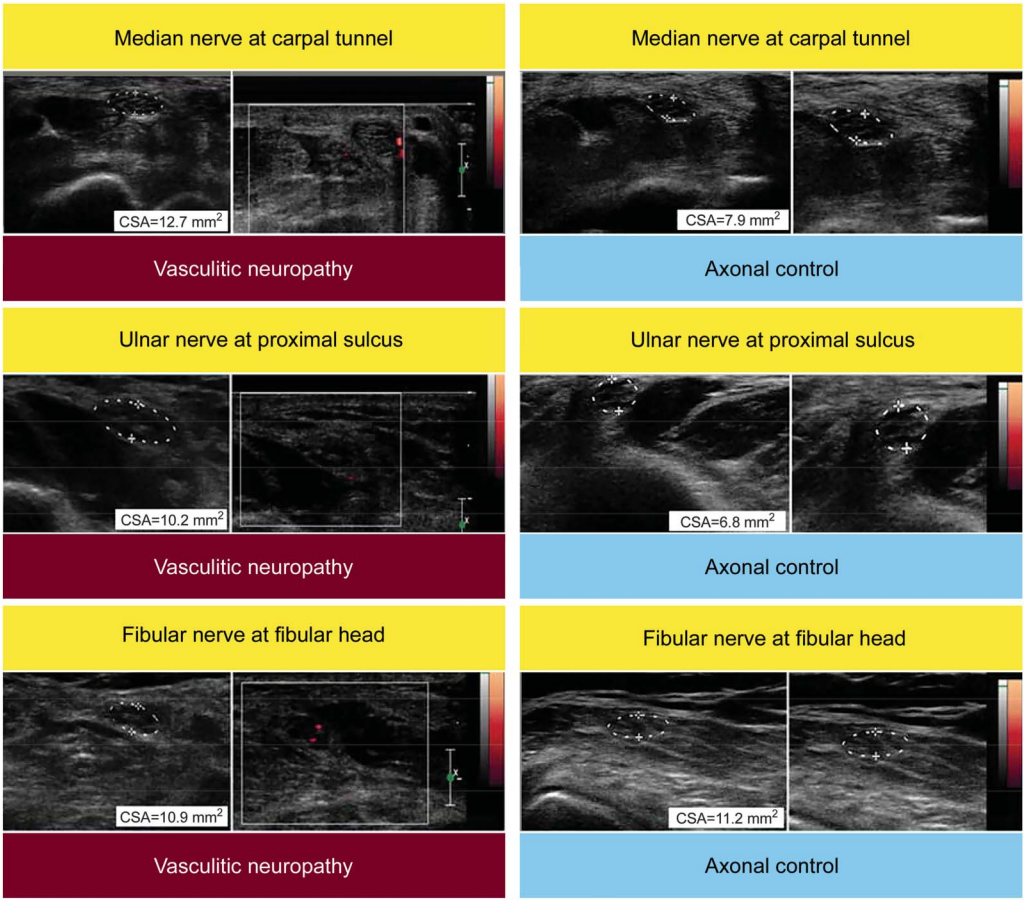
Table 3 Sites and frequencies at which nerve sonography reveals focal enlargement in nerves

	Median nerve	Ulnar nerve	Fibular nerve	Tibial nerve	Sural nerve	Total
Common sites of nerve compression and distal segments: leg nerves						
Vasculitic neuropathy						
Total no. of abnormal nerves	17/32 (53)	24/32 (75)	20/32 (63)	23/32 (72)	12/32 (38)	96/128 (75)
Patients with nerve enlargement	10/16 (63)	14/16 (88)	11/16 (69)	13/16 (82)	9/16 (56)	16/16 (100)
No nerve enlargement	6/16 (37)	2/16 (12)	5/16 (31)	3/16 (18)	7/16 (44)	0
Noninflammatory axonal polyneuropathy disease controls						
Total no. of abnormal nerves	20/32 (63)	17/32 (53)	27/32	29/32 (91)	2/32 (6)	95/32 (74)
Patients with nerve enlargement	11/16 (69)	10/16 (63)	14/16 (88)	15/16 (94)	1/16 (6)	16/16 (100)
No nerve enlargement	5/16 (31)	6/16 (37)	2/16 (12)	1/16 (6)	15/16 (94)	0
Nerve segments proximal to common sites of nerve compression						
Vasculitic neuropathy						
Total no. of abnormal nerves	32/64 (50)	29/96 (30)	10/32 (31)	0		71/192 (37)
Patients with symmetric nerve involvement	8/16 (50)	6/16 (38)	4/16 (25)	0		9/16 (56)
Asymmetric nerve involvement	2/16 (12)	5/16 (31)	2/16 (12)	0		6/16 (37)
Normal	6/16 (38)	5/16 (31)	10/16 (63)	16/16 (100)		1/16 (6)
Noninflammatory axonal polyneuropathy						
Total no. of disease controls	0	4/96 (4)	4/32 (13)	0		8/192 (4)
Patients with symmetric nerve involvement	0	0	2/16 (12)	0		2/16 (12)
Asymmetric nerve involvement	0	2/16 (12)	0	0		2/16 (12)
Normal	16/16 (100)	14/16 (88)	14/16 (88)	16/16 (100)		12/16 (76)

Data are presented as n (%) unless otherwise specified. Number of sites at which nerve sonography reveals focal enlargement in nerves (median, ulnar, fibular, tibial and sural nerve) at common sites of nerve compression and distal segment leg nerves and nerve segments proximal to common sites of nerve compression in the 16 enrolled patients with vasculitic neuropathy and the noninflammatory axonal polyneuropathy disease controls.

of arm nerves proximal to common sites of nerve compression was symmetric in 56% of the patients with vasculitic neuropathy but in none of the disease controls (table 3, table e-2). Ulnar (69%) and median (62%) nerves were the most frequently affected nerves (table 3). None of the patients with vasculitic neuropathy had enlargement of the brachial plexus (table 3). Proximal nerve segments were more frequently enlarged in the 5 patients with nonsystemic vasculitic neuropathy (28 sites) than in the 11 patients with systemic vasculitic neuropathy (33 sites; $p = 0.02$). Nerve size did not correlate with age, sex, or disease duration. Hypervascularization was present in 3 patients (19%) with systemic vasculitis: 3 nerves in one patient (left median nerve at carpal tunnel and left ulnar nerve at sulcus, right fibular nerve at fibular head) and 1 nerve in 2 patients (left ulnar, right sural

Figure 2 Doppler ultrasound findings in a representative patient with vasculitic neuropathy and a noninflammatory axonal disease control



Increased nerve vascularization in the patient with vasculitic neuropathy (left panels) in the median, ulnar, and fibular nerve, but not in the noninflammatory axonal disease control (right panels). CSA = cross-sectional area.

nerve, respectively [figure 2, table e-3]); 2 of these patients were treatment-naive and 1 had undergone a longstanding immune-modulating (prednisone, azathioprine, and cyclophosphamide) treatment.

Correlation with clinical findings

Sonography abnormalities were not only found in weak limbs of patients with vasculitic neuropathy. We found nerve enlargement in 16/19 (84%) arms and 11/12 (92%) legs with normal muscle strength, and in 13/15 (87%) arms and a single leg with normal sensory function. The number of enlarged nerves, echogenicity, and fascicle size did not correlate with MRC sumscore or the specific sumscore of muscle groups innervated by individual nerves.

Correlations with electrodiagnostic findings

In patients with vasculitic neuropathy, we found nerve enlargement in 51% of the nerves with no signs of clinical or electrodiagnostic involvement (table 4). We found nerve enlargement in 12/14 (86%) ulnar, 6/9 (67%) tibial, 8/13 (62%) median, and all 3 fibular nerves without clinical and electrodiagnostic signs of involvement in the vasculitic neuropathy group. None of the recorded distal CMAP, DML, or SNAP of the investigated nerves correlated with age, sex, or disease duration. The number of enlarged nerves, echogenicity, and fascicle size did not correlate with decreased distal CMAP, prolongation of DML, decreased SNAP, or reduction in MCV.

Our data indicate that ultrasound may represent a valuable tool for the detection of peripheral nerve involvement in vasculitic neuropathies.

DISCUSSION

We found multiple focally enlarged nerves outside common sites of nerve compression in all patients with vasculitic neuropathy. Symmetric enlargement of peripheral nerves was more common than asymmetric involvement and we did not find enlargement of the brachial plexus in any patient with vasculitic neuropathy. Nerve enlargement was prominent in both arms and legs, even in the absence of clinical weakness, sensory deficits, and nerve conduction abnormalities. This pattern of nerve involvement, i.e., of at least one proximal segment of median or ulnar nerve and sparing of the brachial plexus, was both sensitive and specific for vasculitic neuropathy. Our data indicate that ultrasound may represent a valuable tool for the detection of peripheral nerve involvement in vasculitic neuropathies.

Two previous studies (a case report and case series) documented nerve enlargement in patients with vasculitic neuropathies.[14,15] The standardized and extensive ultrasound protocol that we used to investigate nerve enlargement in patients with both systemic and nonsystemic vasculitic neuropathy and a relevant disease control group allowed us to assess patterns of nerve enlargement and usefulness of sonography during the clinical workup. The finding of multiple, focally enlarged nerves outside common sites of nerve compression in arms and legs, but not in the brachial plexus, may represent a characteristic pattern of sonographic nerve involvement in vasculitic neuropathy. Our data suggest that ultrasound sensitivity may be slightly higher in leg nerves, which may reflect their relatively low endoneurial capillary density,[23] while specificity is higher in arm nerves. We found frequent nerve enlargement in proximal nerve segments, in line with observations that nerve infarction commonly occurs here.[24] Normal findings in the brachial plexus, which may reflect its relatively high endoneurial capillary density and thus a potentially higher resistance to ischemic injury,[23–25] can help to distinguish vasculitic neuropathy from demyelinating asymmetric neuropathies such as multifocal motor neuropathy and Lewis-Sumner syndrome.[26,27] The finding of symmetric nerve enlargement would further support the diagnosis of vasculitic neuropathy. Systematic assessment of the presence of fascicle size and echogenicity revealed that these parameters

Table 4 Additional diagnostic value of nerve sonography in patients with vasculitic neuropathy

		Abnormalities detected by			
Nerves		**EDX only**	**Sonography only**	**Both EDX and Sonography**	**None**
Clinically affected	59 (50)	17 (29)	10 (17)	25 (42)	7 (12)
Clinically normal	59 (50)	4 (7)	30 (51)	15 (25)	10 (17)
All nerves	118 (100)	21 (18)	40 (34)	40 (34)	17 (14)

Data are presented as n (%) unless otherwise specified. Number and percentage of affected nerves in 16 patients with vasculitic neuropathy, stratified for clinical signs of involvement and grouped in only electrodiagnostic (EDX), only sonographic, or combined EDX and sonographic abnormalities. Involvement was defined as weakness or sensory disturbance (clinically), EDX evidence of loss of sensory or motor axons, or sonographic nerve enlargement.

probably do not have added value. Taken together, our data indicate that ultrasound investigation of the large arm nerves on both sides (and, if normal, the leg nerves) in combination with the brachial plexus can be used to discriminate vasculitic neuropathies from other axonal and asymmetric neuropathies. This sonographic protocol takes only a small time effort, in general less than 15 minutes.

We found hypervascularization, which may reflect inflammation[28,29] or angiogenesis,[30,31] in 3 vasculitic neuropathy patients, but in none of the disease controls. We previously reported hypervascularization in chronic inflammatory demyelinating neuropathy, but all these patients had a clinically symmetric neuropathy.[20] These findings suggest that increased neural vascularization might be specific for vasculitic neuropathy in the setting of a subacute progressive asymmetric neuropathy. With the recognition that it was seen only in 3 patients, this hypervascularization indicates focal disease activity and may represent inflammatory cell infiltration of neural vessels in vasculitic neuropathy. Other sonography parameters, including fascicle size and echogenicity, did not correlate with any clinical and nerve conduction study findings. It is not known how the central pathogenetic processes of vasculitis neuropathy, i.e., vessel wall inflammation, destruction of the vessel wall, occlusion of the vessel lumen, and nerve ischemia, eventually lead to focal enlargement of nerves.[5,8] Although the usefulness of other sonography parameters than cross-sectional area may useful for the dissection of pathogenetic properties of vasculitis neuropathies, they do not have diagnostic added value.

Our study has some limitations. Our patient group was heterogeneous with respect to disease duration and treatment (duration). Treatment effects and incremental sonomorphologic alterations with longer disease duration cannot be completely ruled out at this stage. It is unlikely, however, that they affect the presence of nerve enlargement as we found this in patients with both short and long disease durations, and before and after the start of treatment.

Both ultrasound and nerve conduction abnormalities were common in nerves that seemed clinically unaffected.[3,32–34] Sonography is more time-efficient and has better patient compliance than NCS, which may be poorly tolerated in patients with vasculitic neuropathies due to pain. It may have higher sensitivity for detecting inflammatory neuropathy than nerve biopsy, which suffers from obvious limitations of sampling from the sural or superficial fibular nerve and has limited sensitivity. In this context, nerve sonography may represent a sensitive and patient-friendly technique for detection of peripheral nerve involvement in vasculitic neuropathies.

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AUTHOR CONTRIBUTIONS

H.S. Goedee: patient enrollment and evaluation according to the study protocol, acquisition of data, contribution to study design, analysis and interpretation of data, statistical analysis, drafting/revision

of the manuscript, obtaining funding. W.L. van der Pol and L.H. van den Berg: patient enrollment, contribution to study design, analysis and interpretation of data, revision of the manuscript, obtaining funding. A.F.J.E. Vrancken and NC Notermans: patient enrollment and revision of the manuscript. J.-T.H. van Asseldonk and L.H. Visser: analysis and interpretation of data, revision of the manuscript, obtaining funding.

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