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REVIEW

Review Article "Spotlight on Ultrasonography in the Diagnosis of Peripheral Nerve Disease: The Evidence to Date"

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Abstract: Neuromuscular ultrasound is rapidly becoming incorporated into clinical practice as a standard tool in the assessment of peripheral nerve diseases. Ultrasound complements clinical phenotyping and electrodiagnostic evaluation, providing critical structural anatomical information to enhance diagnosis and identify structural pathology. This review article examines the evidence supporting neuromuscular ultrasound in the diagnosis of compressive mononeuropathies, traumatic nerve injury, generalised peripheral neuropathy and motor neuron disease. Extending the sonographic evaluation of nerves beyond simple morphological measurements has the potential to improve diagnostics in peripheral neuropathy, as well as advancing the understanding of pathological mechanisms, which in turn will promote precise therapies and improve therapeutic outcomes.

Keywords: neuromuscular ultrasound, peripheral neuropathy, entrapment neuropathy, CIDP, hereditary neuropathy, amyotrophic lateral sclerosis

Introduction

Entrapment mononeuropathies are common and contribute to considerable morbidity in the community. The most common entrapment is carpal tunnel syndrome, with an estimated incidence of 197 per 100,000 women,[1,2] and much higher rates among employees in certain industries (eg, up to 42% prevalence in poultry workers).[3,4] Early diagnosis is essential in entrapment mononeuropathy, to limit nerve injury and associated morbidity. Unfortunately, electrodiagnostic studies (EDX) are frequently non-localising in entrapment neuropathy, and this is the most frequent indication for nerve ultrasound in clinical practice.[5] In addition, a significant proportion of EDX are non-diagnostic, between 10% and 25% in CTS for instance, depending on the severity of presentation and EDX protocol used.[6,7]

Separately, peripheral neuropathy (PN) represents a major cause of morbidity globally,[8] and it's prevalence is increasing. This has been attributed to the ageing population, an increased prevalence of diabetes and use of neurotoxic drugs such as chemotherapeutics and antiretrovirals.[9–14] The assessment of PN has traditionally relied on neurological assessment, close review of comorbidities and EDX testing. EDX enables neuropathy to be diagnosed, providing information on the pattern of involvement, severity, distinction between axonal and demyelinating pathologies, as well as allowing prognostication and monitoring.[15] The clinical and EDX

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assessment has several limitations however, including a lack of precise anatomical information,[15] difficulty diagnosing proximal demyelinating PN,[16] and difficulty in distinguishing hereditary from acquired demyelinating PN.[17,18] Consequently, there is a need for newer techniques to better diagnose and monitor patients with PN.

Ultrasound using modern, high-frequency probes and image processing provides excellent visualisation of the peripheral nerve, with good spatial resolution and the ability to assess vascularisation with power Doppler. Ultrasound has the further advantage of being able to assess the entire nerve course in real time, whilst being quick, painless, non-invasive, free of radiation and relatively cheap. Ultrasound therefore provides the ideal tool for assessing PN, entrapment mononeuropathy and complements the clinical and EDX assessment. Given the rapid uptake of ultrasound by clinicians, the present review is designed as a practical resource to promote an understanding of the basics of peripheral nerve ultrasound as well as current and emerging applications of ultrasound in the diagnosis of neurological disease.

Ultrasound Physics as Relevant to Nerve and Muscle

An ultrasound system uses a transducer to convert electrical current into ultrasound waves via the piezoelectric effect. These waves travel through tissue and are either reflected, refracted, scattered, or absorbed. The amount of resistance an ultrasound beam experiences as it travels through a tissue is referred to as acoustic impedance and is dependent on tissue density. The degree of ultrasound reflection is dependent on the relative differences in tissue densities at a tissue interface, as well as the angle of insonation. Reflected waves are recorded by the transducer and converted into electrical energy which is used to generate our image. The brightness of this image is labelled echointensity (EI) and is proportional to the amount of reflection. This signal is amplified (gain), which can be adjusted. Anisotropy is the loss of echogenicity when an ultrasound beam is not perpendicular to the structure imaged and can be exploited to distinguish peripheral nerves (low anisotropy) from adjacent structures such as tendons (high anisotropy).

The ultrasound image resolution is determined largely by the frequency of the waves, recorded in megahertz (MHz). Higher frequencies allow for greater image resolution, and frequencies greater than 12 MHz are typically utilised for peripheral nerve imaging. In contrast, higher frequencies undergo greater attenuation at increasing depths, and therefore lower frequency ultrasound with better penetration is preferable when imaging deeper structures such as muscle. Consequently, ultrasound imaging is a trade-off between resolution and penetrance, which is achieved in neuromuscular ultrasound by using a transducer with a range of frequencies, for example, 18–6 MHz. Linear array transducers are typically used in neuromuscular diagnosis, providing a narrower field of view but better resolution at the edges of an image than curvilinear transducers. A smaller footprint probe is sometimes desirable when imaging structures where only limited contact between a probe and the body surface is possible, for instance the hands and feet.

Ultrasound Changes in Neuropathy

Normal Nerves

The appearance of peripheral nerves on ultrasound correlates with the microscopic and macroscopic anatomy.[19] When viewed longitudinally nerves appear as linear hypoechoic fascicles surrounded by hyperechoic perineurial connective tissue, both enclosed by the bright epineurial connective tissue layer (Figure 1). In cross section, nerves take on a "honeycomb" appearance of rounded hypoechoic fascicles surrounded by hyperechoic connective tissue (Figure 1). The size and fascicular pattern of healthy nerves can vary depending on location. More proximal nerve segments are typically larger in cross-sectional area (CSA) with fewer or no fascicles, meaning they appear more hypoechoic. This is the result of densely packed fascicles with less connective tissue.[20] This process also occurs at fibro-osseous boundaries, for instance the ulnar nerve at the level of the medial epicondyle also appears relatively more hypoechoic even in normal limbs[21] (Figure 2D).

When differentiating nerves from other structures the following key features can be utilised. Firstly, nerves are surrounded by a hyperechoic rim due to epineurial connective tissue. Secondly, they are more anisotropic than muscle and tendons, meaning tilting the transducer will markedly change the echointensity of these other structures when compared to nerves. Thirdly, unlike blood vessels they are non-compressible, with no pulsatile movement or Doppler flow.

Abnormal Nerves

There are several characteristic sonographic features in peripheral nerve injury, including changes in nerve size,

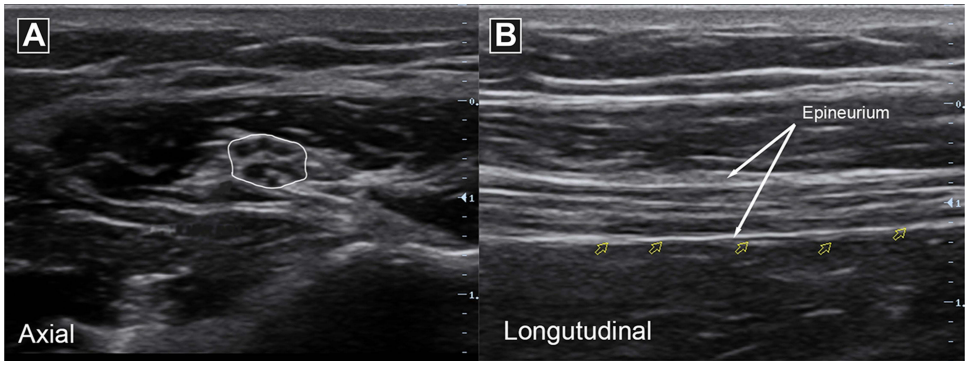

Figure 1 Ultrasound appearance of normal nerves. Ulnar nerve imaged in axial/cross-sectional view with "honeycomb" pattern (**A**) and longitudinal view with "tram track" pattern (**B**).

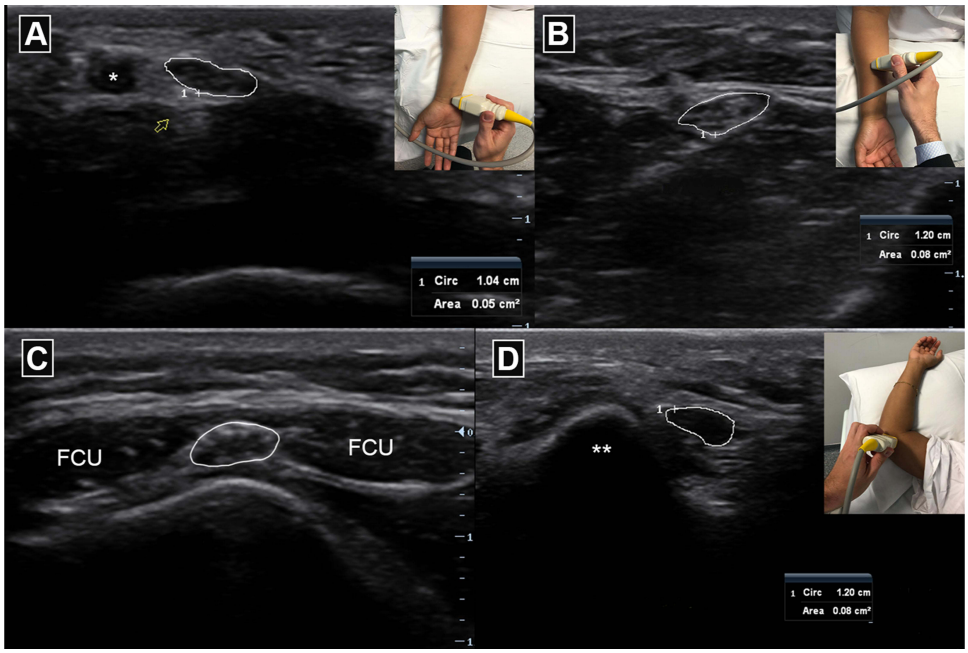

Figure 2 Normal ulnar nerve and ulnar artery (artery denoted *) in cross section at the wrist (**A**) in Guyon's canal. Ulnar nerve in cross section in the forearm (**B**), cubital tunnel between two heads of flexor carpi ulnaris (FCU) muscle (**C**) and between the medial epicondyle (**) and olecranon at the elbow (**D**).

echointensity, fascicle dimensions, epineurial boundaries and Doppler signal. Peripheral nerve size increases focally with entrapment and more diffusely in some patients with PN. The cross-sectional area (CSA), measured by tracing inside the hyperechoic epineurium, has a high inter and intraobserver reliability and is highly reproducible.[22] The CSA has been widely used to quantify PN, by reference to established normal values for several key peripheral nerves and the brachial plexus.[23–26] It is important to adjust CSA for normal variability seen across age, sex, height, and BMI.[23,24]

Echointensity is typically reduced in nerve injury and is usually assessed qualitatively and is usually associated with loss of the normal fascicular architecture described above. Nerve echogenicity can be measured quantitatively using mean gray-scale analysis.[21,27,28] Quantitative measures are specific to the individual ultrasound machine used to establish the normative data, limiting their broader application, unless values are normalized using standardized phantoms.

Improvements in ultrasound technology has facilitated measurement of individual nerve fascicles,[29] for instance ultra-high frequency ultrasound can identify increased fascicular diameter in immune-mediated PN.[30] Fascicular architecture varies from person to person, nerve to nerve and from one anatomical location to another, and there is more work needed to characterise this metric in health and disease.

The Doppler effect is a change in ultrasound frequency reflected from an object, such as a red blood cell, moving toward or away from the transducer. This can be used to demonstrate changes in vascularity of peripheral nerves and surrounding structures. Normal nerve does not have any detectable blood flow. Hence, the presence of Doppler flow is abnormal in peripheral nerves and indicates hypervascularity, which has been described in compressive and inflammatory and some axonal neuropathies.[31–33]

Elastography is a technique used to determine the elasticity of tissue. This is in the form of either strain elastography, in which tissue displacement from extrinsic compression or ambient tissue oscillations is used, or shear wave elastography (SWE), produced by acoustic radiation force impulses generated by the ultrasound probe. Peripheral nerve injury involves the destruction of myelin, which is more compliant, and a proliferation of stiff connective tissue.[34] This results in increased stiffness on elastography. There are now several studies supporting the role of both strain and shear wave elastography in diagnosing carpal tunnel syndrome, ulnar neuropathy at the elbow, diabetic PN and even optic neuropathy.[35] Further research is ongoing to assess the ability of elastography to diagnose nerve injury in preclinical neuropathy, and to evaluate elastography as a monitoring tool for longitudinal assessment.

Compressive Mononeuropathies

Peripheral nerve compression results in nerve enlargement proximal /or distal to the entrapment site on cross-sectional imaging and can appear as an hourglass configuration on longitudinal views (Figure 3).[5,36,37] The entrapped nerve may also appear flattened, hypoechoic, immobile and hypervascular.[37–39] Importantly, up to 42% of mononeuropathy cases studied with ultrasound detect a pathology that alters diagnosis or management, for instance nerve strictures, ganglion cysts or other intraneural or extraneural lesions.[40]

Interestingly, a "Sonographic Tinel" sign may be present, with clinical symptoms elicited by mechanical pressure from the ultrasound probe at a compression site. Of further interest, chronic nerve compression may result in "neurogenic" changes to the muscle supplied, such as hyperechogenic and eventually atrophied muscle with fasciculations. The sonographic findings for specific mononeuropathies are summarised below and in Table 1.

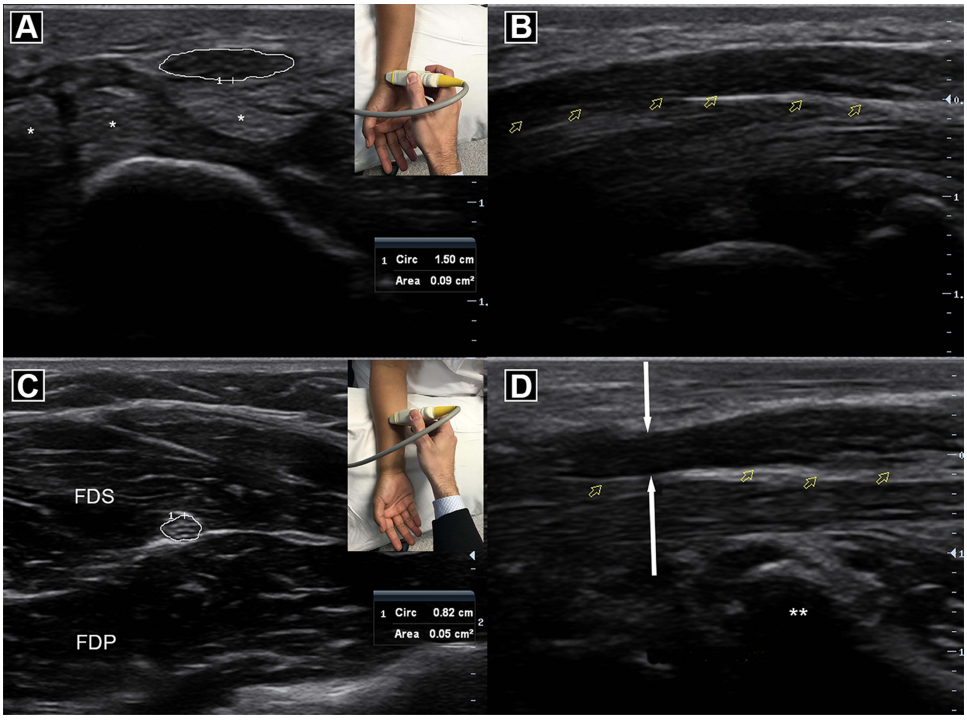

Figure 3 Normal median nerve and flexor tendons (*) in cross section (**A**) and longitudinal view (**B**). Normal median nerve in the forearm (**C**) superficial to flexor digitorum profundus (FDP) and deep to flexor digitorum superficialis (FDS) muscles. Abnormal median nerve at the wrist (**D**) with hourglass constriction (white arrows) with swelling proximally at the carpal tunnel entrance (**).

Table 1 Diagnostic Sonographic Findings in Compressive Mononeuropathies

	Sonographic Findings	Diagnostic Utility
Carpal tunnel syndrome	CSA distal wrist crease > 8.5–10 mm^2[2,39]	Sensitivity 65–97% Specificity 73–98% PPV 79–97%
	WFR > 1.4[252]	Sensitivity 100% Specificity*
	If EDX normal > 14 mm^2 WFR > 1.8[5]	
	Hypoechoic proximal to compression[39,253,254]	Sensitivity 100% Specificity*
	Loss of fascicular architecture[255] Shear wave elastography: increased stiffness[34,256–261]	Sensitivity 95%, Specificity 71%, PPV 94%
	Shear wave elastography: increased stiffness[34,256–261]	Sensitivity 65–100%, Specificity 45–100%
	Increased vascularity[37] Reduced nerve mobility[262,263]	
	Reduced nerve mobility[262,263]	
	Anatomical anomalies: Bifid median nerve,[264] persistent median artery,[264] anomalous muscle[265]	
Ulnar neuropathy at the elbow	Maximum CSA >8.3–11 mm^2[255]	Sensitivity 88–100% Specificity 71–97%
	Swelling ratios (CSA elbow vs upper arm) > 1.5[266]	Sensitivity 74–100% Specificity 96.7%
	Shear wave elastography: increased stiffness[267,268]	Sensitivity 100%, Specificity 100%
	Loss of internal fascicular structure[269]	
	Increased vascularity[57] in 15%. Correlates with severity and axonal damage.	
Radial neuropathy at the spiral groove	CSA > 5.75 mm^2 [270]	Sensitivity 52.9%, specificity 90%
	CSA symptomatic minus asymptomatic side > 1.75 mm^2 [270]	Sensitivity 58.8%, specificity 100%
Fibular neuropathy at the knee	CSA fibular head > 11.7 mm^2 [271]	Sensitivity 85.0%, Specificity 90.0%
	CSA symptomatic minus asymptomatic side > 1.70 mm^2	Sensitivity 83.3%, Specificity 97.0%
	Fibular head to popliteal fossa CSA ratio > 1.11	Sensitivity 47.1%, Specificity 93.3%
	Hypoechoic at fibular head on quantitative ultrasound[83]	Sensitivity 82–84%, Specificity 83–95%
Tarsal tunnel syndrome	CSA tarsal tunnel > 15–19 mm^2 [272,273]	Sensitivity 61–74% Specificity 100%
	Within tunnel-to-proximal tunnel CSA ratio1[272]	

Abbreviations: CSA, cross sectional area; WFR, wrist to forearm ratio measured at distal wrist crease and 12cm proximal; EDX, electrodiagnostic studies; Specificity*, specificity could not be calculated due to the design of the study, as all patients imaged had the disease.

Median Neuropathy at the Wrist (Carpal Tunnel Syndrome)

The median nerve is optimally studied with the patient seated or lying with the palm facing upward. Imaging can begin at the distal wrist crease, with a cross-sectional view of the median nerve at the entry to the carpal tunnel. The nerve can then be traced proximally as it dives between the flexor digitorum superficialis and profundus in the forearm, and then between the two heads of the pronator teres (another potential site of entrapment).[41,42] At the elbow, it runs with the brachial artery, and it can be traced with the artery up to the axilla.

Carpal tunnel syndrome (CTS) results in increased median nerve CSA at the wrist (Figure 3). The ratio of CSA between the wrist and forearm (12 cm proximal to the distal wrist crease), known as "wrist to forearm ratio" (WFR) will also be increased (Table 1). The median nerve may also be swollen distally at the carpal tunnel outlet,

and scanning this region increases the diagnostic sensitivity by 15%–20%.[43,44] The presence of an immobile, hypoechoic or hypervascular median nerve at the wrist also aids in diagnosis.[39] There are several clinical and EDX mimics for CTS, such as benign tumours (neuroma, schwannoma, hamartomas), ganglion cysts, thrombosed vessels or tenosynovitis.[45] These are easily diagnosed with ultrasound.[45,46] A bifid median nerve can also be identified, which is more prevalent in patients with CTS.[47] Ultrasound is useful to assess persistent symptoms post-surgical carpal tunnel release, where it can detect a compressive post-operative scar, a residual anatomical constriction point suggesting incomplete release or an alternative cause for neuropathy.[48]

In addition, ultrasound can localise a proximal median nerve injury and may help establish a cause, such as entrapment by the ligament of Struther's,[49] pronator teres muscle,[50] or an accessory palmaris longus muscle,[51] as well as vascular pathology[52] and iatrogenic injury.[53]

Ulnar Nerve (Cubital Tunnel)

The ulnar nerve is ideally studied with the elbow flexed at 90 degrees, palm facing upwards and the patient either seated or supine. The Ulnar nerve can be easily located at the elbow in the groove between the olecranon and the medial epicondyle of the humerus (Figure 2C). The nerve can be traced proximally as it runs between the biceps brachii and medial head of triceps brachii en route to join the axillary artery. The nerve can then be traced from the elbow distally as it travels between the two heads of the flexor carpi ulnaris muscle (forming the cubital tunnel) (Figure 2C), before travelling between the flexor digitorum profundus and superficialis as it approaches the ulnar artery (Figure 2B). The ulnar nerve together with the ulnar artery enter the hand superficially via the guyon's canal (Figure 2A).

Approximately 76% of ulnar neuropathies are localised to the olecranon groove[54] and are typically caused by extrinsic compression or stretch of the nerve resulting in focal demyelination. Focal increase in the ulnar nerve CSA at or above the olecranon is diagnostic.[55] The next most common site for injury is at the cubital tunnel due to ulnar nerve entrapment, referred to as "cubital tunnel syndrome". Ultrasound demonstrating focal nerve constriction at the entry to the tunnel with proximal swelling is diagnostic. Longitudinal views can aid in localising compression. Both the degree of swelling and hypervascularity are markers of severity[56] and axonal loss.[57,58] It is important to differentiate cubital tunnel entrapment from compression in the olecranon groove because the former is amenable to surgical release.[59] Less common aetiology of ulnar nerve injury can also be identified with ultrasound, including Struthers arcade compression in the upper arm,[60] ganglion at the elbow, benign tumours, abscess or anomalous muscles (anconeus epitrochlearis).[55] Dynamic ultrasound can also detect a subluxing ulnar nerve, which refers to the migration of the ulnar nerve to the medial epicondyle tip with elbow flexion. Studies assessing the causative role of this abnormality in ulnar neuropathy are conflicting.[61–63] An elegant study by Omejec et al demonstrated higher rates of ulnar nerve subluxation in patients without a clinical neuropathy, especially those with subclinical ulnar nerve changes on EDX.[64]

A common dilemma when assessing ulnar neuropathy electrodiagnostically is the inability to localise the dysfunction, and between 14% and 25% of EDX studies are "non-localising".[65,66] Importantly, the majority of these electrodiagnostically "non-localising" ulnar neuropathies can be localised with ultrasound.[65,66] In addition, ultrasound can readily diagnose ulnar nerve injury at Guyon's canal for example due to cycling-related wrist compression,[67] intraneural ganglion cyst[68] or ulnar artery thrombosis.[69]

Radial Neuropathy at the Spiral Groove

The radial nerve is best imaged with the elbow flexed and the dorsal upper arm directed toward the examiner, so that the posterior course of the nerve above the elbow can be easily traced. The nerve is readily identified in the lateral antecubital fossa, lying above the brachialis and beneath the brachioradialis muscles (Figure 4A). At this location, the nerve starts to divide into the superficial and deep branches. The radial nerve can be traced proximally as it wraps behind the humerus. The radial nerve is then followed up to the spiral groove, between the medial and lateral heads of the triceps brachii muscle (Figure 4B). The nerve can be traced from the antecubital fossa distally as it divides. The superficial branch travels laterally, beneath the brachioradialis and next to the radial artery, before perforating the extensor facia in the distal forearm to reach the anatomical snuff box and provides sensation to the dorsolateral hand and dorsal aspect of digits 1–3. The deep branch travels medially and dives through the arcade of Frohse (a fibrous arch extending from supinator muscle to lateral epicondyle) as it pierces the supinator muscle (Figure 4C). The nerve then becomes the posterior

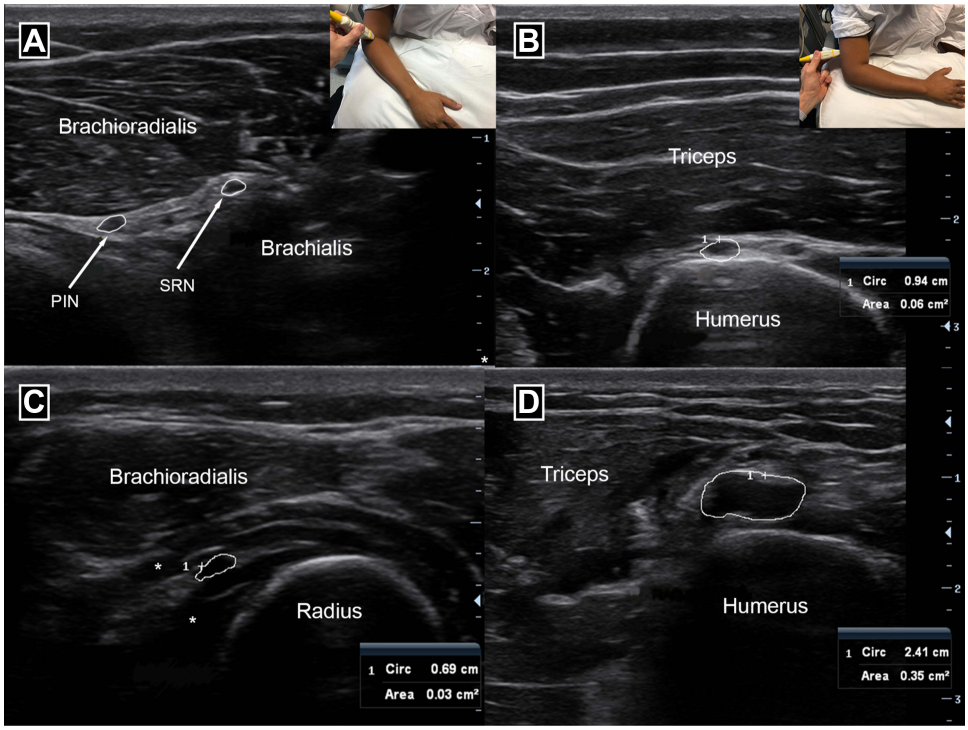

Figure 4 Posterior interosseus nerve (PIN) and Superficial radial nerve (SRN) branches of the radial nerve in the cubital fossa (**A**). Radial nerve branches deep to brachioradialis and superficial to brachialis muscles. Cross section of normal radial nerve in the spiral groove between the triceps muscle and humerus bone (**B**). Posterior interosseus nerve travelling between the two heads of supinator muscle (*) overlying the proximal radius bone (**C**). Cross section of abnormal enlarged radial nerve in spiral groove with CSA measuring 35 mm^2 (**D**).

interosseus nerve travelling over the interosseus membrane and supplying the extensor compartment of the forearm.

The commonest cause of radial neuropathy is compression at the spiral groove due to extrinsic pressure, known as the "Saturday night palsy" because it may be associated with sleeping awkwardly when sedated. Ultrasound will show focally increased radial nerve CSA in the spiral groove (Figure 4D). This can be based on absolute increase in CSA or side-to-side comparison (Table 1). Swelling in the radial groove also has prognostic value and predicts a worse clinical outcome at 3 months then radial palsy with normal nerve calibre.[70] Another common cause for proximal radial neuropathy is a humeral shaft fracture. Nerve injury secondary to fracture is readily diagnosed with ultrasound.[71] The deep motor branch, the posterior interosseus nerve, can be injured at the arcade of Frohse. Causes of this "Posterior Interosseus Syndrome" may be diagnosed with ultrasound including iatrogenic injury,[72] ganglion cysts,[73,74] vascular abnormalities,[75] tumours[76] and entrapment from other structures.[77] The superficial radial sensory nerve is susceptible to injury from extrinsic compression, trauma, or mass lesions[78–80] which may be seen on ultrasound.

Fibular Neuropathy at the Knee

The fibular nerve can be identified on ultrasound by first imaging the sciatic nerve in the proximal popliteal fossa (Figure 5A) and tracing it distally as it bifurcates into the fibular (lateral) and tibial (medial) nerves (Figure 5B). The common fibular nerve can then be traced around the head of the fibular bone (Figure 5C). An enlarged and hypoechoic nerve at the fibular head support a diagnosis of compression,[24,81–83] although care must be taken to not image the nerve obliquely at this location. The deep and superficial fibular nerve branches are more difficult to visualise distally due to their small size and depth, although the deep fibular nerve is readily identified in the anterior ankle. The most common cause for fibular nerve injury at the fibular head is stretch or contusion,[84] often associated with significant weight loss, sustained immobility and excessive leg crossing.[85,86] However, in one series, as many as 18% of patients presenting with foot drop, have an intraneural ganglion of the fibular nerve identifiable with ultrasound.[87] Entrapment of the fibular nerve in the fibular tunnel is a rare cause of fibular neuropathy,[88] but this can be seen on ultrasound as a focal stricture of the nerve just prior to the fibular (Figure 5). It is critical to

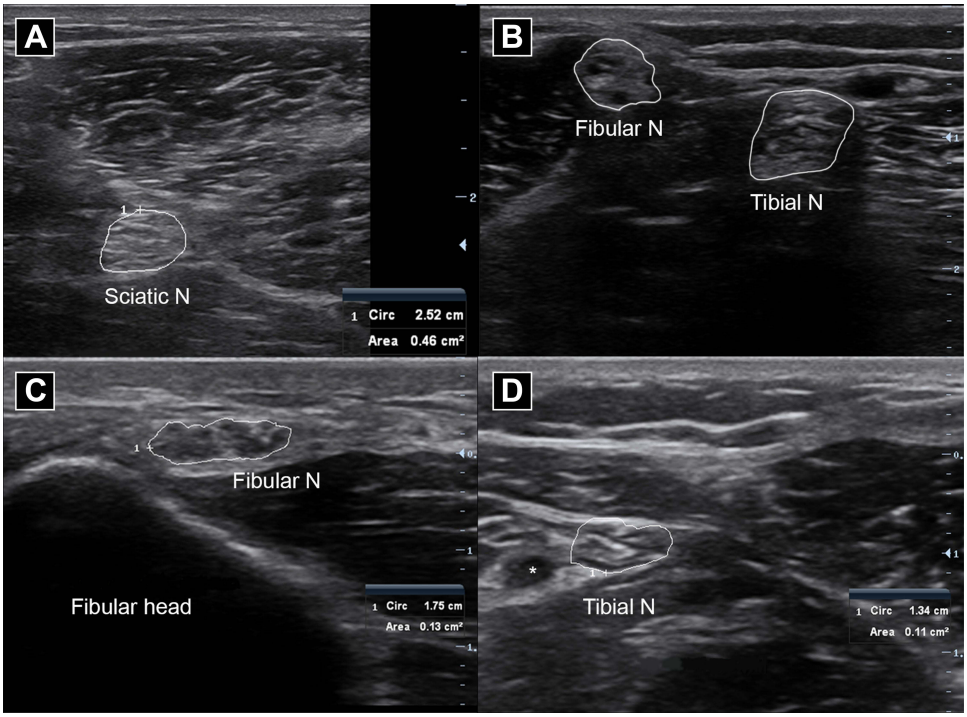

Figure 5 Cross-sectional view of the normal sciatic nerve in the distal thigh (**A**), fibular and tibial nerves in the popliteal fossa (**B**), fibular nerve at the fibular head (**C**) and tibial nerve just above the ankle, * denote the ulnar artery (**D**).

image patients with fibular neuropathy to exclude entrapment and intraneural ganglion, as these patients require surgical decompression whereas non-operative management is indicated for other causes.

Tibial Neuropathy at the Ankle (Tarsal Tunnel Syndrome)

The tibial nerve can also be identified in the popliteal fossa (Figure 5B) before it dives between the heads of the gastrocnemius muscle. The patient is usually examined in the prone position. The tibial is more difficult to identify when running deep in the calf due to the overlying gastrocnemius and soleus muscles but the nerve can be imaged distally as it travels behind the medial epicondyle of the ankle, beneath the flexor reticulum (also known as the tarsal tunnel), in the company of the posterior tibial vessels, tibialis posterior, flexor digitorum longus and flexor hallucis longus tendons. The tibial nerve then branches into the medial and lateral plantar nerves to innervate the sole of the foot.

Ultrasound can identify a cause for distal tibial neuropathy in up to 94% of presentations.[89] In one series of 81 ultrasound cases the most prevalent causes were varicose plantar veins, static foot disorders, epineurial ganglion cysts, neuropathies, and iatrogenic injuries. Tarsal tunnel syndrome is a rare compressive mononeuropathy which may be diagnosed on ultrasound by demonstrating an enlarged tibial nerve CSA within the tunnel (Table 1). Ultrasound may also detect a cause in proximal tibial neuropathies, such as baker's cyst[90] or soleus arcade/sling.[91,92]

Traumatic Peripheral Nerve Injury

After significant nerve trauma we may see "axonotmesis" with interruption of axons but intact connective tissue which acts to guide axonal regrowth. If severe axonotmesis occurs, axonal regrowth occurs proximal to distal at a rate of 1 mm per day. Alternatively, nerve trauma may result in "neurotmesis" with interruption of both axon and connective tissue. In this circumstance, axonal regeneration is precluded by scar tissue.[93] There are several limitations to clinical and EDX evaluation of traumatic peripheral nerve injury. EDX in the acute setting cannot differentiate between a nerve with damaged axons but intact connective tissue and a complete nerve transection.[94] This is crucial, however, because complete transection can improve with time-critical surgical intervention. In addition, without imaging one cannot identify other specific anatomical lesions that may require surgery, for instance a painful chronic neuroma,[95] or ongoing nerve

injury from bone spurs, haematoma, or surgical hardware.[96]

Importantly, ultrasound can assist in diagnosing and localising a traumatic peripheral nerve injury.[95,96] This is visualised by focal swelling and reduced echogenicity, altered fascicular architecture, discontinuity[97] or neuroma formation.[95] In addition, ultrasound allows the detection of muscle hyperintensity and atrophy secondary to nerve trauma, which often precedes other sonographic and EDX changes.[98] In addition, ultrasound can be used to assess whether surgical intervention is required in the setting of nerve discontinuity,[96] neuromas[99] or bony entrapment.[100,101] It is worth noting that ultrasound will not differentiate between severe axonal injury with and without intact epineurium.

Ultrasound also plays a role in surgical planning, by identifying the exact location and length of nerve injury as well as associated structures.[20,96,102] Intraoperative high-resolution nerve ultrasound monitoring can also be used[103] as it matches closely with intraoperative neurophysiological and neuropathological findings. Following surgical peripheral nerve repair[104] ultrasound has a role in identification of partial discontinuity, neuroma formation and compression by overlying scars that may require surgical re-exploration. In a retrospective series of 143 consecutively imaged traumatic peripheral nerve injuries[96] ultrasound was 90% sensitive for any nerve injury. The most common abnormalities seen were nerve swelling, followed by neuroma, scar tissue, and discontinuity. Complete nerve transections were infrequent, but readily identified by swollen nerve stumps proximally and distally. The degree of nerve swelling did not correlate with severity of motor dysfunction on EDX.

Thus, ultrasound is an important tool in diagnosing and localising nerve trauma, grading injury, determining the need for surgery and provides useful information in the intra and post-operative setting. In concert with improvements in ultrasound, MRI techniques to visualize the peripheral nervous system such as Diffusion tensor imaging (DTI) have undergone rapid development. DTI with tractography uses water diffusion anisotropy along longitudinal fibre tracts to image nerve pathways.[105] DTI has the capability to image nerve injury not identified using EDX or standard imaging techniques.[93] In addition, DTI can identify axonal regeneration following traumatic nerve injury with the potential to guide the need for surgical intervention.[106]

Generalised Peripheral Neuropathies

Generalised peripheral neuropathy may be associated with changes on nerve ultrasound. The most prominent changes are identified in demyelinating neuropathies where nerve enlargement is characteristic. Axonal neuropathies are perhaps surprisingly only infrequently associated with reduction of nerve size. The role for ultrasound in diagnosing PN is increasing, and it has the potential to streamline diagnostic algorithms, reduce the need for expensive or invasive investigations and even rationalise costly immunomodulatory and genetic therapies. The following section explores the current ultrasound findings in hereditary, immune mediated and axonal PN.

Immune Mediated Polyneuropathy

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is an immune-mediated process typified by multifocal demyelinating nerve pathology in proximal and distal limbs, leading to weakness, sensory loss and reduced deep tendon

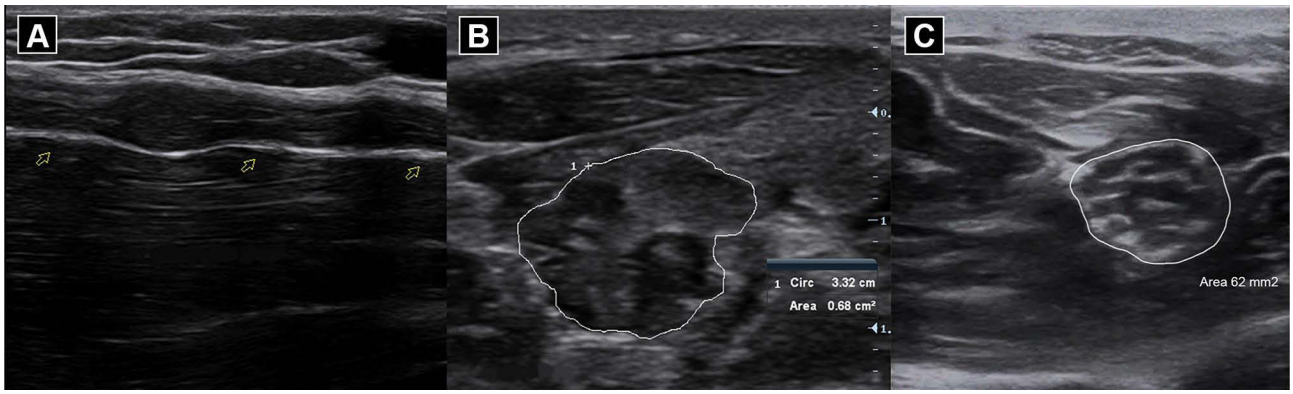

Figure 6 Abnormal median nerve in the forearm in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), demonstrating multifocal nerve enlargement in longitudinal views (**A**). Heterogeneous hypo and hyperechoic fascicular enlargement seen of the same nerve in cross section (**B**) with CSA measuring 68 mm^2. Cross sectional view of enlarged median nerve in the forearm with uniform fascicular enlargement seen in Charcot Marie Tooth Type 1A (**C**) with CSA measuring 62 mm^2.

reflexes. The presentation of CIDP is variable and includes atypical forms such as pure motor or pure sensory CIDP, multifocal acquired demyelinating sensory motor neuropathy (MADSAM) and distal acquired demyelinating sensory (DADS) neuropathy. Abnormal nerve morphology is identified on ultrasound in 64–87% of patients.[107–109]Typical sonographic findings are increased nerve CSA in a multifocal pattern, affecting proximal and distal segments and non-entrapment sites[110] (Figure 6). Like clinical features, ultrasound findings are similarly variable, with some patients even demonstrating normal nerve size on ultrasound.[107]

MADSAM is an asymmetric CIDP variant with a more asymmetrical, multifocal pattern of nerve enlargement on ultrasound.[111,112] Enlarged hypoechoic fascicles are typically seen in segments with past or present conduction block[112,113] and seem to reduce in response to treatment.[114]

Several distinct ultrasound patterns in CIDP have been identified which correlate with disease duration. Three ultrasound classes were described by Padua et al[108] based on CSA and echogenicity. Large hypoechoic nerves (class 1) were associated with the shortest disease duration (0–4 years) when compared to normal size nerve with hyperechoic changes (class 3) (7–11 years duration). Large nerves with heterogeneous hypo- and hyperechoic fascicles (class 2) were also heterogenous regards disease duration (0.5–16 years).

Ultrasound can increase diagnostic accuracy in CIDP, especially when proximal segments and the brachial plexus are imaged.[115] This is important because misdiagnosis is common in CIDP, especially in the atypical variants.[116] One prospective study assessed 100 suspected chronic immune mediated polyneuropathy referrals with EDX and ultrasound.[115] Enlargement in the proximal median nerve or C5 root (referred to as the "Short Ultrasound Protocol") was diagnostic with a sensitivity of 84.6–96.4% and specificity of 44.9–72.8% depending on the reference standard. Importantly, 25% (11/44) of the those ultimately diagnosed as CIDP/MMN had normal EDX but abnormal ultrasound and were responsive to immunotherapy.

Ultrasound has also been researched as a tool to differentiate between hereditary demyelinating neuropathies, CIDP and other immune mediated PN (Table 2). Various schema has been proposed to quantify these differences. CMT1A is typically associated with the largest nerves, which are homogeneously/diffusely enlarged.[107,117] The pattern of enlargement is more variable and to a lesser degree in CIDP. Normal nerve calibre, focal and diffuse enlargement resembling CMT have all been described in CIDP.[23,107,109,118] Mild, regional, asymmetrical or heterogenous enlargement all point towards atypical CIDP, MMN, or GBS.[23,107] Various imaging protocols and scoring systems have been proposed eg, the homogeneity score and the regional nerve enlargement index.[119] The more focal pattern of nerve enlargement seen in inflammatory neuropathies can also be quantified using the intranerve variability (maximum CSA/minimum CSA for a given nerve) and the internerve variability (maximum intranerve variability/minimum intranerve variability for a given patient).[120] However, these patterns and scores are predominantly based on relatively small retrospective cohorts, and larger prospective studies are required to define the optimal ultrasound protocols to differentiate these disorders.[119]

Ultrasound provides surrogate markers for disease severity in CIDP, such as hypervascularity, number of nerves involved and cervical nerve root CSA.[121,122] Larger nerve CSA has been correlated with slower conduction velocities on EDX testing in many[123,124] but not all studies.[125] Nerve enlargement has also been associated with clinical weakness and disability.[124,125] Additionally, ultrasound provides prognostic information in CIDP, with both decreasing intra-nerve CSA variability and normal or decreasing nerve calibre predicting treatment responsiveness.[126]

Furthermore, ultrasound has potential as an outcome measure in CIDP. A study of 23 consecutive patients with CIDP followed with serial ultrasound measurements over 3-years, noted CSA increased in 51% of nerve segments, and was associated with increased functional disability and decreased motor nerve amplitudes on EDX.[124]

Guillain-Barre Syndrome (GBS)

GBS is an acute immune mediated generalised polyneuropathy, characterised by ascending sensory disturbance and areflexic weakness, with both demyelinating (acute inflammatory demyelinating polyneuropathy – AIDP) and axonal forms (acute motor/sensory axonal neuropathy – AMAN/AMSAN). The nadir is typically reached by 6 weeks, and diagnosis is clinical, supported by EDX and cerebrospinal fluid studies.

Proximal nerve and nerve root enlargement has been reported on ultrasound, although the degree and frequency are less then CMT1A and CIDP.[23,107] For example, mild enlargement was reported in 8/17 upper limb nerves in one cohort,[23] and 5/6 patients in another cohort, although this involved only 9% of the studied nerve segments.[127] Importantly, nerve enlargement can be seen as early

Table 2 Diagnostic Sonographic Findings in Peripheral Neuropathies

Neuropathy			Characteristic Nerve Ultrasound Findings
Hereditary			
	CMT	1A	Enlarged diffusely, uniformly, and symmetrically
		1B	Enlarged proximal segments. Reduced CSA lower limbs
		1X	Enlarged proximal and lower limb segments
		2	Normal or enlarged
	HNPP		Focal enlargement at entrapment sites
	ATTRv		Enlarged proximal segments and entrapment sites
Sensory neuronopathies	SCA/CANVAS FRDA		Reduced nerve calibre Enlarged upper limb and normal lower limb nerves
Acquired			
Immune mediated	AIDP/GBS		Mild proximal nerve and nerve root enlargement. Vagus nerve enlargement associated with autonomic dysfunction.
	CIDP		Multifocal enlargement of proximal and distal segments with hypervascularity.
	MADSAM		Asymmetrical multifocal enlargement
	MMNCB		Multifocal enlargement at proximal sites with/without conduction block
	Anti MAG		Segmentally enlarged nerve roots, plexus, and proximal nerve with high inter-nerve variability
	POEMS		Focal enlargement at entrapment sites
	Vasculitic		Multifocal enlargement at proximal sites without plexus involvement
	Brachial neuritis		Ipsilateral upper limb nerve enlargement, constriction, fascicular entwinement, and torsion.
Axonal	DPN		Mild enlargement, especially at compression sites. Hypoechoic and hypervascular.
	Chemotherapy		Mild enlargement at compression sites
	Paraproteinaemic		Normal
	Leprosy		Multifocal enlargement ± hypervascularity.

Abbreviations: CMT, Charcot Marie Tooth disease; HNPP, Hereditary Neuropathy with liability to Pressure Palsy; ATTRv, variant transthyretin amyloidosis; GBS, Guillain Barre Disease; CIDP, Chronic Inflammatory Demyelinating Polyradiculoneuropathy; MADSAM, Multifocal acquired demyelinating sensory and motor neuropathy; MMNCB, Multifocal Motor Neuropathy with Conduction Block; Anti MAG, Anti Myelin Associated Glycoprotein; POEMS, Polyneuropathy Organomegaly Endocrinopathy Monoclonal gammopathy and Skin changes; DPN, Diabetic Polyneuropathy; SCA, Spinocerebellar Ataxia; CANVAS, Cerebellar Ataxia Neuropathy and Vestibular Areflexia Syndrome; FRDA, Friedreich's Ataxia.

as day 1–3 of symptoms,[23,128] before EDX changes are apparent.[23] The presence of enlarged cervical nerve roots and vagus nerves, together with normal nerve calibre elsewhere can differentiate GBS from CIDP with a positive predictive value > 85%.[117] Vagal nerve enlargement on ultrasound has also been correlated with autonomic dysfunction in AIDP.[128,129]

Some studies have suggested ultrasound can be used to distinguish demyelinating and axonal variants of GBS,[130] while other studies have found no difference.[131] Mori et al demonstrated enlarged cervical and proximal nerve segments in 6 patients with AIDP, contrasting to enlarged distal nerve segments (forearm, wrist and ankle) in 9 patients with AMAN/AMSAN.[130]

Miller Fisher Syndrome (MFS) is a rare GBS variant characterised by the triad of ophthalmalgia, ataxia and areflexia, and is often associated with bilateral facial weakness. Hsueh et al[132] reported significantly enlarged facial but normal limb nerves in MFS.

Ultrasound has been proposed as an outcome measure for treatment in GBS.[129,131] Grimm and colleagues assessed 27 patients with GBS and 31 controls with

ultrasound at baseline and 6 months follow up.[129] Cervical spinal, medial and vagus nerves were significantly larger in GBS at baseline, but returned to normal at 6 months, except for the vagus nerve which remained enlarged in those patients with significant autonomic dysfunction.

Multifocal Motor Neuropathy (MMN)

MMN is a rare upper limb predominant demyelinating polyneuropathy characterised by slowly progressive weakness and response to treatment with intravenous immunoglobulin.[133–135] In practice, MMN can be difficult to distinguish from certain ALS variants.[136] Sonographically mild multifocal nerve enlargement, typically in proximal sites and the brachial plexus, is seen in up to 90% MMN patients.[137] Ultrasound enlargement can also occur in clinically and electrophysiologically unaffected nerve segments.[137]

Importantly, nerve and nerve root enlargement on ultrasound can differentiate MMN from ALS. Grimm and colleagues demonstrated that 4 enlarged nerves/nerve roots had a 87.5% sensitivity and 94.1% specificity for distinguishing MMN from ALS in their cohort.[138] Others have found that ultrasound is better at distinguishing MMN from ALS then standard EDX assessments.[139,140] Ultrasound can occasionally aid in the distinction of MMN from CIDP by the presence of milder, asymmetric nerve enlargement with greater side-to-side intranerve variability, although considerable overlap exists.[141]

Multiple studies have demonstrated a variable association between ultrasound findings and clinical weakness, disability and EDX abnormalities.[139,141,142] Rattay et al demonstrated that the nerve enlargement reduced in parallel with disability after 6–12 months of treatment in MMN, although baseline nerve enlargement did not correlate with clinical or EDX markers of severity.[143] Thus, nerve ultrasound can not only improve diagnosis but also disease monitoring in MMN.

Anti-Myelin Associated Glycoprotein Neuropathy (MAG)

Anti-MAG is an immune mediated demyelinating neuropathy with distally predominant symmetrical sensorimotor impairment and prolonged distal motor latencies on EDX. Despite this the ultrasound abnormalities tend to be proximal[144] and there are no reports of distal nerve enlargement. Segmental nerve enlargement has been described in cervical nerve roots, brachial plexus, and proximal nerve segments[145] with considerable inter-nerve variability.[146] Nerve ultrasound has been used to distinguish anti-MAG neuropathy from similar pathologies. Specifically, nerve size is greater in MAG positive than MAG-negative paraproteinaemic neuropathy.[146] Some cohorts found nerve calibre in MAG to be smaller than CIDP.[146]

Polyneuropathy, Organomegaly, Endocrinopathy, M-Protein, Skin Changes Syndrome (POEMS)

POEMS is a rare paraneoplastic multisystem plasma cell disorder causing a mixed axonal and demyelinating polyneuropathy that can mimic CIDP. Pathogenesis is attributed to increased vascular endothelial growth factor leading to neovascularisation and peripheral nerve oedema.[147] It is somewhat surprising then, that peripheral nerve ultrasound studies have demonstrated nerve enlargement at entrapment sites only.[148] Indeed, the lack of diffuse/multifocal enlargement has been offered as a means of distinguishing POEMS from CIDP.[148] However, the published cases describe nerve ultrasound in the subacute setting, after significant secondary axonal degeneration has occurred, and thus the ultrasound findings in early disease remain to be defined.

Brachial Neuritis

Brachial neuritis is an idiopathic monophasic inflammatory condition affecting the branches of the brachial plexus. The typical presentation is with severe pain followed by unilateral upper limb weakness. Imaging with ultrasound and other modalities, combined with surgical exploration, have led to greater pathological understanding of this condition. It is now hypothesized that a sequence of nerve enlargement, fascicular adhesion and constriction contributes to ongoing nerve injury.[149] Rotational movements of the upper limb are then thought to cause the adhered nerve to tort, with fascicular entwinement and further constriction which has been associated with poor recovery.[149] The most common finding on ultrasound, seen in 74% of cases, is unilateral focal nerve enlargement, often affecting the median, radial, anterior, or posterior interosseus nerves.[150,151] Other findings include partial nerve constriction, fascicular entwinement or complete nerve constriction with an hourglass morphology, described in up to 50% of cases.[152] Early imaging with ultrasound can potentially identify those cases with partial or complete constriction who may benefit from surgical intervention.[149,151] Diaphragmatic ultrasound can be used to diagnose phrenic nerve involvement in this condition.

Vasculitic Neuropathy

Mononeuritis multiplex is the characteristic pattern of peripheral nerve vasculitis both in isolated nerve and systemic vasculitic disorders. This is reflected on nerve ultrasound by focal, asymmetrically enlarged nerves, in proximal segments without extension to the brachial plexus.[153–155] Enlargement is described in most EDX affected nerve segments, and prominently in the tibial and fibular nerves.[154,156,157] Importantly, nerve enlargement is seen in almost half of all clinically and EDX unaffected nerves.[155] Hypervascularity can support a diagnosis of vasculitis PN and is reported in 19% of cases.[155] The presence of an axonal neuropathy, with multifocal nerve enlargement proximal to compression sites without plexus involvement is argued to be 94% sensitive and 88% specific for vasculitis.[155] Nerve enlargement might reduce with treatment, although this is based on a single case study only.[153] Nerve ultrasound has also been suggested as a tool to guide nerve biopsy. Hence, ultrasound can improve diagnosis in PN vasculitis and has the potential to guide biopsy sites and support treatment monitoring.

Hereditary Neuropathies

Hereditary neuropathies are among the most studied conditions in the field of neuromuscular ultrasound. The disorders discussed below are just some of the hereditary conditions that have been studied. There are many others where no data exists.

Charcot Marie Tooth (CMT)

CMT1A is the most common form of CMT, caused by an autosomal dominant duplication of the peripheral myelin protein 22 gene, resulting in a demyelinating PN. Ultrasound in CMT1A demonstrates diffuse symmetrical nerve CSA increase in 89–100% of patients[158–160] (Figure 6C). This occurs from the brachial plexus and proximal nerve segments to the small sensory nerves such as the sural and auricular nerves.[158] Nerve enlargement is detectable from as young as 19 months of age,[161] and as such ultrasound is an ideal non-invasive diagnostic aid in young children. Larger CSA has been associated with more severe disease, measured with the CMT neuropathy score.[158,162] In addition, a number of studies have demonstrated a correlation between the degree of nerve enlargement and neurophysiological dysfunction,[158,162] although this has not been a universal finding.[159]

CMT1B is another demyelinating form of CMT, due to Myelin Protein Zero mutations. Ultrasound in CMT1B demonstrates nerve enlargement proximally,[163,164] but reduced CSA in the lower limbs, helping to distinguish it from CMT1A.[164] CMT1X is an X linked mutation of the gap junction associated protein and demonstrates symmetrically enlarged CSA in proximal segments and lower limbs on ultrasound.[165] Finally, CMT2 is a heterogenous collection of variably inherited axonal polyneuropathies, with similarly variable findings on ultrasound.[100,166]

Research into nerve ultrasound as a longitudinal biomarker in CMT has been limited to date. A small study of 15 adults with CMT1A over 5 years failed to demonstrate a change in nerve calibre when assessing the sural and median nerves.[167]

Although outside the scope of this review, muscle ultrasound in a cohort with CMT has demonstrated reduced thickness and increased echointensity of the first dorsal interossei and tibialis anterior muscles.[168] This was more pronounced in CMT1A compared to CMTX1 and CMT2A patients, and correlate with degree of muscle weakness. Consequently, nerve and possibly muscle ultrasound can improve diagnosis and assessments of severity in CMT.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

HNPP is caused by an autosomal recessive deletion of the PMP22 gene, leading to multiple painless entrapment mononeuropathies. The classical ultrasound finding in HNPP is multiple areas of nerve enlargement at entrapment sites,[169,170] but enlargement at non entrapment sites have also been described.[171] Sonographic findings such as CSA do not correlate with neurophysiological parameters, such as the distal motor latency.[172]

Hereditary ATTR Amyloidosis

Variant or hereditary transthyretin amyloidosis is an autosomal dominant disorder, where point mutations in the transthyretin gene results in an axonal sensorimotor and autonomic neuropathy. The recent development of disease modifying therapy has prompted great interest in diagnostic and treatment biomarkers. Ultrasound studies in vATTR Amyloidosis have reported increased nerve CSA at entrapment sites, proximal nerve segments and the brachial plexus when compared to healthy controls.[100,173] CSA is also greater in symptomatic vATTR then asymptomatic carriers[100] and in those with abnormal motor conduction studies.[174] While carpal tunnel syndrome is common in vATTR, the median nerve CSA at the wrist is smaller than in idiopathic CTS and is discordant with

EDX severity.[175] This has been suggested as an early clinical clue for vATTR in patients presenting with CTS.

Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome (CANVAS)

CANVAS is an adult-onset disorder caused by mutation in the RFC1 gene. A sensory neuronopathy is universally seen in patients with CANVAS,[176] and can be detected on ultrasound as a reduction in CSA of the median, ulnar, tibial, and sural nerves.[177] A reduced median and ulnar nerve CSA < 5 mm^2 in the mid-forearm or mid-humerus demonstrate a sensitivity of 79–93%, specificity 100% and area under the curve (AUC) of 0.97–0.99[178] for distinguishing CANVAS from healthy controls.

Spinocerebellar Ataxia (SCA) 2

SCA 2 is an autosomal dominant CAG triplet repeat mutation in the Ataxin 2 gene, resulting in cerebellar ataxia, sensory motor neuropathy, pyramidal and extrapyramidal dysfunction.[179] Reduced nerve CSA on ultrasound is seen in the majority (74%) of patients and correlates with the presence of a sensory neuronopathy.[177]

Friedrich Ataxia

Friedrich Ataxia is an autosomal dominant GAA triplet repeat disorder affecting the Frataxin gene, leading to cerebellar ataxia, cardiomyopathy and sensory neuropathy/neuronopathy. Interestingly, upper limb nerve CSA is enlarged in Friedrich ataxia, attributed to dysmyelintation and perineurial connective tissue proliferation,[180] while lower limb nerve CSA is normal.

Axonal Neuropathies

The utility of ultrasound in axonal PN is less well characterised. It was hypothesized initially that nerve calibre would be reduced in axonal neuropathies. However, ultrasound has revealed that nerves are typically either normal or slightly enlarged.[23,119] The potential application of nerve ultrasound to many forms of axonal neuropathy, eg, toxic, metabolic, inflammatory aetiology remains to be defined by future research.

Diabetic Polyneuropathy (DPN)

DPN is characterised sonographically by mild hypoechoic nerve enlargement, notably at compression sites. Several studies have reported enlarged CSA for the median and tibial nerves of Type 1 and Type 2 Diabetics with PN when compared to healthy controls.[181–184] Nerve enlargement can also predate clinical neuropathy,[185] and increases further once DPN develops.[186] In addition, the degree of enlargement and vascularity are biomarkers of severity, and correlate with clinical and EDX parameters.[182,184,185] Further, in type 2 diabetics nerve ultrasound can demonstrate enlarged fascicles and marked hypoechogenicity when compared to controls, and this to correlates with EDX abnormalities.[184,185] Type 2 diabetics with metabolic syndrome also demonstrate larger nerves and more severe neuropathy then diabetics without metabolic syndrome.[187] Furthermore, increased tibial nerve stiffness on shear wave elastography is 90% sensitive and 85% specific for diabetes and increases with the development of DPN.[188]

Chemotherapy-Associated Neuropathy

Chemotherapy-associated PN demonstrates mild, often asymptomatic nerve enlargement at compression sites in 69% of patients and may point to nerve vulnerability to mechanical stress.[188] In contrast, Lycan et al studied 20 patients with breast cancer exposed to taxane-based chemotherapy and reported reduced sural nerve calibre on ultrasound.[190] Nerve size was further correlated with older age, longer time since exposure and intraepidermal nerve fibre density on skin biopsy.

Leprosy

Leprosy secondary to infection with Mycobacterium leprae is a prevalent cause for PN outside the western world[191] and has been well studied with peripheral nerve ultrasound. Leprosy is characterised by both axonal and segmentally demyelinating PN with palpably thickened nerves and skin changes. Leprosy typically manifests with recurrent immune reactions referred to as "active leprosy". Ultrasound studies have reported multiple asymmetric nerve enlargement with epineurial thickening.[32,192–195] "Active leprosy" is associated with nerve hypervascularisation in 55–71% of patients and decreases to 2.7–5.9% with treatment.[193,195] Thus, peripheral nerve ultrasound has potential as both a diagnostic and monitoring tool in Leprosy.[193]

Paediatric Nerve Ultrasound

EDX in children is challenging. EDX testing is potentially painful, with pain more frequently experienced when EMG is performed, when greater than one muscle and proximal muscles are tested.[196] It is unsurprising therefore that younger age, especially under 3 years, is associated with inadequate and incomplete EDX in paediatric cohorts.[196] Furthermore, EMG relies on active muscle

recruitment and patient participation which is limited in the very young.[197] Nerve imaging with MRI in children is also challenging due to the need to lie still for prolonged periods which may necessitate sedation. Nerve ultrasound on the other hand is painless, quick, adaptable, cost effective and well tolerated in paediatric patients.[198] It seems natural therefore to see a recent growth in paediatric neuromuscular ultrasound research.[107,199]

Peripheral nerves increase in size as we age, meaning children with enlarged nerves may be incorrectly interpreted as normal if adult references values are applied. Therefore, the accurate interpretation of abnormal nerve CSA is reliant on the ongoing expansion age-specific normative ultrasound data.[200,201] Zaidman et al[23] examined 40 healthy children aged 2–17, among a larger cohort of 90 adults and children, and reported a range of normal CSA values. Of interest, an association between height and nerve CSA was seen, and was stronger in children ($r = 0.9$, $P < 0.001$) than adults ($r = 0.5$, $P < 0.001$). Cartwright et al[202] recorded peripheral nerve CSA in a further 43 children aged 3 months to 16 years as well 160 adults. Age was the strongest predictor of nerve CSA, although height and BMI were also predictive. Druzhinin et al[201] systematically collected ultrasound CSA measurements in an children and young adults, scanning 72 healthy subjects aged 2–30 years. Their data suggest that nerve CSA is independently associated with age and weight but not height, differing from previous studies by Zaidman[23] and Cartwright.[201] Zaidman and Cartwright analysed for associations using pooled CSA values from all nerve measurements while Druzhinin analysed each nerve measurement individually, and this may explain their different findings. All three studies found nerve size plateaued at 12–14 years leading the authors to conclude that paediatric specific normative values are essential to interpret imaging in subjects below this cut off. The intra and inter-nerve variability was measured in Zaidman and Druzhinin's populations and interestingly did not differ significantly with age.[23,201] This may be a potential age-independent measure to use where normative data is limited.

Entrapment mononeuropathies are uncommon in children, and when they do occur ultrasound can detect unusual causes such as mucopolysaccharidosis.[203,204] Research in adult populations has been used to argue for supplementation or even replacement of standard EDX assessments with neuromuscular ultrasound in certain focal mononeuropathies such as carpal tunnel syndrome.[46,205,206] A similar argument could be made for children with mononeuropathies but will require further studies to evaluate.

Polyneuropathies on the other hand are common in children and sonographic nerve changes are detectable in certain hereditary neuropathies such as CMT from a very young age.[107,161] Further, nerve CSA in children with CMT1A correlates with disease severity, as well as age, height and weight.[161] Furthermore, ultrasound can aid in the distinction between hereditary and acquired inflammatory polyneuropathies in this age group.[107,119] Zaidman et al performed nerve ultrasound in 128 adults and children with a range of hereditary and acquired peripheral neuropathies. Thirty-five CMT1 patients age 2–71 years were examined and 8 out of 9 children with CMT demonstrated diffuse sonographic nerve enlargement.

Ultrasound has also been used to assess neonatal brachial plexopathy, which occurs in up to 3 in 1000 live births.[207] The current standard is a 3-month period of observation for spontaneous recovery followed by surgical exploration where recovery is poor.[208] In 2015, Somashekar et all compared preoperative US to surgical exploration in the detection of traction neuromas in 33 children.[209] Of their cohort, 31 of the 33 surgically identified neuromas were detectable on US. Furthermore, muscle atrophy was identified in 11 children and guided spinal accessory and supra scapular nerve transfers in 8 of those patients.

Another advantage of ultrasound is its potential to limit the amount of EDX testing required to achieve a diagnosis. Rardin et al[210] compared retrospective data from 21 children who were assessed by ultrasound prior to EDX with 84 aged-matched control subjects who had EDX assessment alone. Those subjects investigated with ultrasound first required less EDX tests, with fewer nerve stimulations and fewer muscles sampled by EMG. This led the authors to conclude an ultrasound first approach should be considered in paediatric patients to limit EDX testing.

Therefore, ultrasound has a number of distinct advantages in paediatric neuromuscular assessment and its role is likely to grow in this population. Further studies are needed to better define normal nerve size, as well as more detailed structural assessment such as fascicle measurements, echotexture and elastography.

Motor Neuron Diseases

Disorders of the motor neuron include Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA) and Spinal Bulbar Muscular Atrophy (SBMA or Kennedy's disease) and Poliomyelitis. Diagnostic delay is

a significant issue in these disorders, for instance in ALS the median time to diagnosis is 11.5 months after onset of symptoms.[210] In SMA, the emergence of disease modifying therapy has generated the need for accessible, accurate, responsive, and reliable outcome measures. Hence, ultrasound has clear potential to improve the diagnosis and monitoring of motor neuron disease, and there is a growing body of literature supporting its use in ALS and SMA.

Amyotrophic Lateral Sclerosis

ALS is a fatal neurodegenerative disorder affecting the motor neuron, with a median survival of 3–5 years,[212–214] characterised by dysfunction of both upper and lower motor neurons (UMN and LMN) as well as cognition.[213] Clinical heterogeneity exists, and there is an absence of pathognomonic investigations, leading to significant diagnostic delay.[215] To better define the investigations of ALS and to promote recruitment of patients to clinical trials, the El Escorial and revised El Escorial (rEEC) were developed incorporating the presence of upper (UMN) and lower motor neuron (LMN) signs.[216–218] It was argued that the rEEC, although specific, was lacking in sensitivity, particularly in the early stages of disease, and consequently the Awaji criteria and more recently the Gold Coast criteria were developed.[220–224] These included the identification of fasciculations on EMG as an LMN sign and have contributed to the increased sensitivity in diagnosing ALS.[216,224–226] Neuromuscular ultrasound offers greater sensitivity then EMG in the detection of fasciculations especially in bulbar structures and thus has the potential to further improve the diagnostic sensitivity of the criteria.[228] Further, muscle ultrasound in ALS can improve diagnosis through the detection of reduced muscle thickness and increased muscle echointensity[98,227–229] (Figure 7). Furthermore, quantitative measures of muscle echotexture have been used as diagnostic biomarkers and responsive outcome measures in ALS.[230,231]

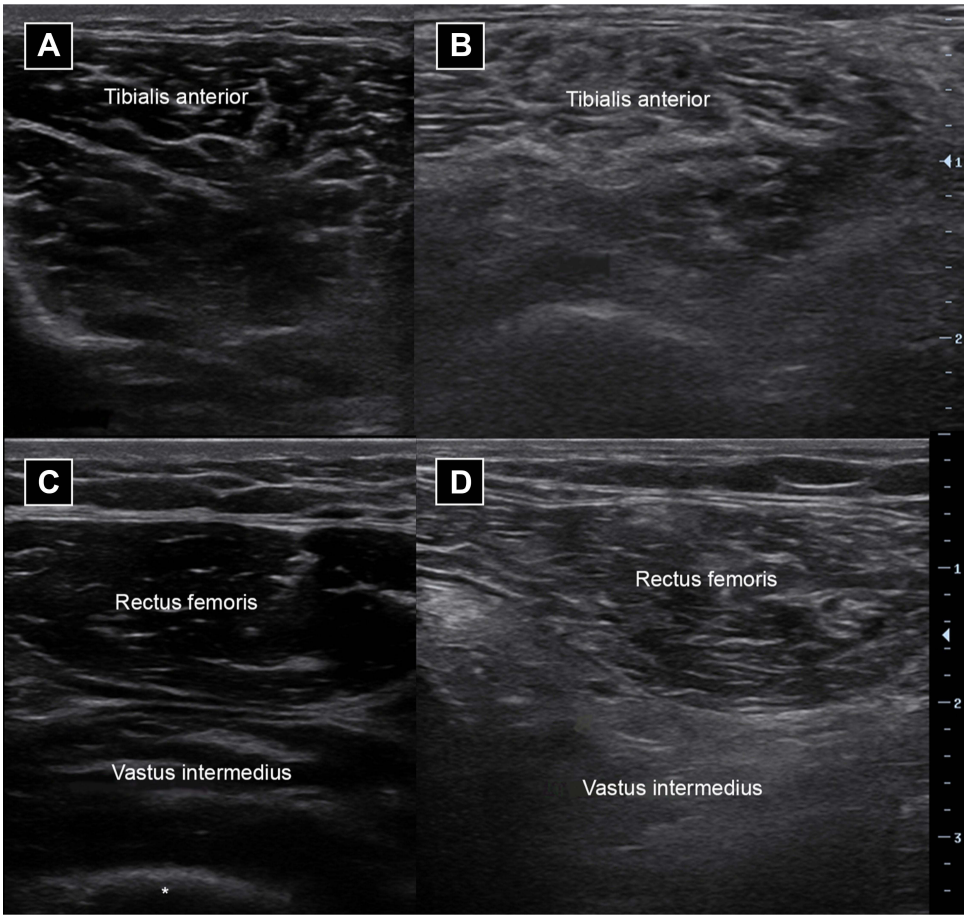

Figure 7 Cross-sectional image of a normal tibialis anterior muscle (**A**) and quadriceps muscles (**C**) in a healthy individual. Cross-sectional image of abnormal tibialis anterior muscle (**B**) and vastus intermedius muscle and to a lesser extent rectus femoris muscle (**D**) in a person with amyotrophic lateral sclerosis. Note in the abnormal muscles there is atrophy with increased brightness or echointensity with a loss of the underlying bone reflection (*).

A reduction in motor nerve and cervical nerve root calibre with a sparing of sensory nerves has been consistently described in ALS[232–235] and is likely to reflect motor axon loss. This occurs in both clinically affected and unaffected regions.[233] Nerve ultrasound can distinguish ALS from mimic disorders such as MMN and peripheral nerve hyperexcitability syndromes.[236] Specifically an increased distal:proximal CSA ratio of the median nerve can distinguish ALS and reflects the relative density of motor fibres in the proximal portion of the nerve.[236] Additionally, nerve ultrasound is abnormal in preclinical ALS where axonal degeneration is compensated and thus muscle wasting/weakness not yet apparent.[233,237] Detecting the submillimetre nerve CSA changes in this preclinical state will likely improve as higher frequency ultrasound probes are developed and in wider use.[237,238] One current limitation of nerve ultrasound is its insensitivity as a tool to monitor disease progression.[238] Furthermore, nerve ultrasound measurements are not consistently correlated with disease severity on clinical and EDX measures, in part due to the confounding effect of UMN dysfunction.[235]

Bulbar motor neuron dysfunction, associated with dysphagia, is common in ALS, and can be measured by ultrasound in several ways. Video ultrasonography, a technique to dynamically assess tongue position and morphotexture during attempted swallow, is an early and sensitive measure of dysphagia in ALS.[239] Further, ultrasound measures of tongue thickness are reduced in ALS, and this is most marked in those patients with bulbar onset disease and lower BMI.[240] Furthermore, tongue thickness decreases with disease progression and may be used to monitor dysphagia and potentially guide timing of nutritional interventions such as parenteral feeding which are associated with improved survival in ALS.[241,242] Lastly, minimal change in tongue thickness during swallowing, measured as a reduced "thickness ratio" is a specific marker of UMN bulbar dysfunction.[243] Thus, dynamic tongue ultrasound has potential as a diagnostic and prognostic biomarker of bulbar dysfunction in ALS.

Respiratory dysfunction is universal in ALS as the disease progresses.[244] Monitoring respiratory dysfunction, traditionally with spirometry, is essential to guide institution of non-invasive ventilation which can improve survival and quality of life.[244–246] A major limitation of spirometry in ALS is its poor reliability in the setting of bulbar and facial weakness as well as cognitive impairment. Dynamic diaphragmatic ultrasound thickness, measured as inspiration:expiration thickness or "thickening ratio", offers an alternative measure in such patients. Ultrasound diaphragm thickness and thickening ratio are reliable in ALS,[247] and correlate with vital capacity, hypercapnia, hypoventilation and motor disability more broadly.[247] Thus, diaphragmatic ultrasound represents an important diagnostic biomarker for respiratory dysfunction in ALS,[248] although at this stage it remains experimental and is not a substitute for standard measurements.

Spinal Muscular Atrophy (SMA)

SMA is an autosomal recessive disorder of spinal lower motor neurons, caused by the mutation in the survival motor neuron (SMN1) gene. This ranges in severity from the severe type 1 SMA with onset before 6 months of age to Type 4 SMA with adult onset. There is considerable interest in biomarkers for diagnosis and disease progression in SMA due to the emergence of disease modifying therapy in the form of antisense oligonucleotides (Nusinersen and Risdiplan) and the gene replacement therapy (onasemnogene abeparvovec-xioi). Nerve ultrasound can distinguish adult onset SMA from mimicking disorders such as CIDP and MMNCB, based on reduced proximal nerve and nerve root CSA in SMA.[249]

In addition, high-frequency nerve ultrasound may provide prognostic information. This was suggested in a pilot study of 3 SMA patients using ultra high-frequency median nerve imaging.[250] A reduced median nerve CSA and fascicle number was seen in the most severely affected subject (SMA I) relative to controls. Further, quantitative muscle ultrasound echo intensity, expressed as a "Luminosity ratio", was increased in a cohort of SMA II and III subjects compared to healthy controls.[251] Luminosity ratio was higher in more severe disease (SMA II) and correlated with dynamometry measures of strength. This suggests the diagnostic and monitoring potential for muscle ultrasound in SMA. Further research is needed to assess the role of nerve and muscle ultrasound in SMA.

Conclusion

The use of ultrasound to assess peripheral nerves in routine clinical practice is increasing due to its safety, accessibility, and dynamic quality. Current ultrasound technology provides excellent resolution of peripheral nerves and the flexibility of point of care machines allow easy integration into neuromuscular and electrodiagnostic clinics. Ultrasound adds critical structural information to compliment clinical and EDX assessments, contributing to improved diagnosis and

pathophysiological understanding of peripheral nerve disorders. While nerve ultrasound is most frequently used to diagnose focal compressive mononeuropathy, its application has grown to include traumatic nerve injury, generalised peripheral neuropathy, motor neuron diseases and a range of other neuromuscular conditions in both adult and paediatric populations. Despite the operator-dependant nature of ultrasound, further development of quantitative measures, standardised protocols and consensus scoring frameworks will allow wider application and lead to improved diagnosis of peripheral nerve disease.

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