Nerve ultrasound for the diagnosis and follow-up of peripheral neuropathies

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Purpose of review
The purpose if this review is to provide an overview of the available data on the use of nerve ultrasound for the diagnosis and follow-up of peripheral neuropathies.

Recent findings
During the last decade, nerve ultrasound has been established as a complementary tool for the evaluation of morphological changes mostly for immune-mediated polyneuropathies. Through the development of ultrasound protocols for evaluation of disease-specific sites, nerve ultrasound has proven to be a practical, widely available, reproducible diagnostic tool with no relevant contraindications.

Summary
Cross-sectional area, echogenicity, morphology of the individual nerve fascicles, thickness of the epineurium, vascularization and mobility of the nerve are the main parameters evaluated with nerve ultrasound in polyneuropathies. Patients with typical chronic inflammatory demyelinating polyneuropathy show multifocal nerve enlargements easily visible on the upper extremities and the brachial plexus, whereas its variants show focal nerve enlargements. On the other hand, axonal neuropathies including diabetic neuropathy present with isolated nerve enlargement mostly in compression sites.

Keywords
chronic inflammatory demyelinating polyneuropathy, cross-sectional area, echogenicity, nerve ultrasound, polyneuropathy

INTRODUCTION

Polyneuropathies are the most common diseases of the peripheral nervous system with a high heterogenicity regarding cause and clinical symptoms [1]. Their prevalence is 5–8% in the normal population and increases at the age of over 55 years up to 13% [2,3]. The confirmation of the diagnosis traditionally includes thorough clinical examination and nerve conduction studies.

Imaging methods of the peripheral nervous system have been increasingly established during the past 10 years and are mostly used for the highly relevant distinction of immune-mediated neuropathies from other neuropathies. The development of high-resolution ultrasound probes (>12 MHz) in the last 20 years enables the detailed examination of nerve structures. With its restrictions (e.g. contraindications, time required, availability), standard MR-neurography is hardly an easily accessible alternative in everyday clinical practice for the diagnosis of inflammatory polyneuropathies.

We provide an overview of the available data on the use of nerve ultrasound for the diagnosis and follow-up of polyneuropathies with a focus on chronic inflammatory demyelinating polyneuropathy (CIDP). Ultrasound examination for other inflammatory polyneuropathies, such as, sarcoidosis, vasculitis, POEMS (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasmacytoma, skin changes) have not yet become established in daily practice [4–6].

For this review, the Medline database was searched through its interface PubMed (2000 to January 2022) using the term 'nerve ultrasound' combined, using the operator 'AND', with the term 'polyneuropathy' or 'neuropathy'. After applying the filters, 'humans' and 'English', the newest articles were selected for each of the neuropathies. The list of citations and bibliography of every

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KEY POINTS

- Nerve ultrasound evaluates the cross-sectional area, echogenicity, fascicle structure, thickness of the epineurium, vascularization and mobility the peripheral nerves.
- Nerve ultrasound is a supportive tool in the EAN/PNS guideline on diagnosis and treatment of CIDP.
- Patients with CIDP show multifocal nerve enlargements primarily with hypoechoic changes.
- Patients with Charcot-Marie-Tooth Type 1a show homogenously increased CSA of the peripheral nerves.
- Noninflammatory axonal neuropathies show CSA increase mostly in compression sites.

identified article was further scanned for potentially relevant articles.

NERVE ULTRASOUND ALGORITHMS AND EXAMINATION PROTOCOLS

Superficial (median, ulnar, radial, and sural nerve) as well as deeper nerves of the body (tibial and peroneal nerve at the popliteal fossa and upper leg, brachial plexus, vagus nerve) can be visualized (Figs. 1–3). The transducer must be kept perpendicular to the nerves to avoid anisotropy (dependence of the echogenicity of the nerve on the direction of the ultrasound). Sonographically, the peripheral nerves show a homogeneous, tubular echo-structure, with alternation of parallel, hypoechoic (fascicles) and hyperechoic (perineurium) zones in the longitudinal plane. In the axial plane, the nerves present with a 'honeycomb' or fascicular impression (hypoechoic fascicles and hyperechoic epineurium).

The goals of the sonographic evaluation of a patient with polyneuropathy are:

(1) detection of pathological, structural changes in the peripheral nerves and/or the brachial plexus,
(2) documentation of the morphology and distribution pattern of these changes,
(3) quantification of these changes in order to carry out a reliable follow-up.

The examiner should evaluate the following parameters: cross-sectional area (CSA), the echogenicity, size and symmetry of the individual nerve fascicles, thickness of the epineurium, and vascularization and mobility of the nerve.

(1) The CSA is measured to the inner border of the hyperechoic epineurium. According to the novel recommendations of the EAN/PNS, enlargements of median nerve and/or the cervical nerve roots indicate a CIDP [7▪,8▪▪,9▪▪]. Various other scoring systems have been introduced to further improve the sensitivity and specificity of the method, for example, the Bochum Ultrasound Score for distinguishing Guillain-Barré Syndrome (GBS) and CIDP [10], the inclusion of vagus nerve for the GBS diagnosis [11], the axonal Bochum ultrasound score for distinguishing noninflammatory from inflammatory polyneuropathies with axonal damage [12]. In Table 1, the different scoring systems are presented with the mean values for healthy individuals from different study groups as well as the mean values from the existing meta-analysis [13▪–15▪].
(2) The *echogenicity* of the nerve can be evaluated during the examination qualitatively, depending

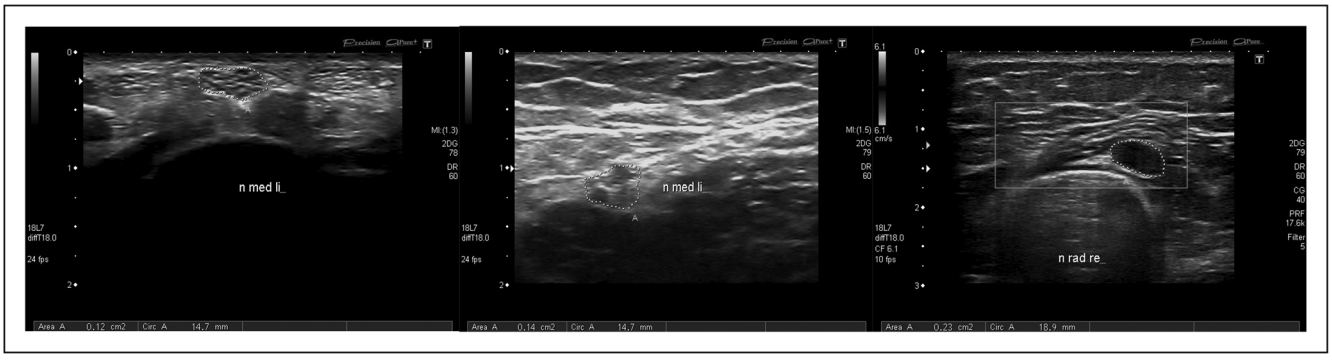

FIGURE 1. From left to right depicted: The median nerve at the carpal tunnel (normal fascicular structure with homogenously, hypoechoic fascicles, CSA 12 mm^2) and at the forearm (hypoechoic nerve, homogeneous increase in the CSA of all fascicles, CSA 14 mm^2). The radial nerve at the upper arm, Canalis spiralis (hypoechoic nerve, no distinct fascicular structure, CSA increase of a single fascicle, CSA 23 mm^2). CSA, cross-sectional area.

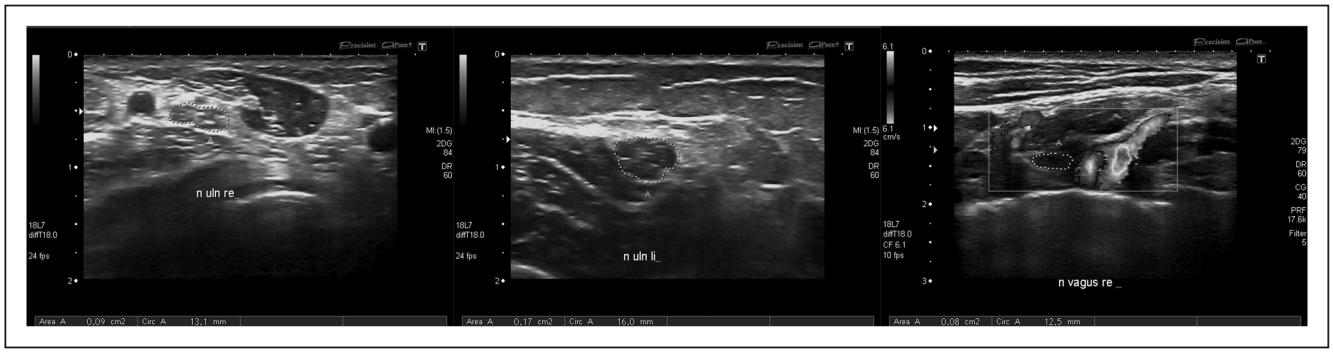

FIGURE 2. From left to right depicted: The ulnar nerve at the Loge de Guyon (mixed echogenicity, cross-sectional area 9 mm^2) and at the upper arm (hypoechoic nerve, homogeneous increase in the cross-sectional area of all individual fascicles, CSA 17 mm^2). The vagus nerve at the level of the bifurcation of the common carotid artery (hypoechoic nerve, no vascularization, CSA 8 mm^2). CSA, cross-sectional area.

on the experience of the examiner. In recent years, novel measurement techniques have been introduced to achieve a reproducible quantification of echogenicity by postprocessing the ultrasound images. Nerves and fascicles of patients with inflammatory polyneuropathy are typically hypoechoic. Hyperechoic nerves can occur in patients with severe long-term illness [16].

(3) Regarding the morphology of the individual nerve fascicles, a selective hypertrophy of individual fascicles and fading of the fascicular structure are the most frequent findings for patients with inflammatory polyneuropathy [17,18].

(4) An increased thickness of the epineurium with hyperechoic presentation is a rare finding in peripheral neuropathies due to structural remodeling of the epineurium [19].

(5) The vascularization of a peripheral nerve can be evaluated using the doppler method, but it has not been established in routine diagnostics. In the normal state, the peripheral nerves do not show any detectable Doppler signal. On the other hand, increased intraneural blood flow can often be documented in various immune neuropathies. Possible limitations of the Doppler technique can be the influence of external factors such as temperature. For this purpose, the skin temperature over the examined nerve should be kept at 32 °C [20]. Mobility of the nerve is an important factor in the assessment of entrapment syndromes (i.e. luxation of the ulnar nerve in cubital tunnel syndrome). There is no sufficient data on nerve mobility in polyneuropathies.

Pitfalls and restrictions of ultrasound diagnostics

The validation of normal nerve ultrasound cut-off CSA values for healthy subjects is a critical aspect influencing the wide use of the method. It is currently recommended to generate standard values for healthy control subjects depending on sex and age for each ultrasound laboratory. Furthermore, the intrarater

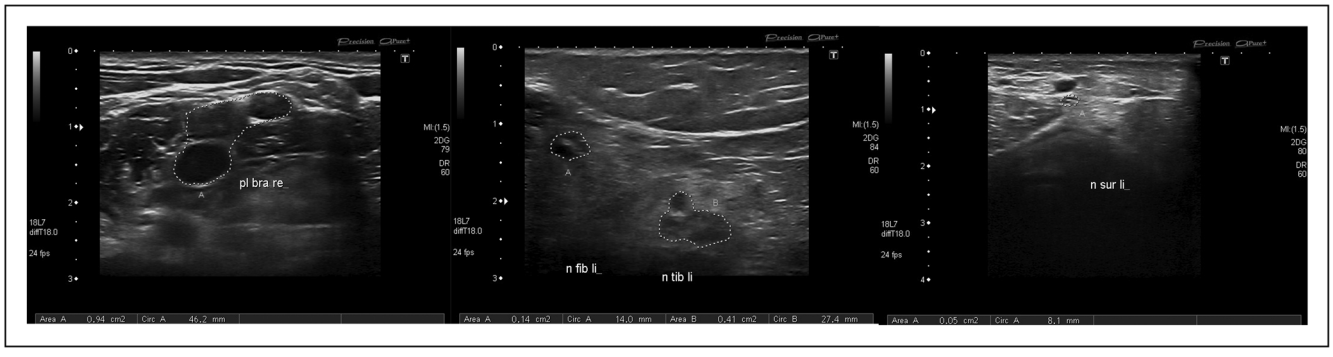

FIGURE 3. From left to right depicted: Brachial plexus between the scaleni muscles depicting a massive increase in cross-sectional area of the C5, C6, and C7 roots in CIDP. The fibular nerve (CSA 14 mm^2) and tibial nerve (CSA 41 mm^2) at the popliteal fossa (hypoechogenic nerves, no distinct fascicular structure). The sural nerve at the middle of the lower leg (CSA 5 mm^2) next to the V. saphena parva. CSA, cross-sectional area.

Table 1. Mean ultrasound values for each nerve segment in normal subjects from different study groups and the mean values from the existing meta-analysis

		Kerasnoudis *et al.* (2014)		Grimm *et al.* (2018)	Fisse *et al.* (2021)		Herraets *et al.* (2020)
Nerve	Site	Mean CSA (mm^2)	Standard deviation	Mean CSA (mm^2)	Mean CSA (mm^2)	95% CI (mm^2)	Upper limit CSA
Median nerve	Wrist	8.43	2.07 (12.57)	10.6	8.3	7.9–8.7	–
	Forearm	6.6	1.6 (6.8)	7.2	6.4	5.9–6.9	10
	Elbow	–	–	9.2	–	–	–
	Upper arm	8.4	2.87 (14.14)	9.1	8.3	7.5–9.0	13
Ulnar nerve	Guyon loge	5.16	1.03 (7.22)		4.1	3.6–4.6	–
	Forearm	5.46	1.26 (10.92)	5.9	5.2	4.8–5.7	–
	Elbow	5.33	1.4 (8.13)	8.7	5.9	5.4–6.5	–
	Upper arm	6.53	1.82 (10.17)	7.0	6.6	5.1–6.1	–
Radial nerve	Upper arm	3.26	1.52 (6.3)	–	5.1	4.0–6.2	–
Vagal nerve	Carotid sheath	–	–	2.2	2.2	1.5–2.9	–
C5		–	–	2.4[a]	5.6	4.6–6.7	8
C6		–	–	3.4[a]	8.8	7.4–10.3	8
C7		–	–	–	9.5	8.0–10.9	8
Brachial plexus	Intrascalene space	30.93	10.82 (52.57)	–	–	–	–
	Supraclavicular space	46.13	18.27 (82.67)	–	–	–	–
Fibular nerve	Fibula head	7,1	2.3 (11.7)	–	8.4	6.8–9.9	–
	Popliteal fossa	8.6	1.77 (12.14)	8.4	7.9	6.6–9.2	–
Tibial nerve	Popliteal fossa	8.43	2.68 (13.79)	23.2	25.9	17.5–34.4	–
	Malleolus	6.36	1.45 (9.26)	10.2	10.0	7.7–12.4	–
Sural nerve	Heads of gastrocnemius muscle	1.82	0.64 (3.1)	2.2[b]	2.4	1.7–3.1	–

CI, confidence interval, CIDP, chronic inflammatory demyelinating polyneuropathy; CSA, cross-sectional area.
[a]Grimm *et al.* (2018) measured distance, not the CSA for C5 and C6 root.
[b]Grimm *et al.* (2018) measured sural nerve at the lateral ankle.

and inter-rater reliability should be evaluated. It must also be critically mentioned that, just like in vascular diagnostics, nerve ultrasound diagnostics is dependent on the experience of the examiner and the anatomical characteristics of the patient. When the examination conditions are not optimal (e.g. obesity) or for nerves in deeper parts of the body (e.g. thighs), ultrasound diagnostics has important limitations.

ULTRASOUND FINDINGS IN SELECTED POLYNEUROPATHIES

Hereditary neuropathies

In the demyelinating form of hereditary sensory motor neuropathy (HMSN), Charcot-Marie-Tooth disease (CMT) type Ia, there is a generalized and homogeneously enlarged CSA in all nerve sections, which corresponds to a uniform chronic demyelination and remyelination of the entire nerve. Studies on the disease course over 5 years, have shown that these CSA enlargements appear essentially constant in CMT I [21–24]. Changes in echogenicity towards hypoechoic nerves have been described in CMT I [25]. In the other subtypes of CMT, the CSA enlargement is less prominent compared with CMT Ia [26]. In hereditary motor neuropathy with a tendency to pressure paralysis (HNPP), nerve enlargements are not generalized but occur only in typical compression and friction sites (carpal tunnel, ulnar sulcus, and fibula head) [20,27]. Slight nerve CSA enlargements of the proximal nerve segments, including the vagus nerve have also been

reported for familial transthyretin amyloidosis even in asymptomatic cases [28,29].

Chronic inflammatory demyelinating polyneuropathy

The diagnosis of CIDP, based solely on clinical examination, nerve conduction studies, lumbar puncture, and nerve biopsy remains challenging. In the past, a large number of diagnostic criteria were proposed, some of which are outdated and differ significantly in terms of sensitivity and specificity.

First applications of ultrasound diagnostics in CIDP showed bilateral thickening of the brachial plexus and multifocal thickening of several peripheral nerves [30]. Similar observations had previously been made from MRI scans [31–33]. A possible explanation for the thickening and thus increases in the CSA of the nerves could be the dynamics of the inflammation with demyelination and remyelination ('onion skin formation'). This morphological correlate fits well with the inflammatory nerve root compromise that leads to elevation of CSF protein. Although multifocal changes in the nerves were detected in CIDP patients in the years that followed, a positive correlation between morphological changes and electroneurography has not yet been shown.

The usefulness of ultrasound in differentiating CIDP from other polyneuropathies has been documented in a number of publications in recent years and has led to nerve ultrasound being included in the revised CIDP diagnostic criteria of 2021 as a supportive examination method for possible CIDP, thereby increasing the sensitivity and specificity of the diagnosis [9▪▪].

In a study with three centers in Holland in a cohort with a total of 100 patients with clinical suspicion of inflammatory neuropathy, Herraets *et al.* validated a short sonographic protocol consisting of the median nerve in the forearm (normal value $<10\,mm^2$), median nerve in the upper arm (normal value $<13\ mm^2$) and the C5 cervical root (normal value $<8\,mm^2$). In this cohort, 39 patients were diagnosed with a chronic autoimmune neuropathy (CIDP or CIDP variant) based on the criteria of EFNS/PNS of 2010, of which 33 patients fulfilled the electrodiagnostic criteria. The added value of nerve ultrasound in identifying treatment-responsive patients compared with nerve conduction studies (NCS) alone was 25% as 11 patients presented with normal NCS but CSA increase in at least one of the above-mentioned nerves [7▪,8▪▪].

The above-mentioned protocol was revolutionary for the revision of diagnostic guidelines of CIDP and, therefore, sets novel standards not only on the use of ultrasound but also on the use of invasive examinations such as the nerve biopsy, which can now be reserved as the last option for unclear cases. However, it has yet to be proven in the clinical routine und research whether this short protocol has sufficient sensitivity and specificity.

The main pitfalls, which have attracted criticism, are the reproducibility of the CSA measurement of the C5 root based on anatomical landmarks, the validity of the normal values and the increasing reports in the literature that further nerves are affected in CIDP and should also be evaluated to increase sensitivity [16,32–37]. Surely, the investigation of these aspects is the next step for the development of a widely accepted protocol of CIDP diagnosis.

It is, however, clear that nerve enlargements in CIDP are not generalized and homogeneous as in hereditary polyneuropathies but that multiple individual nerve segments appear enlarged in noncompression sites, while other segments have normal CSA. To depict this, homogeneity scores have been proposed [17,19]. Also, the evaluation of fascicles can reveal individual enlarged fascicles within a nerve section next to morphologically normal ones (Fig. 3).

The clinical significance of extreme nerve enlargements in CIDP, also called 'giant nerves', remains unclear, although similar enlargements have been reported in POEMS. Probably, this massive enlargement represents an inflammatory component with excessive demyelination/remyelination [36].

The need to evaluate the peripheral nerves in patients with suspected immune-mediated neuropathy more thorough than in the Dutch protocol is compelling, in order to diagnose CIDP variants such as multifocal and distal CIDP. Nerve enlargements in multifocal CIDP (also known as MADSAM or Lewis Sumner syndrome) found not only in the clinically and electrophysiologically affected nerves, for example, at sites with conduction blocks but also in clinically asymptomatic nerves [38]. Nerve enlargements in distal CIDP (also known as DADS) are similar to that of typical CIDP but with less pronounced enlargement and less involvement of the nerve roots [39,40]. In paranodopathies, case reports describe partially not only slightly enlarged nerve sections but also enlarged nerves at typical compression sites, but the studies are still insufficient to make a diagnostic recommendation for paranodopathies [41].

Treatment monitoring in chronic inflammatory demyelinating polyneuropathy

A latency of months to even years before the CIDP diagnosis is confirmed is not uncommon. In these

cases, secondary axonal damage has occurred, so that primarily the nerves of the lower extremities, can no longer be evaluated adequately through the NCS. When the axonal damage has progressed so far at the beginning of treatment, the question arises as to how to adequately evaluate the course of the disease [42–44].

Nerve sonography could assist in filling this gap. The 'intranerve CSA variability' (maximum divided by minimum CSA for each nerve), which reflects the segmental character of the CIDP, was proposed as parameter suited for therapy monitoring. A reduction in the 'intranerve CSA variability' means a reduced degree of swelling within a nerve, so that the ratio of the maximum CSA to the minimum CSA approaches '1' and could indicate a low disease activity [19,42].

Furthermore, nerve echogenicity can be used prognostically: hypoechoic enlarged nerves and fascicles reflect inflammatory edema, which responds to therapy. On the other hand, in patients with progressive disease and severe axonal damage, small hyperechoic nerves are occasionally present, which are considered to reflect a scar-fibrous remodeling difficult to treat with current anti-inflammatory therapies [18,37,42].

Guillain–Barré syndrome

In about 15% of cases, CIDP presents with acute signs so that the clinical picture can resemble the Guillain-Barré syndrome (GBS). GBS also shows treatment-dependent fluctuations in about 15% of cases, which usually occur during the first 8 weeks [45–47]. The distinction of these two disease entities (acute CIDP vs. GBS) can be challenging. The comparison of the clinical phenotype vs. neurophysiological parameters showed that the clinical aspects are better suited to separate acute CIDP from GBS than NCS [48].

In this case, nerve ultrasound can be helpful as patients with CIDP could already present with more increased nerve CSA. Characteristic of GBS are nerve swellings, especially in the cervical plexus and vagal nerves, but CSA increase can also occur in other peripheral nerves with the exception of the sural nerve. Based on 'Bochum Ultrasound Score (BUS)', it is possible to distinguish acute CIDP from GBS with a sensitivity and specificity of up to 80% through the examination of the ulnar nerve in the upper arm and Loge de Guyon, the radial nerve in the radial sulcus and the sural nerve between the heads of the gastrocnemius muscle. A CSA increase in two of the above sites implies a chronic neuropathy [10].

The CSA increase of the vagus nerve in GBS patients also provides a crucial sonological marker, which correlates with autonomic dysfunction and improves after disease [11]. Currently, studies on the correlation of the vagal autonomic function in tilt-test and sonographical findings for patients with extrapyramidal disorders are emerging showing a reduction of the nerve CSA correlating with autonomic dysfunction [49▪].

Multifocal motor neuropathy vs. amyotrophic lateral sclerosis

Multifocal motor neuropathy (MMN) is a motor, immune-mediated polyneuropathy with asymmetric onset and slow clinical progression. The definitive diagnosis requires the detection of conduction blocks, which is not always possible mostly in cases of proximal affection [50].

On the other hand, the diagnosis of the degenerative motor disease amyotrophic lateral sclerosis (ALS) is based on electrophysiological and clinical features with newly revised criteria, which grade the ALS diagnosis based on probability [51]. The differential diagnosis of ALS is a major challenge, especially in the early stages of the disease or in the case of atypical courses [52▪▪].

Ultrasound evaluation of the peripheral nerves can confirm MMN and exclude ALS diagnosis for patients with asymmetrical motor neuropathy as MMN patients present with multifocal CSA increase in the peripheral nerves and nerve roots, even in segments without conduction blocks [53–59]. In contrast, normal CSA or even atrophic nerves are found in ALS. Therefore, sonographical evaluation of the peripheral nerves or at least evaluation of the clinically most affected nerve/nerve root in ALS and MMN can improve diagnostic validity [60▪]. Uniform approaches and multicenter validations are still needed for ultrasound evaluation of ALS patients, as the role of muscle ultrasound for the detection of fasciculations is also crucial in these cases [61].

Other polyneuropathies

There seems to be no specific morphological changes for further neuropathies such as toxic neuropathy, diabetic neuropathy, leprosy, vasculitic neuropathy and sarcoidosis. Normal to slightly enlarged nerve calibers occur in axonal polyneuropathies, with enlargements being observed particularly at compression sites [4,5,62–68]. These results suggest that nerve ultrasound can potentially detect increased susceptibility to pressure damage in axonal polyneuropathies. A summary of the nerve ultrasound findings for the above-mentioned polyneuropathies is provided in Table 2. As pointed out above, because of the different distribution of focal and multifocal

Table 2. Summary of nerve ultrasound findings for different polyneuropathies with selected publications

Type of polyneuropathy	Nerve ultrasound characteristics	Selected literature
Charcot-Marie-Tooth Ia	Generalized and homogeneously enlarged CSA in all nerve sections hypoechoic nerves	Goedee *et al.*, 2015, Grimm *et al.*, 2016, Kojima *et al.*, 2020, Grimm *et al.*, 2020, Winter *et al.*, 2021
Other Charcot-Marie-Tooth subtypes	Less prominent CSA increase than in CMT Ia	Schreiber *et al.*, 2013, Grimm *et al.*, 2016, Kojima *et al.*, 2020, Grimm *et al.*, 2020, Winter *et al.*, 2021
Hereditary motor neuropathy with a tendency to pressure paralysis (HNPP)	CSA enlargement in typical compression and friction sites (carpal tunnel, ulnar sulcus, and fibula head)	Goedee *et al.*, 2015, Steinward *et al.*, 2021
Transthyretin familial amyloid neuropathy	Normal to slightly enlarged nerve calibers including vagus nerve	Salvalaggio *et al.*, 2020
Chronic inflammatory demyelinating polyneuropathy	Multifocal enlargement of nerve segments in noncompression sites, individual enlarged fascicles, cases with 'giant nerves', hypoechoic nerves at early stages, hyperechoic nerves as sign of axonal damage	Padua *et al.*, 2012, Zaidmann *et al.*, 2013, Grimm *et al.*, 2016, 2019, Fisse *et al.* 2018, Härtig *et al.*, 2018, Herraets *et al.*, 2020a,b
Multifocal CIDP acquired demyelinating sensory and motor neuropathy (MADSAM)	focal nerve enlargements also in sites with no nerve conduction abnormalities	Kerasnoudis *et al.*, 2015, Grimm *et al.*, 2016, Drner *et al.*, 2020
Distal acquired demyelinating polyneuropathy (DADS)	Similar to typical CIDP, less pronounced enlargement and less involvement of nerve roots	Vu *et al.*, 2017
Paranodopathies	Case reports with not only partially slightly enlarged nerve sections but also enlarged nerves at typical compression sites	Athanasopoulos *et al.*, 2020
Guillain–Barré syndrome	CSA increase of the vagus nerve and cervical nerve roots, no CSA enlargement of sural nerve	Grimm *et al.*, 2014, 2016, 2019, Kerasnoudis *et al.*, 2014
Extrapyramidal disorders idiopathic Parkinson syndrome, multiple system atrophy	Reduced CSA of vagus nerve – correlations with autonomic dysfunction	Huckemann *et al.*, 2023
Multifocal motor neuropathy	Multifocal CSA increase in the peripheral nerves and nerve roots, even in segments without conduction blocks, detection of fasciculations	Catwright *et al.*, 2011, Kerasnoudis *et al.*, 2014, Grimm *et al.*, 2015 a,b, Schreiber *et al.*, 2016, 2020, Hensiek *et al.*, 2020, Lwenbrück *et al.*, 2021, Suzuki *et al.*, 2022
Diabetic neuropathy	Normal to slightly enlarged nerve calibers, with enlargements mostly at compression sites	Pitarokoili *et al.*, 2016, Breiner *et al.*, 2017
Vasculitic neuropathy	Normal to slightly enlarged nerve calibers, with enlargements mostly at compression sites	Grimm *et al.*, 2014, Uçeyler *et al.*, 2016
Sarcoid neuropathy	Normal to slightly enlarged nerve calibers, with enlargements mostly at compression sites	Kerasnoudis *et al.*, 2014, Kitaoji *et al.*, 2021
Leprosy	Increased nerve CSA for multiple nerves also in cases of normal conduction studies	Chen *et al.*, 2018, Sreejith *et al.*, 2021

CSA, cross-sectional area.

morphological changes in various polyneuropathies, examination protocols in polyneuropathy patients should not substitute the evaluation of the whole length of the peripheral nerves.

CONCLUSION

Nerve ultrasound is a crucial imaging method to support nerve conduction studies for the evaluation of polyneuropathies. As a diagnostic tool, it has been proved to be practical, widely available, reproducible, with no relevant contraindications and cost-effective. Thorough and dynamic examination protocols are necessary to gain adequate information on morphological nerve changes. Specific ultrasound protocols have been developed to distinguish chronic inflammatory demyelinating neuropathy from other polyneuropathies and further studies

are expected to establish examination protocols for further demyelinating and axonal neuropathies as well as monitoring protocols.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Sommer C, Geber C, Young P, *et al.* Polyneuropathies. Dtsch Arztebl Int 2018; 115:83–90.
2. Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: a review. JAMA 2015; 314:2172–2181.
3. Hanewinckel R, Drenthen J, Oijen M van, *et al.* Prevalence of polyneuropathy in the general middle-aged and elderly population. Neurology 2016; 87:1892–1898.
4. Grimm A, Décard BF, Bischof A, Axer H. Ultrasound of the peripheral nerves in systemic vasculitic neuropathies. J Neurol Sci 2014; 347:44–49.
5. Kerasnoudis A, Woitalla D, Gold R, *et al.* Sarcoid neuropathy: correlation of nerve ultrasound, electrophysiological and clinical findings. J Neurol Sci 2014; 347:129–136.
6. Dörner M, Ceanga M, Schreiber F, *et al.* High-resolution nerve ultrasound abnormalities in POEMS Syndrome-a comparative study. Diagnostics (Basel) 2021; 11:264.
7. ■ Herraets IJT, Goedee HS, Telleman JA, *et al.* Nerve ultrasound improves detection of treatment-responsive chronic inflammatory neuropathies. Neurology 2020; 94:e1470–e1479.

This publication introduced a novel ultrasound protocol for CIDP diagnosis.

8. ■■ Herraets IJT, Goedee HS, Telleman JA, *et al.* Nerve ultrasound for diagnosing chronic inflammatory neuropathy: a multicenter validation study. Neurology 2020; 95:e1745–e1753.

This publication established the novel ultrasound examination protocol for CIDP diagnosis.

9. ■■ Van den Bergh PYK, van Doorn PA, Hadden RDM, *et al.* European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force-Second revision. Eur J Neurol 2021; 28:3556–3583.

The new guidelines for CIDP diagnosis.

10. Kerasnoudis A, Pitarokoili K, Behrendt V, *et al.* Nerve ultrasound score in distinguishing chronic from acute inflammatory demyelinating polyneuropathy. Clin Neurophysiol 2014; 125:635–641.
11. Grimm A, Décard BF, Schramm A, *et al.* Ultrasound and electrophysiologic findings in patients with Guillain-Barré syndrome at disease onset and over a period of six months. Clin Neurophysiol 2016; 127:1657–1663.
12. Brünger J, Motte J, Grüter T, *et al.* Nerve ultrasound distinguishes non-inflammatory axonal polyneuropathy from inflammatory polyneuropathy with secondary axonal damage. Front Neurol 2022; 12:809359.
13. ■ Fisse AL, Katsanos AH, Gold R, *et al.* Cross-sectional area reference values for peripheral nerve ultrasound in adults: a systematic review and meta-analysis-Part II: Lower extremity nerves. Eur J Neurol 2021; 28:2313–2318.

The only existing meta-analysis for normal nerve ultrasound values.

14. ■ Fisse AL, Katsanos AH, Gold R, *et al.* Cross-sectional area reference values for peripheral nerve ultrasound in adults: a systematic review and meta-analysis-Part I: upper extremity nerves. Eur J Neurol 2021; 28:1684–1691.

The only existing meta-analysis for normal nerve ultrasound values.

15. ■ Fisse AL, Katsanos AH, Gold R, *et al.* Cross-sectional area reference values for peripheral nerve ultrasound in adults: a systematic review and meta-analysis-part III: cervical nerve roots and vagal nerve. Eur J Neurol 2021; 28:2319–2326.

The only existing meta-analysis for normal nerve ultrasound values.

16. Fisse AL, Pitarokoili K, Motte J, *et al.* Nerve echogenicity and intranerve CSA variability in high-resolution nerve ultrasound (HRUS) in chronic inflammatory demyelinating polyneuropathy (CIDP). J Neurol 2019; 266:468–475.
17. Grimm A, Vittore D, Schubert V, *et al.* Ultrasound pattern sum score, homogeneity score and regional nerve enlargement index for differentiation of demyelinating inflammatory and hereditary neuropathies. Clin Neurophysiol 2016; 127:2618–2624.
18. Gamber D, Motte J, Kerasnoudis A, *et al.* High-resolution nerve ultrasound to assess nerve echogenicity, fascicular count, and cross-sectional area using semiautomated analysis. J Neuroimaging 2020; 30:493–502.
19. Padua L, Martinoli C, Pazzaglia C, *et al.* Intra- and internerve cross-sectional area variability: new ultrasound measures. Muscle Nerve 2012; 45:730–733.
20. Goedee HS, Brekelmans GJ, Visser LH. Multifocal enlargement and increased vascularization of peripheral nerves detected by sonography in CIDP: a pilot study. Clin Neurophysiol 2014; 125:154–159.
21. Grimm A, Rasenack M, Athanasopoulou IM, *et al.* The modified ultrasound pattern sum score mUPSS as additional diagnostic tool for genetically distinct hereditary neuropathies. J Neurol 2016; 263:221–230.
22. Kojima Y, Noto Y, Tsuji Y, *et al.* Charcot-Marie-Tooth disease type 1A: Longitudinal change in nerve ultrasound parameters. Muscle Nerve 2020; 62:722–727.
23. Grimm AS, Schubert C, Grimm A, *et al.* Normative observational nerve ultrasound values in school-age children and adolescents and their application to hereditary neuropathies. Front Neurol 2020; 11:303.
24. Winter N, Vittore D, Gess B, *et al.* New keys to early diagnosis: muscle echogenicity, nerve ultrasound patterns, electrodiagnostic, and clinical parameters in 150 patients with hereditary polyneuropathies. Neurotherapeutics 2021; 18:2425–2435.
25. Goedee SH, Brekelmans GJF, van den Berg LH, Visser LH. Distinctive patterns of sonographic nerve enlargement in Charcot-Marie-Tooth type 1A and hereditary neuropathy with pressure palsies. Clin Neurophysiol 2015; 126:1413–1420.
26. Schreiber S, Oldag A, Kornblum C, *et al.* Sonography of the median nerve in CMT1A, CMT2A, CMTX, and HNPP. Muscle Nerve 2013; 47:385–395.
27. Steinwand P, Grimm A, Potthast GLF, *et al.* Vagus nerve pressure palsy in hereditary neuropathy with liability to pressure palsies confirmed by neurosonography. Clin Neurophysiol 2021; 132:975–976.
28. Du K, Xu K, Chu X, *et al.* Vagus nerve ultrasound in transthyretin familial amyloid polyneuropathy: A pilot study. J Neuroimaging 2022; 32:285–291.
29. Salvalaggio A, Coraci D, Cacciavillani M, *et al.* Nerve ultrasound in hereditary transthyretin amyloidosis: red flags and possible progression biomarkers. J Neurol 2021; 268:189–198.
30. Taniguchi N, Itoh K, Wang Y, *et al.* Sonographic detection of diffuse peripheral nerve hypertrophy in chronic inflammatory demyelinating polyradiculoneuropathy. J Clin Ultrasound 2000; 28:488–491.
31. Mizuno K, Nagamatsu M, Hattori N, *et al.* Chronic inflammatory demyelinating polyradiculoneuropathy with diffuse and massive peripheral nerve hypertrophy: distinctive clinical and magnetic resonance imaging features. Muscle Nerve 1998; 21:805–808.
32. Kronlage M, Pitarokoili K, Schwarz D, *et al.* Diffusion tensor imaging in chronic inflammatory demyelinating polyneuropathy: diagnostic accuracy and correlation with electrophysiology. Invest Radiol 2017; 52:701–707.
33. Pitarokoili K, Kronlage M, Bäumer P, *et al.* High-resolution nerve ultrasound and magnetic resonance neurography as complementary neuroimaging tools for chronic inflammatory demyelinating polyneuropathy. Ther Adv Neurol Disord 2018; 11:1756286418759974.
34. Zaidman CM, Harms MB, Pestronk A. Ultrasound of inherited vs. acquired demyelinating polyneuropathies. J Neurol 2013; 260:3115–3121.
35. Grimm A, Rattay TW, Winter N, Axer H. Peripheral nerve ultrasound scoring systems: benchmarking and comparative analysis. J Neurol 2016; 264:1–11.
36. Grimm A, Schubert V, Axer H, Ziemann U. Giant nerves in chronic inflammatory polyradiculoneuropathy. Muscle Nerve 2016; 55:285–289.
37. Härtig F, Ross M, Dammeier NM, *et al.* Nerve ultrasound predicts treatment response in chronic inflammatory demyelinating polyradiculoneuropathy-a prospective follow-up. Neurotherapeutics 2018; 15:439–451.
38. Kerasnoudis A, Pitarokoili K, Gold R, Yoon M-S. Bochum ultrasound score allows distinction of chronic inflammatory from multifocal acquired demyelinating polyneuropathies. J Neurol Sci 2015; 348:211–215.
39. Vu QD, Cartwright MS. Neuromuscular ultrasound findings in distal acquired demyelinating symmetric variant of chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2017; 56:E44–E45.
40. Feng Y, Zhang Y, Su X, *et al.* The comparison of MRN, electrophysiology and progression among typical CIDP and atypical CIDP subtypes. Sci Rep 2020; 10:16697.
41. Athanasopoulos D, Motte J, Fisse AL, *et al.* Longitudinal study on nerve ultrasound and corneal confocal microscopy in NF155 paranodopathy. Ann Clin Transl Neur 2020; 7:1061–1068.
42. Fisse AL, Pitarokoili K, Trampe N, *et al.* Clinical, sonographic, and electrophysiologic longitudinal features of chronic inflammatory demyelinating polyneuropathy. J Neuroimaging 2019; 29:223–232.
43. Grüter T, Motte J, Bulut Y, *et al.* Axonal damage determines clinical disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): a prospective cohort study of different CIDP subtypes and disease stages. Eur J Neurol 2022; 29:583–592.
44. Fisse AL, Motte J, Grüter T, *et al.* Comprehensive approaches for diagnosis, monitoring and treatment of chronic inflammatory demyelinating polyneuropathy. Neurol Res Pract 2020; 2:42.

45. Ruts L, van Koningsveld R, van Doorn PA. Distinguishing acute-onset CIDP from Guillain-Barré syndrome with treatment related fluctuations. Neurology 2005; 65:138–140.

46. Grimm A, Oertl H, Auffenberg E, *et al.* Differentiation between Guillain-Barré syndrome and acute-onset chronic inflammatory demyelinating polyradiculoneuritis-a prospective follow-up study using ultrasound and neurophysiological measurements. Neurotherapeutics 2019; 10:435–510.

47. Grimm A, Décard BF, Axer H. Ultrasonography of the peripheral nervous system in the early stage of Guillain-Barré syndrome. J Peripher Nerv Syst 2014; 19:234–241.

48. Dionne A, Nicolle MW, Hahn AF. Clinical and electrophysiological parameters distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. Muscle Nerve 2010; 41:202–207.

49. ■ Huckemann S, Mueller K, Averdunk P, *et al.* Vagal cross-sectional area correlates with parasympathetic dysfunction in Parkinson's disease. Brain Commun 2023; 5:fcad006.

The first publication describing the role of vagus nerve ultrasound for the evaluation of Parkinson syndrome.

50. Garg N, Park SB, Vucic S, *et al.* Differentiating lower motor neuron syndromes. J Neurol Neurosurg Psychiatry 2017; 88:474–483.

51. Hannaford A, Pavey N, van den Bos M, *et al.* Diagnostic utility of gold coast criteria in amyotrophic lateral sclerosis. Ann Neurol 2021; 89:979–986.

52. ■■ Goutman SA, Hardiman O, Al-Chalabi A, *et al.* Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis. Lancet Neurol 2022; 21:480–493.

An interesting review on ALS diagnosis.

53. Cartwright MS, Walker FO, Griffin LP, Caress JB. Peripheral nerve and muscle ultrasound in amyotrophic lateral sclerosis. Muscle Nerve 2011; 44:346–351.

54. Kerasnoudis A, Pitarokoili K, Behrendt V, *et al.* Multifocal motor neuropathy: correlation of nerve ultrasound, electrophysiological, and clinical findings. J Peripher Nerv Syst 2014; 19:165–174.

55. Grimm A, Décard BF, Athanasopoulou I, *et al.* Nerve ultrasound for differentiation between amyotrophic lateral sclerosis and multifocal motor neuropathy. J Neurol 2015; 262:870–880.

56. Grimm A, Prell T, Décard BF, *et al.* Muscle ultrasonography as an additional diagnostic tool for the diagnosis of amyotrophic lateral sclerosis. Clin Neurophysiol 2015; 126:820–827.

57. Schreiber F, Garz C, Heinze HJ, *et al.* Textural markers of ultrasonographic nerve alterations in amyotrophic lateral sclerosis. Muscle Nerve 2020; 62:601–610.

58. Schreiber S, Dannhardt-Stieger V, Henkel D, *et al.* Quantifying disease progression in amyotrophic lateral sclerosis using peripheral nerve sonography. Muscle Nerve 2016; 54:391–397.

59. Hensiek N, Schreiber F, Wimmer T, *et al.* Sonographic and 3T-MRI-based evaluation of the tongue in ALS. Neuroimage Clin 2020; 26:102233.

60. ■ Loewenbrück KF, Werner R, Günther R, *et al.* One nerve suffices: a clinically guided nerve ultrasound protocol for the differentiation of multifocal motor neuropathy (MMN) and amyotrophic lateral sclerosis (ALS). J Neurol 2021; 268:1495–1507.

A publication on MMN differentiation from ALS.

61. Suzuki YI, Shibuya K, Misawa S, *et al.* Fasciculation intensity and limb dominance in amyotrophic lateral sclerosis: a muscle ultrasonographic study. BMC Neurol 2022; 22:85.

62. Kitaoji T, Tsuji Y, Noto Y, *et al.* Sonographic nerve enlargement in a patient with sarcoidosis. Internal Med 2021; 60:1469–1473.

63. Pitarokoili K, Kerasnoudis A, Behrendt V, *et al.* Facing the diagnostic challenge: nerve ultrasound in diabetic patients with neuropathic symptoms. Muscle Nerve 2016; 54:18–24.

64. Lee D, Dauphinée DM. Morphological and functional changes in the diabetic peripheral nerve. J Am Podiat Med Assn 2005; 95:433–437.

65. Breiner A, Qrimli M, Ebadi H, *et al.* Peripheral nerve high-resolution ultrasound in diabetes. Muscle Nerve 2017; 55:171–178.

66. Üçeyler N, Schäfer KA, Mackenrodt D, *et al.* High-resolution ultrasonography of the superficial peroneal motor and sural sensory nerves may be a noninvasive approach to the diagnosis of vasculitic neuropathy. Front Neurol 2016; 7:48.

67. Chen X, Zhang L, Huang M, *et al.* Coexistence of nerve enlargement and neuratrophy detected by ultrasonography in leprosy patients. Sci Rep-uk 2018; 8:7812.

68. Sreejith K, Sasidharanpillai S, Ajithkumar K, *et al.* High-resolution ultrasound in the assessment of peripheral nerves in leprosy: a comparative cross-sectional study. Indian J Dermatol Venereol Leprol 2021; 87:199–206.