

Ultrasound scanning in the diagnosis of peripheral neuropathies

Johan A Telleman ¹, Ingrid JT Herraets,¹ H Stephan Goedee,²
J Thies van Asseldonk,¹ Leo H Visser¹

¹Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, Noord-Brabant, The Netherlands

²Neurology, Brain Center UMC Utrecht, UMC Utrecht Hersencentrum, Utrecht, The Netherlands

Correspondence to

Dr Johan A Telleman, Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, Noord-Brabant, Netherlands; j.telleman@etz.nl

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ABSTRACT

Nerve ultrasound scanning has become a valuable diagnostic tool in the routine workup of peripheral nerve disorders, effectively complementing conventional electrodiagnostic studies. The most relevant sonographic features are nerve size and structural integrity. Several peripheral neuropathies show characteristic and distinct patterns of nerve enlargement, allowing their early and accurate identification, and reducing test-burden and diagnostic delay for patients. In mononeuropathies such as carpal tunnel syndrome and ulnar neuropathy at the elbow, nerve enlargement develops only at specific sites of entrapment, while in polyneuropathy the nerve enlargement may be multifocal, regional or even diffuse. Nerve ultrasound scanning can reliably identify chronic inflammatory neuropathies, even when extensive electrodiagnostic studies fail, and it should therefore be embedded in routine diagnostic workup of peripheral neuropathies. In this paper we describe a potential diagnostic strategy to achieve this.

INTRODUCTION

Polyneuropathy is common in neurology practice, with a reported prevalence of 1% up to 7% and increasing with age.¹ There is a wide range of unique causes (table 1), often grouped into ‘axonal’ and ‘demyelinating’ types, and into hereditary and acquired types. The most prevalent phenotypes are the acquired axonal variants, such as diabetic neuropathy, toxic neuropathy and chronic idiopathic axonal polyneuropathy. Hereditary neuropathies are the most common cause of polyneuropathy in children, with demyelinating and axonal subgroups having unique genetic abnormalities. These have expanded substantially since their early description, and now also include more complex phenotypes. Guillain-Barré-syndroom (GBS) is a well-known acute, classically

postinfective inflammatory neuropathy.³ Chronic inflammatory neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP (typical and variants)) and multifocal motor neuropathy (MMN) comprise a much rarer phenotype.^{4–7} Other rare causes of polyneuropathy include vasculitic and paraproteinaemic neuropathies, and neuropathies in systemic disease (eg, in amyloidosis and sarcoidosis).

Acquired axonal polyneuropathies characteristically present as a slowly progressive distal sensory loss, sometimes followed by mild weakness of primarily distal muscle groups. Several distinct clinical features suggest a chronic inflammatory neuropathy. CIDP is characterised by a chronic progressive or relapsing disease course, generalised areflexia or reduced tendon reflexes, and motor dominant features with prominent proximal weakness.^{4,5} Several variants have been included in the CIDP spectrum, including pure sensory, pure motor, exclusively distal, and (multi) focal CIDP (also known as Lewis-Sumner syndrome).^{4,5,8} MMN is characterised by asymmetric and purely motor involvement, predominantly of the upper limbs, and a relatively slow progression.^{6,9} Hereditary neuropathies often have a positive family history combined with morphologic abnormalities (eg, pes cavus with hammer toes, or pes planus), predominantly symmetric distal weakness and atrophy that can lead to an ‘inverted champagne bottle’ appearance of the lower limbs (particularly in demyelinating types such as Charcot-Marie-Tooth type 1A (CMT1A)).¹⁰ Disease progression is often chronic, and sensory disturbances are usually modest, except in hereditary sensory neuropathies and hereditary neuropathy with liability to pressure palsies.¹⁰



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Table 1 Summary of peripheral nerve disorders

Mononeuropathy	
Nerve entrapment	Carpal tunnel syndrome, ulnar neuropathy (at elbow or Guyon's canal), fibular neuropathy, meralgia paresthetica, tarsal tunnel syndrome
Nerve tumours	Neurofibromas, schwannomas, lymphomas
Traumatic	Fractures (humerus, radius, ulna, fibula, pelvis)
Polyneuropathy	
Carcinoma	Lymphoma
Hereditary	Charcot-Marie-Tooth disease, hereditary neuropathy with liability to pressure palsies, neurofibromatosis, porphyria
Idiopathic	Chronic idiopathic axonal polyneuropathy Amyotrophic neuralgia
Infectious	Leprosy, HIV, Lyme disease
Inflammatory	Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, Lewis-Sumner syndrome, multifocal motor neuropathy
Metabolic	Diabetes mellitus, chronic kidney failure, chronic liver failure, hypothyroidism, vitamin deficiencies
Paraneoplastic	Small cell lung cancer
Paraproteinaemic	IgM- monoclonal gammopathy of unknown significance, anti-MAG associated polyneuropathy, Waldenström's, polyneuropathy organomegaly endocrinopathy M-protein and skin changes syndrome
Systemic disease	Amyloidosis, sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis
Toxic	Alcohol abuse, drug associated (chemotherapy, antimicrobials, immunosuppressants, amiodarone, digoxin), toxins (botulism, lead, mercury)
Vasculitic	Polyarteritis nodosa, microscopic polyangiitis, non-systemic vasculitic neuropathy

This table shows an overview of causes of peripheral neuropathy. The list of causes of peripheral neuropathy is extensive and only some (common) examples are shown per type of origin. Small-fibre neuropathy forms a distinct type of peripheral nerve disease, and is therefore not covered in this table.

While several clinical features could point to a potentially treatable neuropathy, such as a chronic inflammatory neuropathy, there may be significant overlap with disease mimics, such as progressive axonal neuropathies, and lower motor neurone syndromes. Chronic inflammatory neuropathies are amenable to immunomodulatory treatment, including intravenous immunoglobulins, corticosteroids and plasma exchange,^{11 12} and so early treatment may prevent significant impairment. However, this treatment is often costly, and may have significant adverse effects.^{11 12} Therefore, early and accurate identification is important, and additional tests are often needed to establish the cause of polyneuropathy.

Conventional diagnostic tools

Nerve conduction studies (NCS) are currently considered the main tool to establish a diagnosis of polyneuropathy, to form the differential diagnosis and to determine further diagnostic workup. Although in patients with a chronic symmetric distal sensory polyneuropathy and a well-known underlying disease (eg, diabetes) NCS often have limited added value, they can provide further insight in the presence, extent and potential cause of neuropathy.^{13 14} In patients with suspected hereditary neuropathy, short NCS protocols are often used to determine the main clinical category (axonal or demyelinating) and to help select adequate genetic testing. The diagnosis of GBS is usually based on clinical features and cerebrospinal fluid (CSF) testing, with only a modest role for routine NCS. In contrast, the diagnosis of chronic inflammatory

neuropathy currently relies primarily on NCS findings and may be complemented by other tests.

In the appropriate context, a reduced sensory nerve action potential, and reduced compound muscle action potential (CMAP) can indicate an axonal polyneuropathy.¹⁵ Electrodiagnostic features suggesting demyelination include prolongation of distal motor latency, distal CMAP and F-wave latency, reduced motor conduction velocity, abnormal temporal dispersion and conduction blocks.^{5 6} NCS are often normal in early GBS or identify only non-specific abnormalities. Repeat studies may help with classification, but do not affect management. For chronic inflammatory neuropathies there are several sets of strict electrodiagnostic criteria to provide sufficient proof of demyelination.^{5 6 16} In short, a diagnosis of possible, probable, or definite CIDP can be made based on the presence of a combination of 'demyelinating' features, while the diagnosis of MMN primarily relies on finding conduction blocks with normal sensory conduction (figure 1).^{5 6 17} However, electrodiagnostic criteria for these demyelinating diseases are often focused on high specificity, while sensitivity is frequently considerably lower. Also, there are few systematic studies on reliability and reproducibility of these demyelinating features, particularly in a live setting. Furthermore, even extensive and often cumbersome NCS protocols (with assessment of conduction blocks up to the point of Erb) needed to detect the randomly distributed demyelinating abnormalities, may fail to meet the criteria.^{16 18}

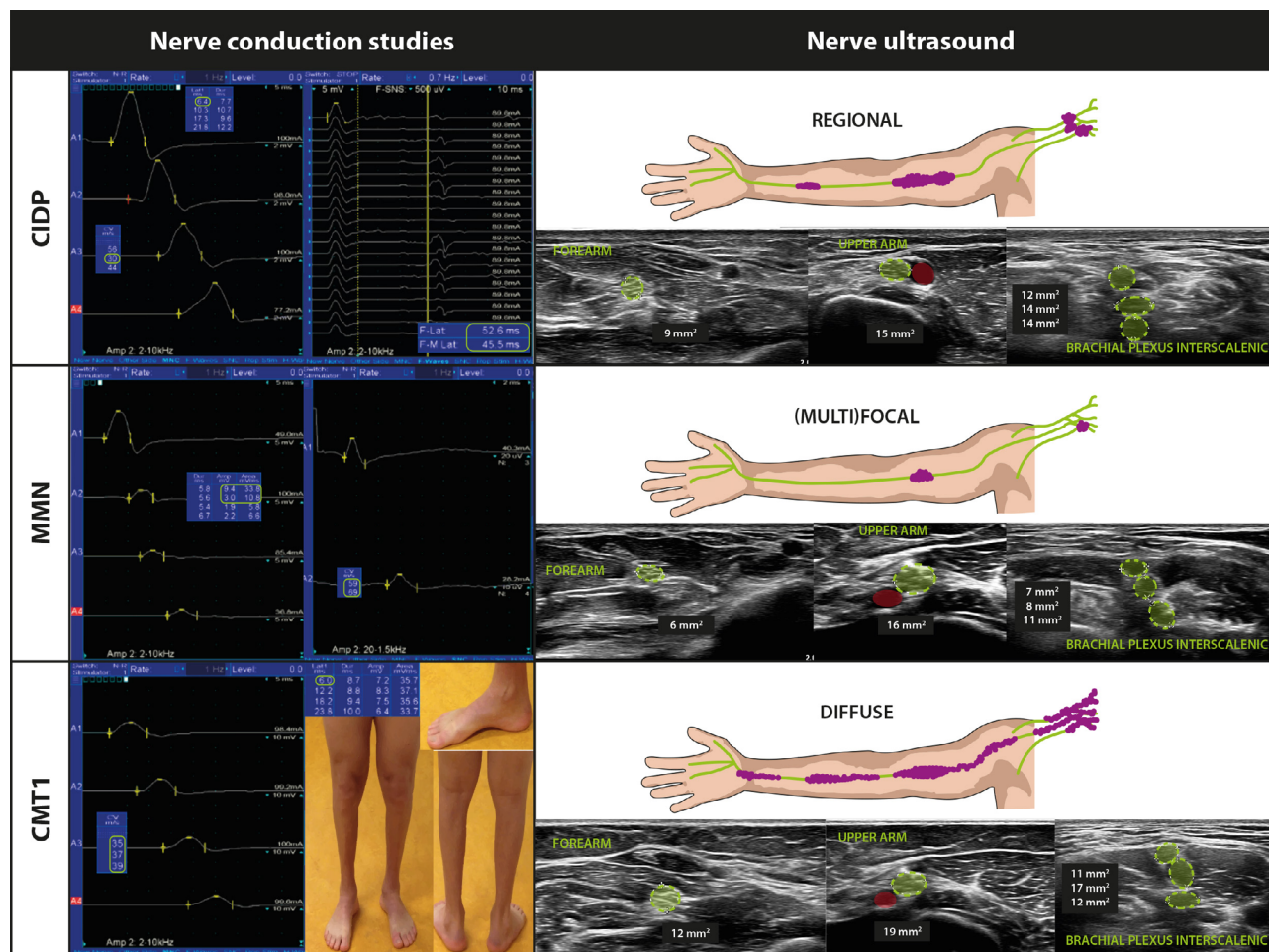


Figure 1 Nerve conduction studies and nerve ultrasound characteristics in chronic inflammatory and hereditary demyelinating polyneuropathies. Chronic inflammatory and hereditary demyelinating neuropathies are characterised by unique electrophysiological and sonographic patterns. On conventional nerve conduction studies, chronic inflammatory demyelinating polyneuropathy (CIDP; typical and variants) commonly shows multifocal electrophysiological features compatible with demyelination (eg, motor conduction slowing, increased F-wave latencies, conduction block and temporal dispersion), whereas demyelinating hereditary neuropathies typically exhibit homogeneous conduction slowing, and multifocal motor neuropathy (MMN) conduction blocks with normal sensory conduction over the same segment. On nerve ultrasound, CIDP may show predominantly regional and occasionally diffuse nerve enlargement, whereas demyelinating hereditary neuropathies commonly have diffuse nerve enlargement, and MMN is often limited to more focal nerve enlargements. CMT1, Charcot-Marie-Tooth type 1A.

While NCS are important to identify polyneuropathy (ie, to confirm loss of sensory and motor axons), further tests are frequently necessary, as they only inform clinicians on nerve function, and not on nerve morphology or underlying cause of nerve disease. Laboratory tests are also important to help identify possible underlying conditions, and they include fasting plasma glucose, HbA1c, liver, kidney and thyroid function, vitamin concentrations (B1, B6, B12 and folic acid), M protein screening, and a full cell blood count.^{13–19} More extensive laboratory tests are appropriate if clinically considering rarer causes (ie, ANA, ANCA, presence of autoantibodies, ACE, soluble IL-2, light chain and VEGF).

To improve diagnostic yield in suspected chronic inflammatory neuropathy supportive criteria have been included in the current consensus criteria. An elevated CSF protein concentration without pleocytosis

(albumin-cytologic dissociation) can be considered suggestive of CIDP and MMN.^{5–7} However, the lack of specificity (it may also be positive in other neuropathies, after spinal surgery and infections) and uncertain sensitivity (cut-offs may differ between laboratories and across different age categories) limit its use in routine practice. Despite these limitations, it should not be omitted when considering infective causes or possible malignancy. MR scan of the brachial or lumbosacral plexus is also a useful supportive tool, and may show nerve root hypertrophy and/or increased signal intensity.²⁰ However, this finding needs careful interpretation as it can also occur in other neuropathies (eg, demyelinating CMT and paraproteinaemic neuropathies) and the current practice of visual rating has low reliability.^{21–22} Objective cut-off values for abnormal MR scan could improve accuracy, although with variable sensitivity.²² The presence of anti-GM1

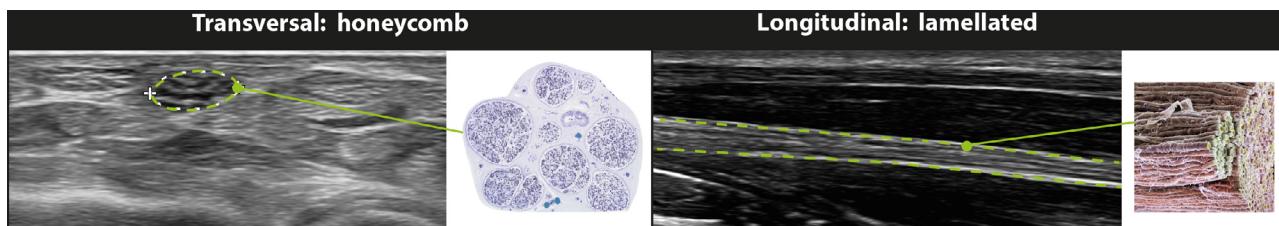


Figure 2 Examples of peripheral nerve sonoanatomy. In a transverse plane, the peripheral nerve appears as a honeycomb structure (left), corroborating the fascicular organisation from detailed histological studies. In the longitudinal plane, the fascicular pattern is lamellated (right). Movement along the length of the nerves and continuous optimisation of scanning angle allows appropriate distinction from associated structures (eg, blood vessels and tendons).

antibodies may support a diagnosis of MMN.⁶⁷ Nerve biopsy should only be considered as a last resort, as its diagnostic performance is highly variable, even in neuromuscular expert centres, and it may carry considerable adverse effects.^{5 17} Finally, objective treatment response is an important supportive criterion on its own in the present consensus guidelines, but this requires considerable experience with these rare disorders and the use of valid outcome measures.^{5 6}

Though diagnosing polyneuropathy is mainly driven by clinical features and supported primarily by routine laboratory and NCS it can remain challenging, especially in chronic inflammatory neuropathy. Current diagnostic sets of criteria for CIDP and MMN are primarily focused on specificity, to prevent patients without a real prospect of treatment-response from receiving expensive and potentially harmful medication. However, this may lead to potentially treatment-responsive cases being missed. Also, diagnostic criteria, especially the NCS criteria, can be complex, and misinterpretation and misdiagnosis is common.²³ Consequently, there is ongoing need for more sensitive, reliable and easily applicable diagnostic tools.

A new diagnostic tool: nerve ultrasound scanning

Nerve ultrasound scanning is a relatively new imaging tool to evaluate peripheral nerves. High-frequency probes have enabled efficient non-invasive assessment of peripheral nerve morphology, especially in superficially located nerves.²⁴ On ultrasound scanning a peripheral nerve can usually be recognised as a honeycomb structure with hypoechoic fascicles (figure 2a, video 1), but varying echotextures can be encountered depending on the investigated nerve site (eg, a diffusely hypoechoic mass in brachial plexus nerve roots (figure 3)). Normal nerve epineurium is hyperechoic on nerve ultrasound. The most relevant sonographic features clinically are nerve size and structural integrity.²⁴ Others include fascicular size and pattern, epineurium and endoneurium, vascularisation and echogenicity.²⁴ Nerve size is commonly assessed in a transversal plane and expressed as a cross-sectional area (CSA) in mm². Measurement of nerve CSA is performed within the hyperechoic rim (figure 2), as

exact delineation of the outer epineurial border is not feasible and would lead to unwanted variation.²⁴

Normal nerve CSA varies along the length of nerves. Table 2 gives the reference values for the upper limit of normal nerve CSA applied in our laboratory (a large general teaching hospital and a tertiary referral centre for neuromuscular disorders in The Netherlands).^{25 26} Some studies have suggested that nerve size depends on age, height, weight, body mass index and/or sex, but others could not confirm this correlation.^{27–32} As a result, we do not usually make standard correction for normal CSA values, but investigators should keep in mind that CSA measurements may differ at extremes (eg, children, very tall (height >2 m), or very old patients). Several studies have shown that race may have an important influence on normal nerve size.^{33 34} Nerve CSA was significantly lower in Indian and Chinese populations compared with a European (mainly Caucasian) population.^{33 34} Investigators should therefore take this into account when assessing for nerve enlargement, and we recommend obtaining and applying specific reference values for these distinct populations.



Video 1 Normal median nerve anatomy. Video 1 shows the normal nerve anatomy of the median along its' course in the arm. Imaging is started distally at the carpal tunnel and the nerve is then followed proximally through the forearm and arm (up to the mid arm point, where it is located next to the brachial artery).

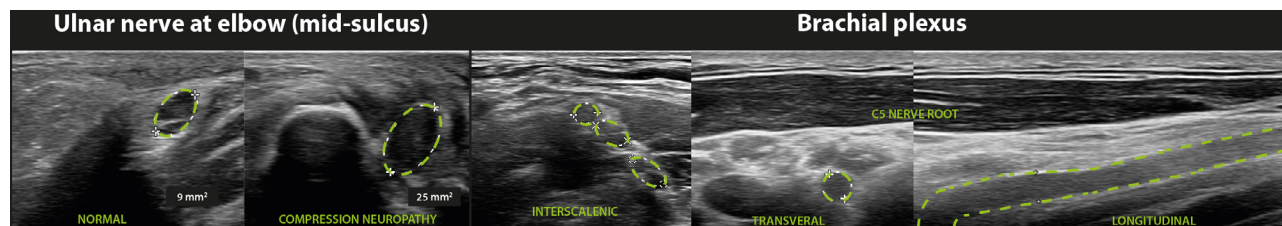


Figure 3 Alternate echo textures in normal sonoanatomy. Peripheral nerves can usually be recognised by their typical honeycomb structure. However, at some anatomic sites normal echo texture differs. The ulnar nerve at the sulcus is usually distinctly hypoechoic, which is also the case in brachial plexus nerve roots.

Although nerve ultrasound scanning is considered operator dependent, we have shown that measurement of nerve CSA is reproducible, with low inter-observer variability, especially in arm nerves.³⁵ Performance of nerve ultrasound on different sonographic devices and in a multicentre setting did not significantly influence reliability, which implies that the tool is suitable for diagnostic purposes in the general neurological practice, provided that the investigator had sufficient training.^{35 36} This also implies that investigators can reliably apply published sonographic cut-off values for nerve enlargement in their own clinic, rather than having to obtain their own normal values first

Table 2 Reference values of sonographic nerve size

Nerve site		Normal values (CSA in mm ²)	Disease specific cut-off values for suspected CIN (CSA in mm ²)
Median nerve	Wrist	11	–
	Forearm	9	>10
	Upper arm	9	>13
Ulnar nerve	Wrist	7	–
	Forearm	6	–
	Distal to sulcus	9	–
	At ulnar sulcus	9	–
	Proximal to sulcus	9	–
	Upper arm	9	–
Brachial plexus	C5 nerve root*	8	>8
Fibular nerve	Popliteal fossa	9	–
	Fibular head	11	–
Tibial nerve	Popliteal fossa	22	–
	Distal lower leg	13	–
	At medial malleolus	13	–
Sural nerve	Distal lower leg	3	–

This table shows the upper limit of normal nerve cross-sectional area (CSA) and cut-off value for nerve enlargement suspect of chronic inflammatory neuropathy (CIN) in upper and lower extremity nerve sites. Normal values shown were obtained in a mainly Caucasian general Dutch population and a population suspected of CIN.

*Elements of the brachial plexus are commonly measured intra-sclenic; normal nerve root sizes at the exit of the neuroforamina are often larger (ie, up to 12 mm²), whereas C6 and particularly C7 nerve roots may be less reliable to assess accurately.³⁵

(taking into account the above-mentioned limitations regarding race and extremes). Thus, reference values may potentially be obtained on a national or even continental base rather than each unit having to obtain its own reference values.

The application of nerve ultrasound scanning in the diagnosis of mononeuropathies, such as carpal tunnel syndrome (CTS) and ulnar neuropathy at the elbow has already become common practice in several countries worldwide.^{37 38} NCS and ultrasound scanning are complementary tools in the diagnostic approach of mononeuropathies, allowing not only early identification but also more precise localisation (eg, site of entrapment, single or ‘double trouble’ traumatic lesions) and identifying underlying cause (eg, compression, ganglion, tumour (figure 4)).^{39 40} Moreover, nerve ultrasound is even preferred over NCS in the evaluation of traumatic lesions and tarsal tunnel syndrome (TTS). In contrast to CTS, isolated nerve swelling in tarsal tunnel is highly uncommon whereas perineural causes are probably more frequent (ie, compression by tendinitis, dilated vein, callus or scar tissue, occasionally intraneural such as ganglion/cyst). One could debate whether all these cases belong to TTS spectrum, or should simply be diagnosed as tibial nerve lesions at the ankle. Nerve ultrasound can readily visualise possible interruptions in nerve integrity (in contrast to common delay with NCS), help to identify secondary lesions (due to traction over distant hinge points), and actually identify the cause of symptoms in TTS.

The evidence on diagnostic applications in polyneuropathy has also recently expanded rapidly. First, studies on nerve ultrasound in polyneuropathy identified nerve enlargement in CIDP and MMN (65%–90%), not present in healthy controls or in diseases such as axonal neuropathy and motor neurone disease.^{41–46} In contrast to mononeuropathies, such as CTS and ulnar neuropathy at the elbow where nerve enlargement develops only at the sites of entrapment,^{37 38} nerve enlargement in these polyneuropathies occurred strikingly at non-entrapment sites in multiple upper and lower limb nerves.^{41–48} The presence of nerve enlargement at non-entrapment sites can therefore help to distinguish CIDP and MMN from non-treatable disease mimics.

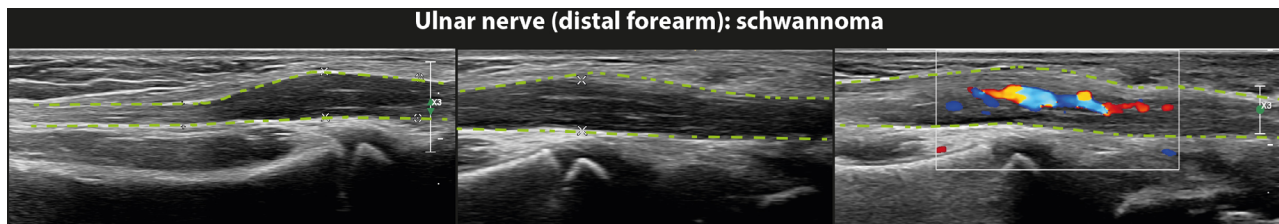


Figure 4 Ultrasound may reveal structural abnormalities. Nerve ultrasound may reveal important additional information on the cause of peripheral nerve disease. Here, a schwannoma of the ulnar nerve, with profound vascularisation, as identified with ultrasound is shown.

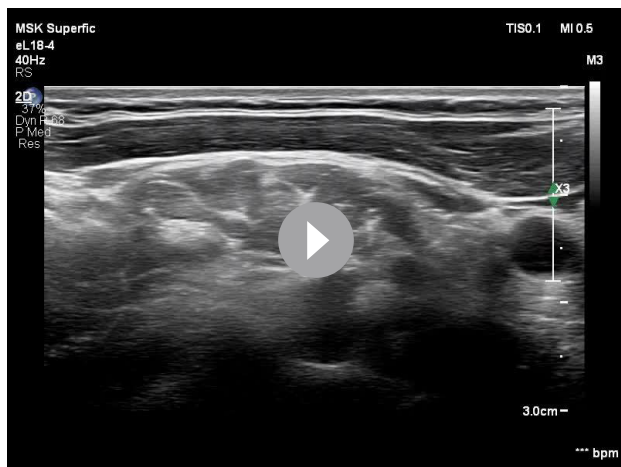
Further studies also noted different patterns of nerve enlargement in different types of polyneuropathy: (multi)focal, regional, and diffuse.^{24 25 41 45–48} Pronounced diffuse nerve enlargement can occur in CMT1A (figure 1), while there is only mild enlargement in ‘axonal’ CMT types, mainly at entrapment sites.^{24 46} This pattern of absent or only mild enlargement, predominantly at entrapment sites, is also consistent with acquired axonal neuropathies. Multifocal or regional nerve enlargement distant from entrapment sites in upper and lower limb nerves and brachial plexus can occur to varying degrees in paraproteinaemic, vasculitic and chronic inflammatory neuropathies.^{49–51} Nerve enlargement is often less diffuse in CIDP than in CMT1A and can occur mainly in proximal nerve segments, including the median and ulnar nerves in the upper arm and the brachial plexus (figure 1, videos 2 and 3).^{24 25 41 45 46} MMN also has predominant involvement of proximal nerve segments, but nerve enlargement often is more focal and asymmetric, and frequently less pronounced (figure 1).^{24 25 43 46 52 53} In vasculitic neuropathy, multifocal or mildly regional nerve enlargement of upper limb nerves with sparing of the brachial plexus may help to distinguish it from asymmetric presentations of CIDP.^{24–26 42 45} The degree of nerve enlargement and the pattern of distribution of enlargement may vary within disease groups (table 3) and we need further studies for a more detailed map of these specific patterns. Despite these limitations, they may still provide helpful clues to identify the cause accurately.

Several nerve ultrasound diagnostic protocols and scoring systems have been developed to help to distinguish chronic inflammatory polyneuropathies from disease mimics. Kerasnoudis *et al* developed the Bochum Ultrasound Score (BUS), which includes measurements of the ulnar nerve at Guyon’s canal and upper arm, radial nerve at the spiral groove, and sural nerve at the calf, to discriminate acute and chronic inflammatory neuropathies.⁵⁴ Grimm *et al* developed the Ultrasound Pattern Score (UPS) in which CMT, CIDP, MMN, GBS and controls can be distinguished using a scoring system based on measurements of the median, ulnar, tibial, fibular, sural and vagus nerves and brachial plexus nerve roots.^{53 55} Both the BUS and UPS showed high sensitivity and specificity in

a population with incident and prevalent CIDP and MMN. We also found a high sensitivity (83%–95%) and specificity (99%) of nerve ultrasound scanning for discriminating CIDP and MMN from relevant disease controls in a cohort of 140 incident and treatment-naïve patients, and we could reduce an extensive set of measurements to a practical short sonographic protocol (bilateral evaluation of the median nerve at the forearm and arm, and interscalenic elements of the brachial plexus).²⁵ In subsequent studies (monocentre and multicentre), including a total of 200 patients with suspected chronic inflammatory neuropathy, we validated our short sonographic protocol (based on the currently commonly used EFNS/PNS criteria for CIDP and MMN).^{56 57} A protocol including measurement of the median nerve at the forearm and arm level and the C5 nerve root bilaterally (the Dutch Ultrasound Protocol for Polyneuropathy (DUP-P)) showed a sensitivity of 87.4% and specificity of 67.3%.⁵⁷ The design of this study approximated clinical practice more, and though the figures are lower than the previously



Video 2 Enlargement of the median nerve in chronic inflammatory demyelinating polyneuropathy (CIDP). Video 2 shows the nerve anatomy of the median along its’ course in the arm in a patient with CIDP. Imaging is started distally at the carpal tunnel and the nerve is then followed proximally through the forearm and arm (up to the mid arm point, where it is located next to the brachial artery). Note the profound nerve enlargement and severely enlarged nerve fascicles, especially proximally at the mid arm level.



Video 3 Enlargement of the brachial plexus in chronic inflammatory demyelinating polyneuropathy (CIDP). Video 3 shows the nerve anatomy of the brachial plexus in a patient with CIDP. Imaging is started distally and followed proximally to the truncal level, after which the entry point of the C8, C7, C6 and C5 nerve roots to the cervical spine can be observed. Note the severe nerve enlargement of all nerve root segments.

reported ones in studies with only confirmed diagnoses, results confirm that this protocol can be applied reliably to detect a chronic inflammatory neuropathy in patients suspected of CIDP and MMN. Importantly, we also showed the DUP-P improved detection of treatment-responsive cases of CIDP and MMN. An additional 21%–27% of treatment-responsive patients were identified with nerve ultrasound compared with conventional NCS only in both our monocentre and multicentre study.^{56 57} These study results indicate that nerve ultrasound significantly enhances detection of treatment-responsive chronic inflammatory neuropathies compared with the conventional diagnostic tools.

With this accumulating evidence, nerve ultrasound is rapidly gaining importance in diagnostic strategies of suspected polyneuropathy. It is a reliable tool to investigate peripheral nerve morphology, presence and pattern of nerve enlargement can be important clues for the underlying peripheral nerve disease, and in chronic inflammatory neuropathy ultrasound even improves detection of treatment-responsive patients. Therefore, we expect nerve ultrasound to gain a prominent place in future diagnostic strategies for polyneuropathy, and we advise clinicians to implement nerve ultrasound in their routine workup of suspected polyneuropathy.

Implementation of nerve ultrasound scanning in routine workup of polyneuropathy

In this review, we propose a new diagnostic strategy in suspected polyneuropathy that incorporates nerve ultrasound scanning (figure 5). Its exact place as a diagnostic tool in polyneuropathy awaits refinement from future studies, and the indications will likely differ depending on the suspected type of polyneuropathy, but this new approach may guide clinicians on how

Table 3 Degree and pattern of nerve enlargement in upper extremity nerves in chronic polyneuropathies

Type of polyneuropathy	Degree of nerve enlargement	Pattern of nerve enlargement
CIAP	Normal nerve size or mild nerve enlargement	Focal Relatively symmetric Mainly at sites of entrapment
CIDP	Moderate-to-severe nerve enlargement	Mainly regional or diffuse, occasionally multifocal Relatively symmetric Mainly proximal nerve segments (upper arm, brachial plexus)
CMT: type 1A	Severe nerve enlargement	Predominantly diffuse or occasionally regional Symmetric Along full length of nerves (including brachial plexus)
CMT: other types	Normal nerve size or mild nerve enlargement	Focal Relatively symmetric Mainly at sites of entrapment, only mild enlargement outside sites of entrapment possible
GBS	Normal nerve size or mild nerve enlargement	Focal Relatively symmetric Mainly at cervical nerve roots, only mild or no enlargement in arm and leg nerves
HNPP	Moderate-to-severe nerve enlargement	Focal At sites of entrapment, usually multiple involved
IgM neuropathy	Moderate-to-severe nerve enlargement	Regional or diffuse Relatively symmetric Proximal and distal segments of arm nerves and brachial plexus
Leprosy	Moderate-to-severe nerve enlargement	Focal Commonly asymmetric Several centimetres proximal to sites of entrapment
LSS	Moderate-to-severe nerve enlargement	(multi)focal or regional Asymmetric Mainly proximal nerve segments (upper arm, brachial plexus)
MMN	Moderate-to-severe nerve enlargement	(multi)focal, occasionally regional Asymmetric Mainly proximal nerve segments (upper arm, brachial plexus)
Vasculitic neuropathy	Mild-to-moderate nerve enlargement	(multi)focal or regional Commonly asymmetric At sites of entrapment, proximal and distal arm, brachial plexus spared

This table shows the degree and pattern of distribution of nerve enlargement frequently found in different types of chronic polyneuropathy. The pattern of nerve enlargement found may be an additional clue to the diagnosis in a patient of suspected neuropathy, but further studies are necessary to determine the specificity and diagnostic value of these specific patterns.

.CIAP, chronic idiopathic axonal polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; ; CMT, Charcot-Marie-Tooth disease; GBS, Guillain-Barré Syndrome; HNPP, hereditary neuropathy with liability to pressure palsies; LSS, Lewis-Sumner syndrome; MMN, multifocal motor neuropathy.

to implement this tool into routine workup. Several nerve ultrasound scanning protocols have been developed. The most efficient set will have to be determined in comparative studies, and the most optimal sonographic protocol likely differs depending on the type

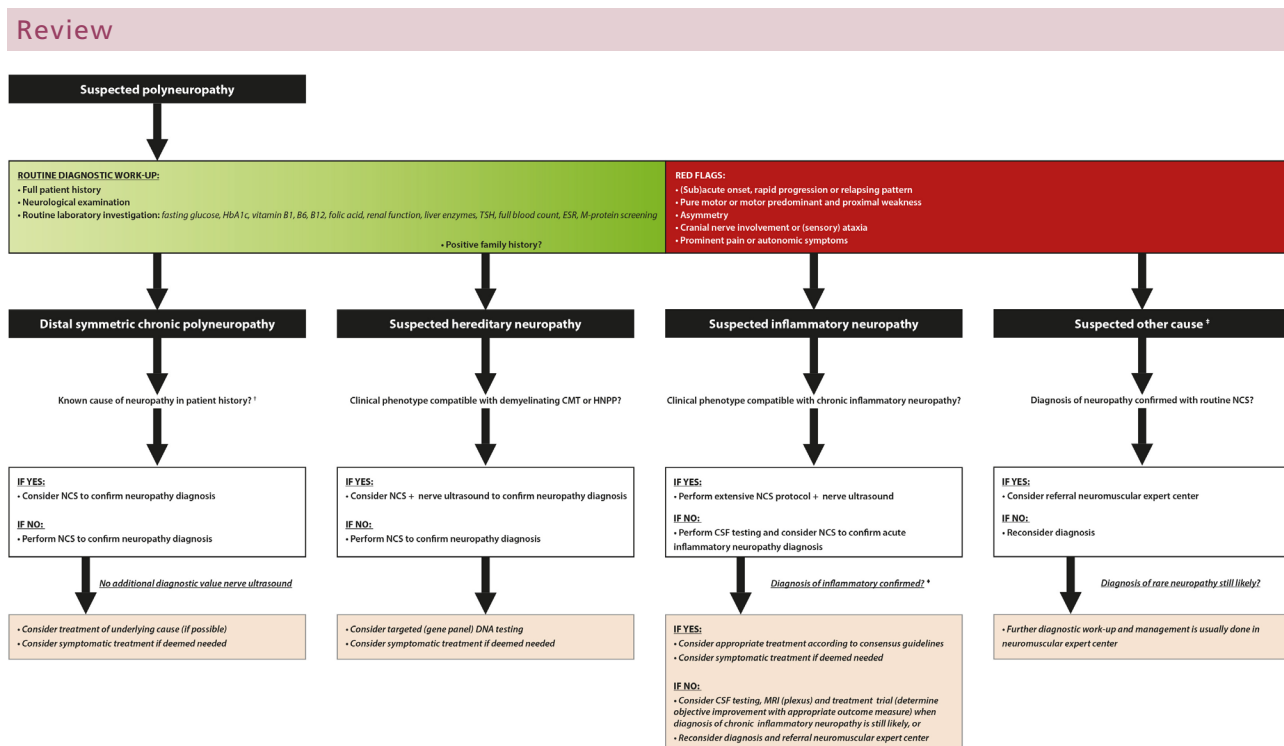


Figure 5 Flow chart on diagnostic strategies in suspected polyneuropathy. Diagnostic workup of patients with suspected polyneuropathy requires a structured approach with the extension of appropriate ancillary investigations. Early recognition of typical clinical features compatible with hereditary or inflammatory neuropathies is important to help guide further testing. This may now also mean to implement nerve ultrasound at relatively early stages of the diagnostic strategy to facilitate early identification and reduce test burden in patients. Patients can be categorised according to four main categories of distinct polyneuropathies: (1) distal symmetric, sensory predominant with indolent progression (including known causes such as diabetes mellitus, chronic kidney failure, or drug associated neuropathy (such as chemotherapy)), (2) hereditary neuropathies (axonal and demyelinating, hereditary neuropathy with liability to pressure palsies (HNPP), but also more complex phenotypes), (3) inflammatory neuropathies (acute and chronic (Guillain-Barré-syndrome (GBS), respectively, chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN))), and (4) † other causes (eg, vasculitic neuropathy, neuropathy in systemic disease (eg, Sjögren's, sarcoidosis, and amyloidosis), or paraproteinaemic neuropathy). In patients with suspected GBS, the diagnostic value of nerve ultrasound is likely limited; however, it could be of help in cases where acute CIDP presentation is suspected (nerve ultrasound may show nerve root enlargement (brachial plexus) in both, but more widespread nerve enlargement in arm nerves in CIDP). Clinicians may consider treatment trial (induction treatment) for CIDP/MMN when both nerve conduction studies (NCS) and ultrasound are compatible with a diagnosis of chronic inflammatory neuropathy. However, if another cause of problems (eg, an infectious disease) is suspected based on clinical findings, clinicians should still perform additional tests (eg, cerebrospinal fluid (CSF) testing in case of infectious disease) to exclude these causes. *Diagnosis of inflammatory neuropathies should fulfil relevant consensus criteria, such as guidelines on diagnosis of CIDP, MMN and GBS.

of suspected neuropathy. Nonetheless, it seems advisable to assess at least upper limb nerves (median, and possibly ulnar nerve) and brachial plexus bilaterally.

A diagnostic strategy in suspected polyneuropathy mainly relies on clinical features, based on a thorough patient history and physical examination. Clinicians need to have a systematic approach, focusing particularly on the type and distribution of symptoms, and the presence of potential red flags (figure 5) indicating a neuropathy other than axonal polyneuropathy. We advise including a family history to explore the possibility of a hereditary neuropathy, especially because NCS may identify features of demyelination in some familial neuropathies, and nerve ultrasound scanning may lead clinicians falsely to suspect the presence of a treatable chronic inflammatory neuropathy. A dedicated set of routine laboratory tests should be able to detect common underlying pathology of (axonal) neuropathy during the primary diagnostic workup.

Clinicians should also consider this in case a patient already has a well-known underlying disease, for example, diabetes mellitus, since a second cause of neuropathy can be identified in up to 9% of cases.¹⁹ We recommend including an M-protein screening in these laboratory investigations, as NCS and nerve ultrasound results in paraproteinaemic polyneuropathy may mimic those of chronic inflammatory neuropathy as well.⁵⁰

When the primary diagnostic workup suggests a chronic acquired axonal polyneuropathy, NCS can be considered to confirm this. If a patient already has an established cause of neuropathy, clinicians may opt to omit NCS as these often have little additional value.¹³ We do not advise including nerve ultrasound scanning routinely in suspected chronic acquired axonal neuropathy, as often this finds only non-specific nerve enlargement at entrapment sites and it currently cannot distinguish different causes of the axonal neuropathy.²⁴

If the primary diagnostic workup suggests a hereditary polyneuropathy, DNA testing may be considered to confirm this diagnosis. The reduced costs have increased the availability of panels or even whole exome sequencing in clinical practice. Despite this, and as a battery of DNA tests can still be expensive or fail to cover some of the known genetic defects, it could be preferable to test for specific genes only (eg, PMP22). In such a scenario, NCS and nerve ultrasound scanning could be helpful to direct DNA testing. NCS may identify homogeneous conduction slowing in demyelinating CMT, and nerve ultrasound may show extensive diffuse nerve enlargement in this type of CMT, but not in other types.^{24 58} Both diagnostic tests could be applied to help guide targeted DNA testing, but nerve ultrasound is generally more patient friendly, and may be preferred in children that are anxious or unable to tolerate NCS.

The diagnosis of GBS primarily relies on clinical features and appropriate laboratory investigations, including CSF testing. In patients where the clinical course still leaves diagnostic doubt, NCS can help, although with careful consideration of timing and interpretation of its results. We do not recommend routine nerve ultrasound studies in patients with suspected GBS, as this currently is of limited value. It may confirm nerve (root) involvement, but diagnostic performance is still uncertain.²⁴ In patients with a suspected acute onset of CIDP, mimicking GBS, ultrasound may provide added value and show nerve enlargement along the length of upper limb nerves that could warrant more close monitoring. However, abnormal ultrasound scanning should never be the sole criterion to consider further treatment.

In people with suspected chronic inflammatory neuropathy, we advise routinely combining NCS and nerve ultrasound scanning to optimise detection of treatment-responsive cases. Omitting nerve ultrasound in these patients may leave up to 25% of treatment-responsive patients undetected.^{56 57} If both tests are compatible with a chronic inflammatory neuropathy (nerve conduction studies showing demyelinating features fulfilling the EFNS/PNS criteria and nerve ultrasound showing nerve enlargement of proximal median nerve segments and/or brachial plexus) — then it is reasonable to consider starting treatment without further tests. However, it is still important to ensure that the patient's symptoms are consistent with isolated chronic inflammatory neuropathy, and not with other underlying disease. For example, patients with a possible underlying infective cause would still need a lumbar puncture. If only nerve ultrasound shows features of demyelination, we advise to obtain additional support for a chronic inflammatory neuropathy (eg, lumbar puncture or MR scan of brachial plexus) and to exclude other causes of neuropathy. If clinical features are still compatible and there is no other identifiable cause of neuropathy, we recommend

a treatment trial, as a treatment-responsive neuropathy may still be present.^{56 57} In such case, we advise obtaining objective measures of treatment response (eg, vigorimetry, Rasch-Built Overall Disability Scale, or hand-held dynamometry) during the treatment trial, to prevent misdiagnosis and long-term treatment based on subjective treatment (potential placebo) effect only. If both NCS and ultrasound scanning identify no signs of demyelination, a chronic inflammatory neuropathy is very unlikely, and clinicians should search for an alternative cause.

When suspecting another cause of chronic neuropathy, for example, vasculitic or paraproteinaemic neuropathy, we advise more extensive NCS and laboratory tests to determine the extent and nature of neuropathy, and to direct further diagnostic testing. Nerve ultrasound may help to map the extent of nerve involvement, and in suspected vasculitic neuropathy there may be a suggestive pattern of enlargement in proximal median and ulnar nerve segments with sparing of the brachial plexus.⁵⁰ However, the potential of nerve ultrasound to help guide additional diagnostic testing is not yet fully clear. Clinicians may therefore consider using nerve ultrasound scanning as a supportive diagnostic tool, but at present we do not recommend it routinely for all patients with suspected other causes of polyneuropathy.

The availability of nerve ultrasound scanning and the logistics involved most likely differ between different health systems or even clinic by clinic. Nerve ultrasound scanning has low inter-observer variability, and can be performed reliably if an investigator (eg, a neurologist, lab technician, or radiologist) has had sufficient training.^{35 36} However, NCS and nerve ultrasound scanning appear to be complementary, and, therefore, in an ideal scenario NCS and nerve ultrasound might be performed in a single session by a well-trained practitioner familiar with both techniques. In such case, the investigator could combine the findings from each, thereby increasing their diagnostic value even further, and improving time and cost efficiency.

CONCLUSIONS

Nerve ultrasound scanning is a reproducible and reliable diagnostic tool that has rapidly gained importance in the diagnostics of peripheral neuropathy. It may help to improve diagnostic yield by boosting sensitivity and allows more accurate localisation and identification of the specific nature of a nerve disorder. In mononeuropathies such as CTS and ulnar neuropathy at the elbow, ultrasound scanning typically shows enlargement at the sites of entrapment, whereas in several type of polyneuropathy there are distinct patterns of nerve enlargement along the entire length of nerves. For example, there is often nerve enlargement in proximal segments of upper limb nerves and brachial plexus in chronic inflammatory neuropathies, but not in most non-treatable disease mimics. As such, nerve

ultrasound scanning can significantly improve detection of potentially treatable patients compared with conventional diagnostic tools, and the ideal way to investigate patients with suspected neuropathy would be a combined assessment by a single well-trained practitioner familiar with both NCS and nerve ultrasound.

Previously, NCS were the main way to determine the differential diagnosis of polyneuropathy and the need for further diagnostic testing. However, pronounced nerve enlargement outside sites of entrapment identified with nerve ultrasound is an important independent indicator of nerve disease that can help in diagnosis and in guiding further investigation, even when nerve conduction studies are relatively 'normal'. Future studies will determine the optimal protocol for ultrasound scanning in polyneuropathy, but we advise investigating at least the median nerve and brachial plexus bilaterally (the DUP-P). In this article, we describe a possible diagnostic strategy to implement nerve ultrasound in routine workup of suspected polyneuropathy. Though its exact place in diagnosis remains debatable, we expect it to gain a prominent place and recommend neurologists to incorporate it into their routine workup.

Key points

- ▶ Nerve ultrasound scanning is a practical and reliable diagnostic bedside tool that allows detailed visualisation of peripheral nerves, with a flexible field of view.
- ▶ In mononeuropathies such as carpal tunnel syndrome and ulnar neuropathy at the elbow, there is nerve enlargement only at specific sites of entrapment, while in polyneuropathy it may be multifocal, regional or even diffuse.
- ▶ Nerve ultrasound scanning can reliably distinguish chronic inflammatory neuropathies from disease mimics by showing nerve enlargement of brachial plexus and proximal arm nerves and it improves detection of treatable causes of peripheral neuropathy.
- ▶ Nerve ultrasound should be embedded in routine diagnostic workup of peripheral neuropathies.

Further reading

- ▶ Telleman JA, Grimm A, Goedee HS, *et al.* Nerve ultrasound in polyneuropathies. *Muscle Nerve* 2018;57:716-728.
- ▶ Herraets IJT, Goedee HS, Telleman JA, *et al.* Nerve ultrasound for diagnosing chronic inflammatory neuropathy: a multicenter validation study. *Neurology* 2020;95:e1745-e1753.

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authors approved the manuscript. The corresponding author takes full responsibility for the analyses and interpretation of the data and conduct of research. The corresponding author has full access to all data and has the right to publish all data separate and apart from any sponsor.

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ORCID iD

Johan A Telleman <http://orcid.org/0000-0002-4065-9999>

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