REVIEW ARTICLE

Neuromuscular Ultrasound: Clinical Applications and Diagnostic Values

Jean K. Mah, Nens van Alfen

ABSTRACT: Advances in high-resolution ultrasound have provided clinicians with unique opportunities to study diseases of the peripheral nervous system. Ultrasound complements the clinical and electrophysiology exam by showing the degree of abnormalities in myopathies, as well as spontaneous muscle activities in motor neuron diseases and other disorders. In experienced hands, ultrasound is more sensitive than MRI in detecting peripheral nerve pathologies. It can also guide needle placement for electromyography exam, therapeutic injections, and muscle biopsy. Ultrasound enhances the ability to detect carpal tunnel syndrome and other focal nerve entrapment, as well as pathological nerve enlargements in genetic and acquired neuropathies. Furthermore, ultrasound can potentially be used as a biomarker for muscular dystrophy and spinal muscular atrophy. The combination of electromyography and ultrasound can increase the diagnostic certainty of amyotrophic lateral sclerosis, aid in the localization of brachial plexus or peripheral nerve trauma and allow for surveillance of nerve tumor progression in neurofibromatosis. Potential limitations of ultrasound include an inability to image deeper structures, with lower sensitivities in detecting neuromuscular diseases in young children and those with mitochondrial myopathies, due to subtle changes or early phase of the disease. As well, its utility in detecting critical illness neuromyopathy remains unclear. This review will focus on the clinical applications of neuromuscular ultrasound. The diagnostic values of ultrasound for screening of myopathies, neuropathies, and motor neuron diseases will be presented.

RÉSUMÉ: Applications cliniques et valeurs diagnostiques des examens d'échographie destinés aux maladies neuromusculaires. Les progrès réalisés en matière d'examens d'échographie haute résolution offrent aux cliniciens d'uniques possibilités d'étudier les maladies du système nerveux périphérique. En permettant d'observer l'étendue des anomalies liées aux myopathies de même que l'activité musculaire spontanée dans des cas de maladies motoneuronales et d'autres troubles, ces examens représentent ainsi un complément aux examens cliniques et électro-physiologiques. Entre des mains expérimentées, la capacité de ces examens à détecter des pathologies du système nerveux central dépasse celle d'un appareil d'IRM. Ils permettent aussi d'orienter le positionnement d'une seringue lors d'un examen d'électromyographie, d'une injection thérapeutique et d'une biopsie musculaire. Il faut également noter qu'ils améliorent la capacité de détection du syndrome du canal carpien et des autres problèmes de compression focale des nerfs mais aussi celle des signes cliniques d'élargissement des nerfs qui sont le propre de neuropathies génétiques et acquises. Qui plus est, ils peuvent potentiellement être utilisés à titre de biomarqueurs dans des cas de dystrophie musculaire et d'amyotrophie spinale. Ainsi, le fait de combiner des examens d'électromyographie et des examens d'échographie peut accroître l'exactitude diagnostique de cas de sclérose latérale amyotrophique (SLA), aider à la localisation de traumatismes du système nerveux périphérique ou du plexus brachial et permettre de surveiller la progression tumorale affectant les nerfs dans des cas de neurofibromatose. Il existe toutefois de possibles limites quant à l'utilisation des examens d'échographie, par exemple l'impossibilité de rendre par images des structures plus profondes ou de détecter, avec des niveaux inférieurs de sensibilité, des maladies neuromusculaires ou des myopathies mitochondriales chez des jeunes enfants, le tout pouvant être attribué à une évolution subtile de ces maladies ou au fait qu'elles en soient encore à une phase précoce. De plus, l'utilité de ces examens dans le cas de neuromyopathies graves demeure vague. Cette étude entend donc mettre l'accent sur les applications cliniques des examens d'échographie neuromusculaire. Les valeurs diagnostiques de ces examens en vue de dépister des cas de myopathie, de neuropathie et de maladies motoneuronales seront également présentées.

Keywords: Neuromuscular disorders, Ultrasound, Neurological practice

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Introduction

High-resolution ultrasound is a novel non-invasive tool that is increasingly used to screen, diagnose, and facilitate the treatment of patients with suspected neurologic disorders. In particular, it has been used as part of a comprehensive evaluation of neuromuscular diseases. Such an approach requires the integration of clinical assessments, electrodiagnostic tests, neuroimaging, pathology, and laboratory investigations including targeted genetic testing. Muscle and nerve imaging complements the clinical and electrophysiology exam by accurately depicting the specific area or pattern of abnormalities, allowing direct

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visualization of spontaneous muscle movements, as well as monitoring for other associated pathologies.

In the early years of neuromuscular imaging (1985-2000), muscle computed tomography (CT) was developed as a tool to scan the whole body in search of decreased tissue density caused by fatty degeneration that would point to a pattern of involvement in a specific myopathy or neuropathy.[1,2,3] However, CT has two main drawbacks, including low-tissue resolution and the use of ionizing radiation that make it a less desirable option since more patient-friendly, high-resolution techniques including high-frequency neuromuscular ultrasound and magnetic resonance myography and neurography have become available.[4,5]

MRI of muscle or nerve can accurately depict tissue size, texture, composition, organization, and anatomical context, both in superficial and deep body layers. It can either create a large overview of body regions to help search for a pattern of muscle involvement,[6,7] or can very focally depict specific tissue changes within a certain body region to look for atrophy, fatty degeneration, edema, inflammation, morphological or tissue texture changes, and continuity.[7–9] Both visual evaluation and quantified measurement, for example, of fat fractions or nerve size, are possible. The main drawbacks of MRI seem to be the limited availability of the necessary dedicated protocols, software or coils at many centers, and the need for sedation in young children or claustrophobic patients.

Ultrasound is a feasible alternative to MRI for neuromuscular imaging of superficial structures; it is a portable and readily available technology that can be used in children and adults. Recent studies have shown that neuromuscular ultrasound can reliably screen for myopathies and neuropathies, can help provide a more certain diagnosis of amyotrophic lateral sclerosis (ALS) at the time of presentation, and can be used as a non-invasive biomarker for treatment trials in muscular dystrophy and other neuromuscular diseases.[10–15] This review will focus on the clinical applications of neuromuscular ultrasound. It offers added diagnostic values that adult and pediatric neurologists, clinical neurophysiologists, and other specialists can use for patient-friendly, point of care imaging of muscles and nerves.

Practical Uses of Muscle Ultrasound

As a Screening Tool for Neuromuscular Diseases

Ultrasound is a valid and reliable diagnostic imaging technique for the evaluation of nerves and muscles.[16] A recent systematic review based on publications from 2000 to 2014 confirmed the utility and acceptability of ultrasound for the diagnosis of pediatric skeletal muscle disorders.[17] In comparison to electromyography (EMG), muscle ultrasound is better tolerated. Among 498 children with suspected neuromuscular diseases, Hellmann et al[18] reported that 17% of EMG studies were suboptimal due to intolerance to pain, even though EMG was very sensitive in detecting neurogenic disorders. As well, EMG had more difficulty in detecting myopathies in young children; the sensitivity increased from 25% in infants to 91% in children above 5 years of age.[18] Alternatively, MRI can visualize deeper muscles and detect changes that are indicative of disease progression in neuromuscular diseases; however, as mentioned above, MRI has a number of potential limitations, especially in the pediatric population. Furthermore, Zaidman et al[19] found that nerve ultrasound was more sensitive than MRI in detecting focal neuropathies or brachial plexopathy.

The potential diagnostic benefit of muscle ultrasound was highlighted in several pediatric studies. Following an initial pilot study of 33 children, Pillen et al prospectively studied 150 (90 males, age ranged from birth to 18 years) children referred consecutively for suspected neuromuscular disorders.[20,21] The presenting symptoms were muscle weakness, fatigue, myalgia, hypotonia, and motor developmental delay. A 15-minute standard muscle ultrasound protocol (see Figure 1A) including measurement of muscle thickness (MT) and echo intensity (EI) in two proximal (i.e. biceps brachii, see Figure 2; and rectus femoris, see Figure 3) and two distal (i.e. flexor carpi radialis, see Figure 4; and tibialis anterior, see Figure 5) muscles were used in this study, and the results were compared with their published pediatric normative values;[22] additional investigations included EMG, biochemical and genetic evaluations, plus muscle biopsies were performed as clinically indicated. In total, 65 (43%) patients were subsequently diagnosed with a neuromuscular disease; 54 (36%) did not show any evidence of a neurogenic or myopathic disorder; and 31 (21%) were excluded from further analysis due to inconclusive results.[21] According to Pillen et al,[21] the EI of all examined muscles were found to be significantly higher in patients with neuromuscular diseases than those without. Abnormal muscle ultrasound in their study was defined by an EI >3.5 standard deviation (SD) in one muscle, or >2.5 SD in two muscles, or >1.5 SD in three muscles; these ultrasound criteria were associated with a sensitivity of 71% (95% confidence interval [CI] 60%-82%), a specificity of 91% (CI 83%-99%), and a positive predictive value (PPV) of 91% (CI 82%-98%) in diagnosing pediatric neuromuscular diseases. Normal muscle ultrasound in turn was defined by an EI of less than 2.0 SD in all four muscles, plus <1.5 SD in three muscles, and <1.0 SD in two muscles; these parameters were associated with a sensitivity of 91% (CI 84%-98%), a specificity of 67% (CI 54%-80%), and a negative predictive value (NPV) of 86% (CI 76%-96%).[21]

The sensitivity of muscle ultrasound in detecting neuromuscular diseases was lower among 43 patients who were less than 3 years of age, with a false-negative rate of 25%, but no false positives were found in this age group (PPV 100%); the false negatives were seven children with early stages of neuromuscular diseases or metabolic myopathies, including one case of congenital myopathy with fiber-type disproportion, two with mitochondrial cytopathies, one with Pompe disease, one with an unspecified myopathy, one with pre-symptomatic Duchenne muscular dystrophy (DMD), and one with early spinal muscular atrophy (SMA).[21] As well, two children were presumed to be false positives, with abnormal EI on ultrasound but no other evidence of neuromuscular diseases.[21] Furthermore, the authors reported in a companion study that muscle ultrasound was less sensitive (25%-46%) as a screening tool in young children with mitochondrial disorders, due to only subtle structural changes in the muscles.[23]

In addition, the distribution of ultrasound abnormalities as well as the pattern of muscle involvement can aid in the diagnosis of neuromuscular diseases. The common patterns of ultrasound abnormalities in specific neuromuscular disorders are summarized in Table 1. Although MT measurements showed more prominent atrophy of the lower extremities in neurogenic disorders, discrimination between neurogenic disorders and myopathies based on the degree of muscle atrophy alone had low diagnostic accuracy, with an area under the receiver operating characteristic curve of <0.72.[21] Instead, a combined

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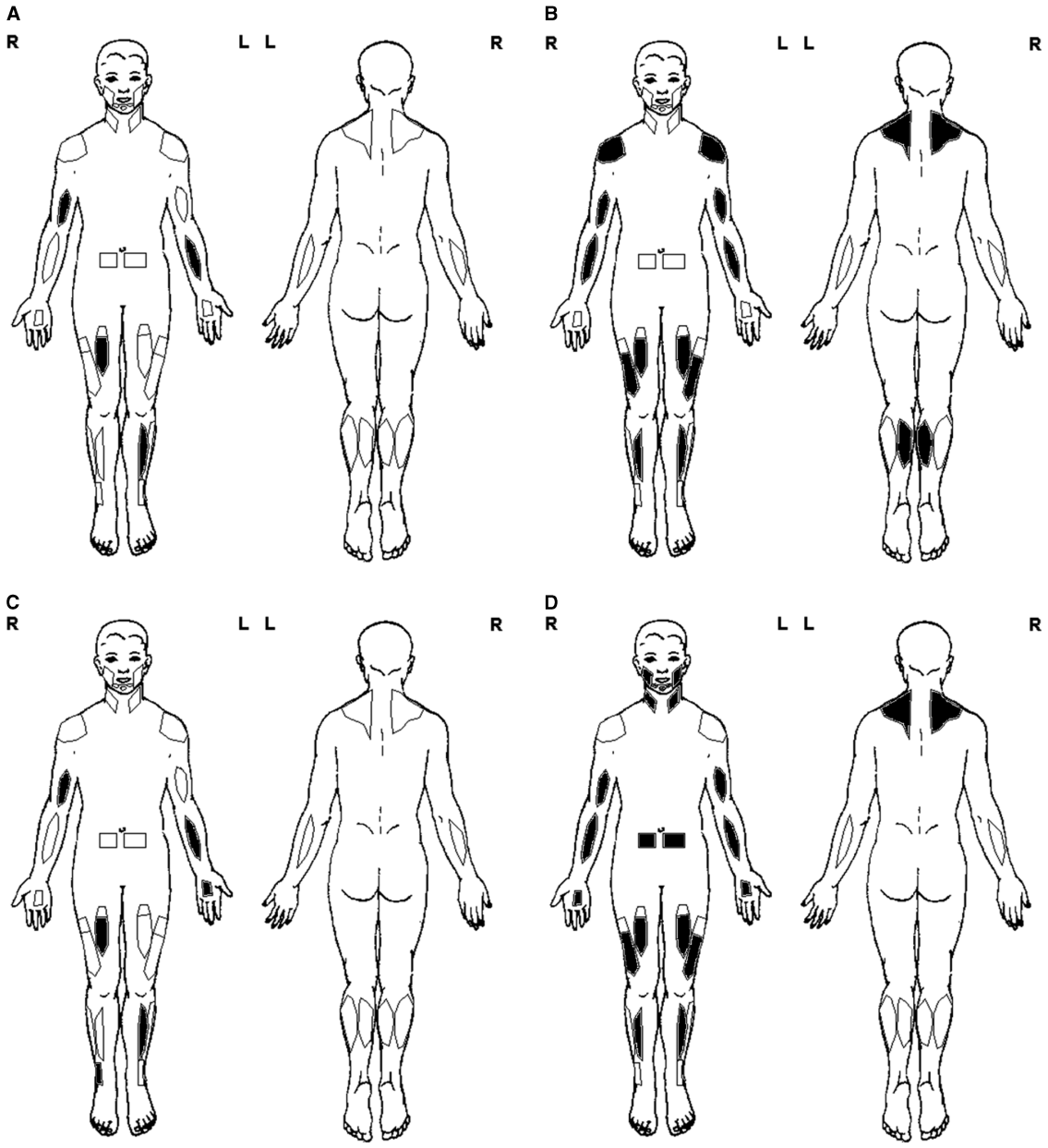

Figure 1: *Basic muscle ultrasound protocol. (A) General screen—unilateral exam of the biceps brachii, flexor carpi radialis, rectus femoris, and tibialis anterior. (B) Myopathy screen—bilateral exam of the trapezius, deltoid, biceps brachii, flexor carpi radialis, rectus femoris, vastus lateralis, tibialis anterior, and medial gastrocnemius. (C) Polyneuropathy screen—general screen protocol (A) and additional exam of distal muscles such as the peroneus tertius and first dorsal interosseous. (D) Motor neuron disease screen—myopathy screen protocol (B) and additional exam of rectus abdominis, sternocleidomastoid, trapezius, masseter, first dorsal interosseous, and submental muscles, plus fasciculation screening of 30-second scan time per muscle.*

cut-off based on EI (increased in legs by more than 1 SD than arms) and MT (atrophy greater in legs than arms) was better at detecting neurogenic disorders, with a sensitivity of 67% (CI 49%-85%), a specificity of 94% (CI 87%-100%), a PPV of 86% (CI 71%-100%), and a NPV of 84% (CI 74%-94%); further discrimination of myopathies from neurogenic and non-neuromuscular disorders was limited by disease heterogeneity in the study cohort.[21]

Similarly, others authors have used ultrasound parameters such as muscle inhomogeneity, echogenicity, and thickness in a quantitative or qualitative approach to help differentiate between myopathies and neuropathies among adults and children with suspected neuromuscular disorders.[24,25,26] Interestingly, a recent study found that boys with DMD may not show significant muscle atrophy over the course of their disease,[11] and muscle pseudo-hypertrophy can occur in both neurogenic and myopathic disorders.[27,28] Both findings might explain why MT is not a very good discriminator for detecting and differentiating neuromuscular diseases.

On the other hand, selective pattern of muscle involvement can provide important diagnostic clues for the differential diagnosis of various myopathies. A systematic approach involving bilateral

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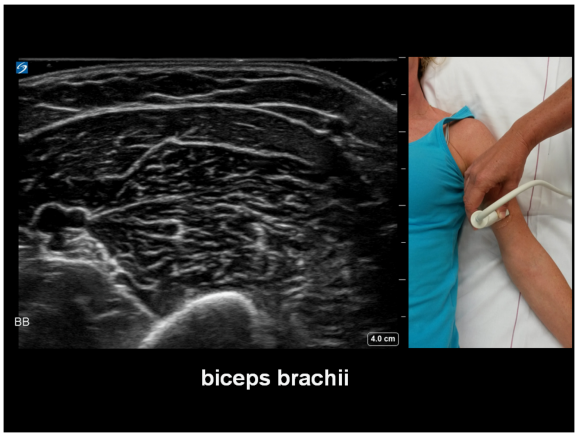

Figure 2: *Muscle ultrasound image of the biceps brachii, as recorded at 2/3 of the distance from the acromion to the antecubital crease.*

ultrasound exam of muscles as described in the standard ultrasound protocol, plus other proximal and distal muscles such as the trapezius, deltoid, vastus lateralis, and medial gastrocnemius are recommended as part of a myopathy screen (see Figure 1B). The presence of a peripheral rim of abnormal signal in the vastus lateralis and a central area of abnormal signal within the rectus femoris can be found in collagen VI myopathies, and early selective involvement of the rectus femoris and vastus lateralis is typically seen in *RYR1*-related central core myopathies (Figure 6).[14,29–31] As well, muscle ultrasound can detect a greater degree of muscle changes in patients with myotonic dystrophies and other non-dystrophic myotonic disorders, at times better than muscle MRI.[32,33]

Improving the Diagnosis of Motor Neuron Diseases

Ultrasound enhances the ability to detect fasciculations in 10% to 30% of muscles that may be subclinically involved or negative on EMG, thus increasing the diagnostic certainty for patients with motor neuron diseases and other neuromuscular disorders.[34–37] In addition to bilateral examination of the muscles as described in the standard muscle ultrasound protocol, screening of lower motor neuron disease usually involves additional scanning of the rectus abdominis, sternocleidomastoid, trapezius, masseter, first dorsal interosseous, and

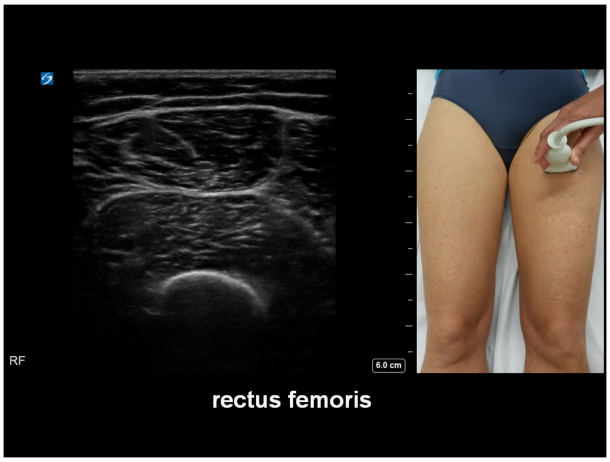

Figure 3: *Muscle ultrasound of the rectus femoris, as recorded at 1/2 of the distance between the anterior superior iliac spine and the upper pole of the patella.*

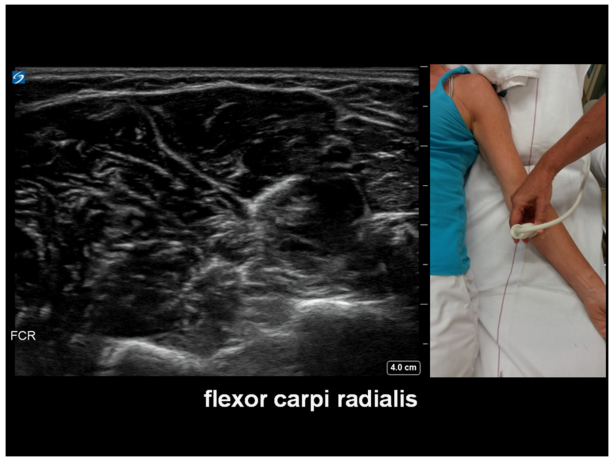

Figure 4: *Muscle ultrasound of the flexor carpi radialis, as recorded at 1/3 of the distance from the antecubital crease to the distal radius.*

submental muscles, with fasciculation screening of up to 60-second scan time per muscle (see Figure 1D).

Arts et al[35] used ultrasound as part of a cross-sectional study to examine ten muscles in each of their 48 patients with ALS and 27 patients with ALS mimics; their study found that the increase in EI was more striking than the reduction of MT in ALS. Fasciculations were identified in all but one of the 25 patients screened using a 10-second scan time, with a mean of 6.5 (range 0-10) muscles showing fasciculations; the authors concluded that ultrasound could detect muscle changes during the early phase of ALS.[35] In another prospective study of 59 adults with suspected ALS, muscle ultrasound was able to differentiate patients with ALS ($n = 27$) from others ($n = 32$) with ALS mimics (see example in Figures 7A–7B); the corresponding sensitivity and specificity was 96% and 84%.[38] In two recent studies, fasciculations were detected in 58%[37] to 68%[39] of patients with ALS based on an ultrasound scan time of 10 or 60 seconds per muscle, respectively; higher sensitivities were reported when the results of ultrasound were combined with EMG. In the cranial region of ALS patients, the muscle ultrasound detection rate for fasciculations was found to be similar to that of EMG, although frequent fasciculations were again more easily detected with ultrasound.[40]

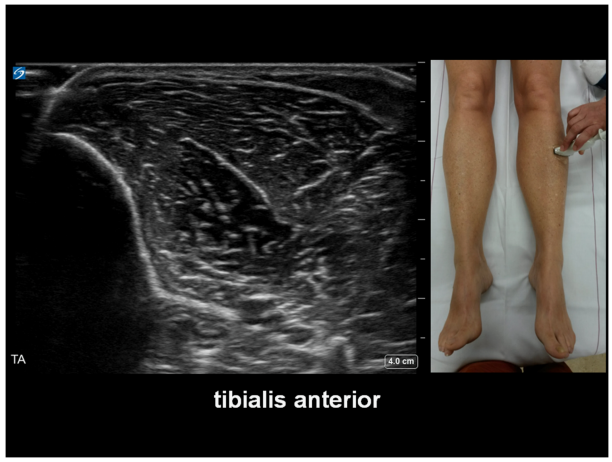

Figure 5: *Muscle ultrasound of the tibialis anterior, as recorded at 1/3 of the distance from the inferior border of the patella to the lateral malleolus.*

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Table 1: Common patterns of ultrasound abnormalities in neuromuscular disorders

Neuromuscular diseases	Echo intensity (EI)	Muscle thickness (MT)	Remarks
General	N to ↑↑↑	N to ↓↓↓	EI often more abnormal than MT in myopathic disorders
Myopathies			
Muscular dystrophies	↑↑↑	N to ↓↓	Homogeneous increases in EI with "ground glass" appearance. Normal or decreased EI in deeper areas of affected muscle due to increased attenuation. Preclinical cases can be normal
Congenital myopathies	N to ↑↑↑	↓ to ↓↓	Homogeneous increases in EI
Metabolic myopathies	N or ↑	N or ↓	Normal or mild homogeneous increases in EI
Inflammatory myopathies	↑↑	Acute—N to↑, Chronic—↓	Slight increases in EI during acute phase, more severe in chronic phase; EI is often focally increased
Inclusion body myositis	↑↑↑	↓↓ to ↓↓↓	Focal asymmetric pattern, especially in distal muscles, with increased EI in affected muscles
Neuropathies			
Polyneuropathy	↑ to ↑↑	↓↓ in distal muscles	Inhomogeneous increases in EI, distal more severe than proximal muscles
Focal neuropathy	N to ↑↑	↓↓↓ in affected muscles	First US abnormalities visible after 10 days, EI more abnormal than atrophy. Areas without reinnervation may show "moth-eaten" pattern. Persistent denervation of the muscle will lead to fully white atrophic appearance with now black fascial lines
Motor neuron disease			
Spinal muscular atrophy	↑↑↑	↓↓↓	Inhomogeneous "moth-eaten" pattern. Can be normal in very young patients
Amyotrophic lateral sclerosis	↑↑	↓↓↓	Fasciculations most prominent feature, EI more abnormal (increased) than atrophy

Modified from Pillen et al.[124]
↑ = slightly increased echo intensity or muscle thickness; ↑↑ = moderately increased echo intensity; ↑↑↑ = severely increased echo intensity; ↓ = slight atrophy; ↓↓ = moderate atrophy; ↓↓↓ = severe atrophy; N = normal echo intensity or muscle thickness; US = ultrasound.

As well, among 81 adults consecutively referred for suspected ALS, Misawa et al reported that the combination of ultrasound and EMG increased the diagnostic category of probable or definite ALS from 48% (based on the revised El Escorial criteria) to 79% (based on the Awaji criteria), in part due to the enhanced ability of muscle ultrasound to detect fasciculations.[36] In ALS patients who had fasciculations, a score based on the ultrasound results of nine muscles was able to discriminate between ALS and ALS mimics with 92% sensitivity and 100% specificity.[41] Other publications also confirmed the utility of muscle ultrasound as part of a comprehensive assessment of patients with suspected ALS.[37,42] Nerve ultrasound can also help differentiate between patients with ALS and multifocal motor neuropathy (MMN), with a sensitivity ranging from 87% to 100%, and a specificity of 92% to 94%.[43,44] Furthermore, ultrasound can potentially be used to monitor for disease progression in adults with ALS,[13] although others have found conflicting results.[45]

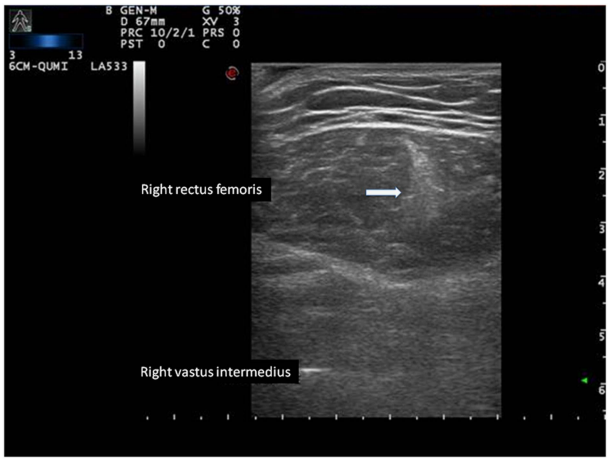

Figure 6: *Transverse axis ultrasound of the quadriceps showing increased echo intensity of the rectus femoris and vastus intermedius in an adult with RYR1-related central core myopathy.*

Improving the Diagnosis of Metabolic Myopathies

Although earlier studies suggest that muscle ultrasound has lower sensitivity in detecting metabolic myopathies compared with structural myopathies and muscular dystrophies in children, more recent studies show that muscle ultrasound can still be clinically useful, for example, in the diagnosis of Pompe disease due to acid-maltase deficiency, or by showing muscle changes in other glycogen storage diseases.[46] In one study, muscle ultrasound showed focal abnormalities affecting the deeper layers of biceps brachii, with relative sparing of the triceps brachii; more severe involvement of the vastus intermedius in comparison with the rectus femoris was also reported in adults with Pompe disease.[47] Vill et al[48] did not find a selective pattern of muscle vulnerability in patients with Pompe disease; instead, they reported that bone echogenicity was less attenuated even in advance stages of the disease, and muscle ultrasound was used as a screening tool for adults (but not in infants) with late-onset disease. More recently, Hwang et al[49] advocated for the use of semi-quantitative muscle ultrasound as a diagnostic tool to help discriminate between neonates with low acid alpha-glucosidase activity related to infantile or late-onset Pompe disease; the sensitivity of muscle ultrasound was reported as 100% (CI 69.2%-100%) and the specificity was 84% (CI 63.9%-95.5%).

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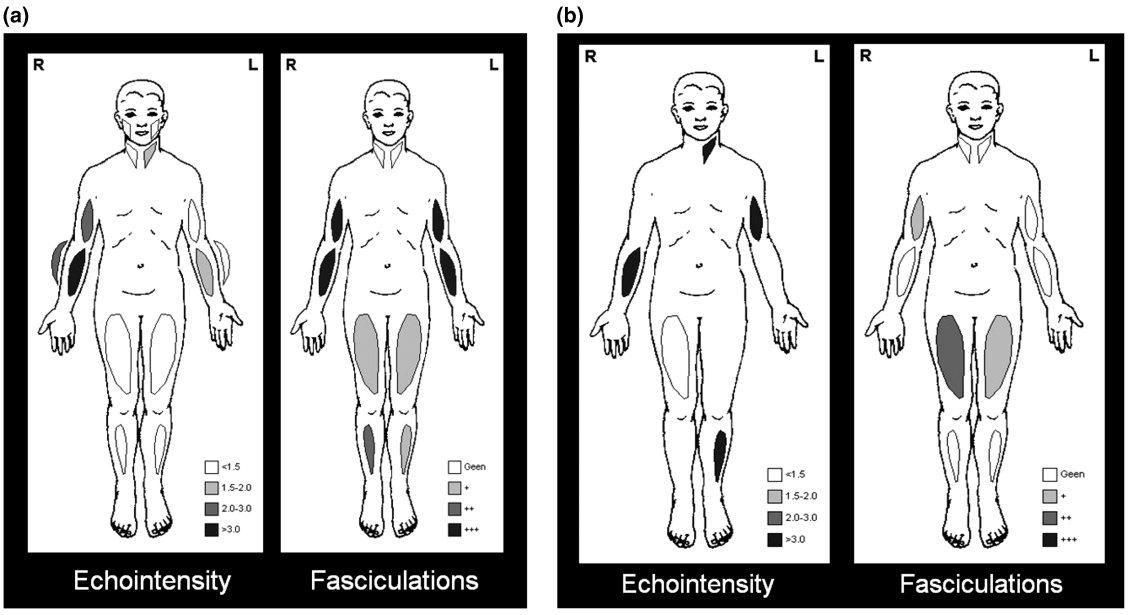

Figure 7: *Example of muscle ultrasound showing different pattern of involvement in amyotophic lateral sclerosis (ALS) versus ALS mimics. (a) ALS, with mild to moderately increased echo intensity, diffuse fasciculations, and atrophy of paretic muscles; (b) Inclusion body myositis, with severely increased echo intensity, either none or some fasciculations, and pronounced atrophy.*

Guiding Needle Placement

Ultrasound has been used increasingly to guide botulinum toxin injections and other bedside treatment procedures.[50,51] For the treatment of spasticity and dystonia with botulinum toxin, ultrasound guidance has been shown to improve clinical outcomes,[52,53] and ultrasound-guided needle muscle biopsy offers a viable alternative to open biopsy for the diagnosis of neuromuscular diseases, with comparable tissue samples results.[54] Ultrasound can help determine the optimal muscle biopsy site; the use of tissue Doppler evaluation before and after the biopsy can also help minimize potential complications by avoiding vessels and nerves.[54] Furthermore, ultrasound can be used to guide needle EMG to distinguish muscles in close proximity,[55] and to enhance patient safety when needling the diaphragm,[56] the periscapular muscles,[57] or other muscles in patients on anticoagulants.[58] In a cadaveric study, ultrasound greatly improved needle EMG placement accuracy in most muscles.[59] As well, a recent review showed that ultrasound guidance increased the success rates of lumbar puncture and reduced the procedural time in patients with poorly palpable landmarks related to obesity, prior spinal surgery, and other difficult clinical circumstances.[60] Further studies are needed to determine whether ultrasound may facilitate the delivery of novel disease-modifying treatment such as intrathecal injections for patients with SMA.

Assessing Muscles that Cannot be Easily Accessed with EMG

Dysphagia is a common symptom in patients with neuromuscular diseases. A recent systematic review of dysphagia in children focused primarily on boys with DMD; there was a lack of widely accepted screening or evaluation protocol for other pediatric neuromuscular disorders.[61] Boys with DMD were found to have

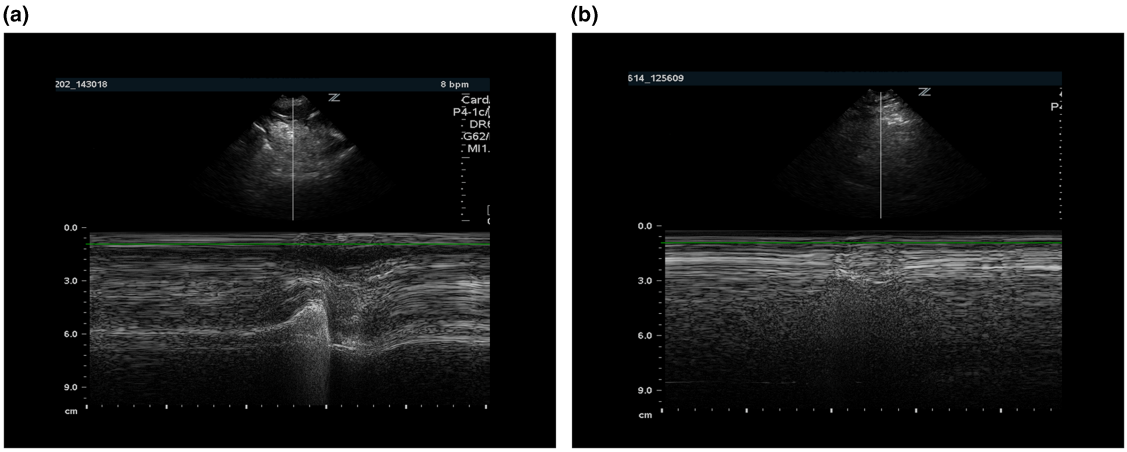

Figure 8: *Dysphagia evaluation using Motion mode (M-mode) ultrasound of the tongue while swallowing 5 ml of water. (a) Healthy control showing clearly defined phases of tongue movement; (b) Young adult male with Duchenne muscular dystrophy showing minimal tongue movement due to severe weakness.*

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progressive involvement of the oropharyngeal muscles, necessitating the modification of feeding strategies to minimize dysphagia.[62] As transporting and swallowing requires the use of more than 25 pairs of oral and masticatory muscles that are difficult to be assessed by EMG, van den Engel-Hoek et al[63] proposed to use muscle ultrasound as a standard diagnostic tool for the assessment of dysphagia (Figures 8A–8B), based on their extensive experience with ultrasound in the neuromuscular population.

As well, ultrasound can be used as a non-invasive diagnostic test to determine the functional status of facial muscles, and to help identify ideal candidates for facial nerve reconstruction surgery even after an extended period of denervation.[64,65]

Patients in the intensive care unit (ICU) are at risk of developing critical illness neuromuscular disorders. Traditionally, the clinical history, physical exam, and electrophysiological evaluations such as EMG and nerve conduction study are essential for the diagnosis of critical illness neuromyopathy; however, these assessments may be limited by a lack of patient cooperation due to sedation or encephalopathy, electrical interference, treatment with anticoagulants, or other confounding factors in the ICU. Therefore, Cartwright et al[66] proposed that serial quantitative ultrasound can be used to study ICU-acquired weakness and muscle atrophy, without requiring patient cooperation. However, more recent studies suggest that ultrasound has difficulty detecting early changes (less than 2 weeks) in muscles of patients with ICU-acquired weakness, and the reliability of muscle ultrasound in this disorder is not fully established.[67–68] In a recent review, Ong et al[69] summarized the limitations of ultrasound, including a substantial intra-rater variability in quadriceps MT that resulted in its low reliability and accuracy as a marker for critical illness neuromyopathy in the pediatric population. The diagnostic utility of ultrasound in this clinical context remains undefined.

In contrast to evaluating ICU-acquired weakness, ultrasound is an ideal non-invasive bedside procedure for the detection of early neuromuscular diaphragmatic dysfunction of any cause, with a sensitivity of 93% and a specificity of 100%.[70,71]

Biomarker for Treatment Trials

A longitudinal observational study of 18 boys with DMD showed high correlations of increasing muscle echogenicity with disease progression and functional status.[11] As well, among 5 young boys (age 0.5-2.8 years) with DMD, there was evidence of disease progression with increased muscle EI over 2.5 years, despite functional improvements during early childhood;[72] quantitative muscle ultrasound by backscatter or grayscale analysis from superficial regions of muscles provided comparable measures of disease pathology in this population.[73] More recently, Zaidman et al[15] examined 36 ambulatory boys (age 2-14 years) with DMD for up to 2 years; the authors found that ultrasound was more sensitive in detecting clinical deterioration in DMD than motor functional assessments, including the 6-minute walk test or the supine-to-stand test. Boys with DMD showed significant increases in muscle EI due to progressive fibro-fatty tissue replacement (Figure 9); the changes were significant as early as 6 months from baseline for boys less than 7 years old, and at 12 months for boys 7 years or older when compared with age- and gender-matched healthy controls.[15] Therefore, muscle ultrasound may serve as a potential biomarker for disease progression as well as a non-invasive outcome measure in multicenter drug trial for DMD, without requiring patient cooperation.[74]

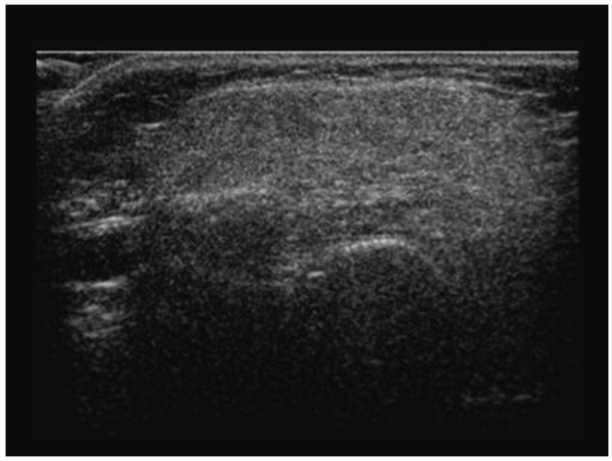

Figure 9: *Abnormal transverse axis quadriceps muscle ultrasound in a child with Duchenne muscular dystrophy; diffuse fibro-fatty tissue replacement in this disorder is shown with increased echogenicity, leading to a "ground glass" appearance.*

Similarly, Ng et al[12] found evidence of progressive quadriceps atrophy and increased muscle EI in three infants with SMA type 1 at 2-4 months after initial assessments (Figure 10). The rapid decline in ultrasound measures was consistent with the severe phenotype of early onset SMA; ultrasound could potentially be used as a biomarker for disease progression and to determine responsiveness to new emerging treatment for this disease.[12]

Practical Uses of Nerve Ultrasound

High-resolution ultrasound has been helpful in the evaluation of genetic and acquired neuropathies, as recently reviewed by a number of leading experts.[13,56,75] Ultrasound offers superior spatial resolution and ability to detect subtle structural abnormalities in peripheral nerves through the availability of high-frequency (12-18 MHz) transducers, advances in image processing, and sensitive Doppler technology.[76]

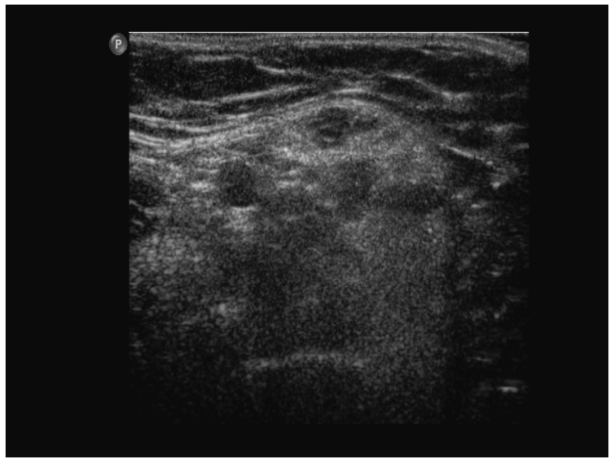

Figure 10: *Abnormal transverse quadriceps muscle ultrasound in a child with spinal muscular atrophy. The image shows increased subcutaneous fatty tissue, and a "moth-eaten" appearance representing areas of denervated atrophic fibers versus reinnervated, hypertrophic muscle fibers (the "moth holes").*

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Common clinical applications of nerve ultrasound include screening for entrapment, diagnosing genetic and acquired neuropathies, complementing EMG in the assessment of nerve trauma, surveying for tumor progression, and providing precise landmark for nerve injections. In experienced hands, ultrasound is more sensitive than MRI (93% vs. 67%) and has a comparable specificity (86%) for detecting peripheral nerve pathology.[19] As well, ultrasound examination was able to identify degenerative or post-traumatic changes, soft-tissue masses, and other distinct extraneural findings in nearly one-quarter of patients without peripheral nerve abnormalities; many of these patients benefited from the additional evaluation of these extraneural findings.[77]

Screening for Nerve Entrapment

Peripheral nerve injury leads to a number of anatomical changes, including altered dimension, echogenicity, and vascularity. In nerve entrapment syndromes, there may be focal areas of nerve enlargement just proximal to the site of the compression, with associated loss of the internal fascicular architecture, and reduction in nerve echogenicity.[78] Ultrasound has been helpful in confirming the precise anatomic localization of the injury, assessing for nerve continuity, as well as identifying other structural changes in a number of neuromuscular conditions.

Carpal Tunnel Syndrome (CTS)

Median mononeuropathy across the wrist is the most common type of nerve entrapment, and it has been studied extensively with the use of ultrasound (Figures 11A–11B).[79] A systemic review confirmed that the accuracy of ultrasound is comparable to EMG and nerve conduction studies for the diagnosis of CTS; based on a median nerve cross-sectional area (CSA) cut-off value of 8.5 mm^2 to 10 mm^2, Cartwright et al[10] concluded that ultrasound had an overall sensitivity of 65% to 97%, a specificity of 72.7% to 98%, and a PPV of 79% to 97% for the diagnosis of CTS. A greater than 40% increase in nerve size from the forearm to carpal tunnel was also found to be suspect for entrapment in patients with CTS,[80] but later studies have emphasized that the CSA itself remains the most robust measure to confirm the disorder.[81] Scanning the whole carpal tunnel instead of just the proximal inlet increased the sensitivity by 15% to 20%.[82,83] Additionally, as ultrasound can detect other anatomic abnormality such as a ganglion cyst or accessory muscle, the authors concluded that ultrasound provides additional value to electrodiagnostic studies when assessing patients with CTS.[10] The use of tissue Doppler plus standard

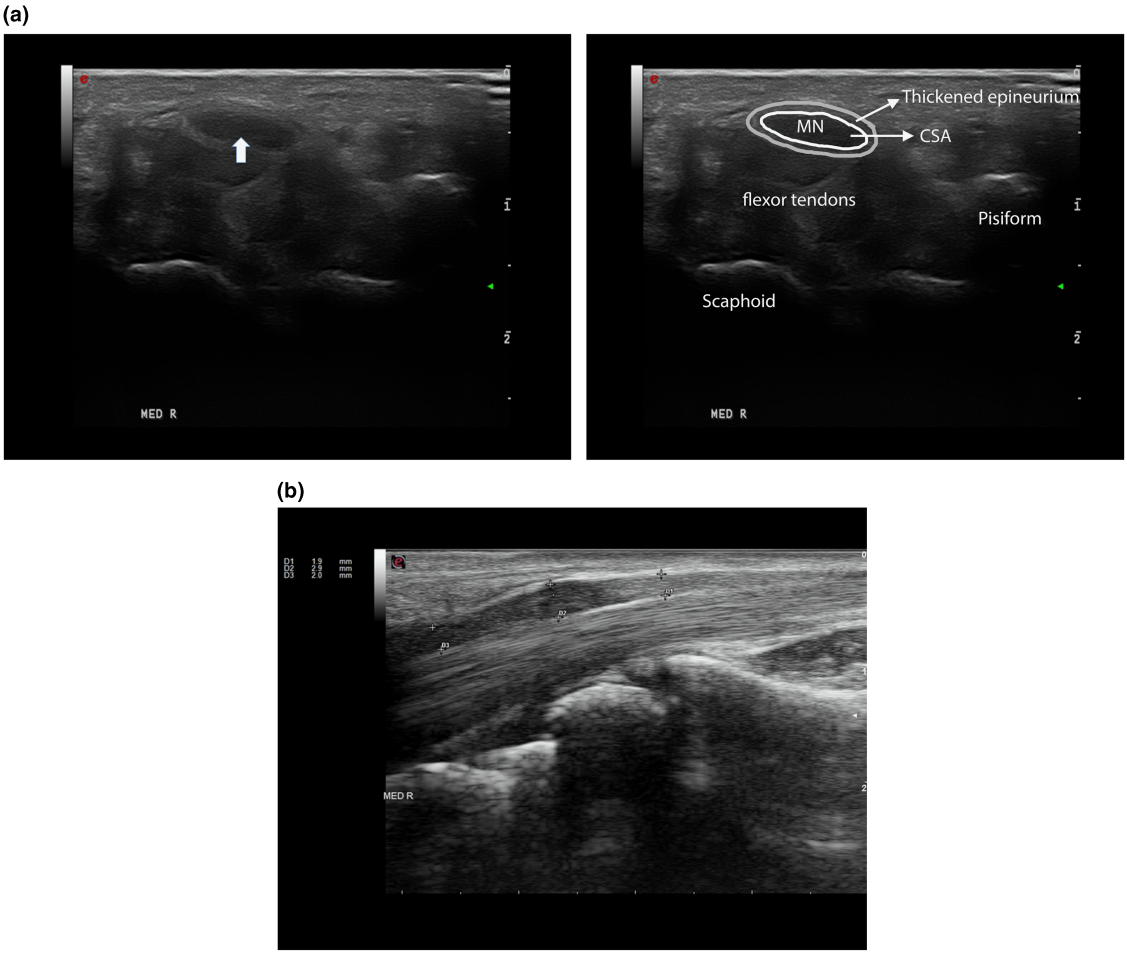

Figure 11: *An example of a patient with Carpel tunnel syndrome. (a) Right median nerve in short axial view, with a cross-sectional area (CSA) of 17 mm^2 (see arrow), normal < 11 mm^2. (b) Same nerve in longitudinal view showing focal nerve enlargement (marked by arrows) just proximal to notching caused by compression of the carpal ligament.*

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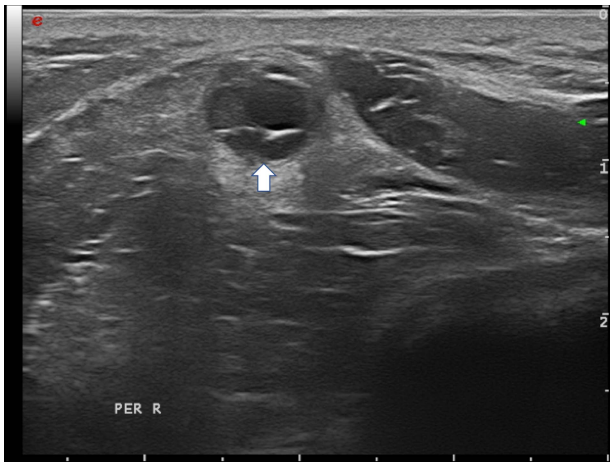

Figure 12: *Fibular nerve with intraneural ganglion cyst (arrow); the hypoechoic cystic areas can be seen on the right, while the displaced fascicles are on the left side in the nerve.*

ultrasound parameters may help confirm the diagnosis plus identify optimal treatment and improve surgical outcomes for CTS.[79,81]

Other Entrapment Syndromes

Other entrapment syndromes including ulnar neuropathy at the elbow or wrist, and fibular neuropathy at the knee (Figure 12) can be evaluated according to specific nerve ultrasound study protocol.[78] As well, ultrasound has been useful for the diagnosis of meralgia paresthetica[84] and neurogenic thoracic outlet syndrome.[85]

Neuropathy in Hereditary Diseases

A recent cross-sectional study showed that nerve ultrasound is a useful screening tool for CTS in children with mucopolysaccharidosis type 1, 2 and 6, with higher (92%) sensitivity than EMG (77%) or clinical exam (26%) alone.[86] One year post carpal tunnel release surgery, there was improvement in the median distal motor latencies and compound motor action potential (CMAP) amplitudes; however, the median nerve CSA at the wrist and the wrist to forearm ratio remained unchanged.[86] As well, ultrasound was able to detect multifocal nerve enlargement in two siblings with neuropathies secondary to mucolipidosis type 3; electrophysiological studies were normal in both patients apart from distal median neuropathies.[87]

Beyond the diagnosis of entrapment syndromes in lysosomal storage diseases, ultrasound has been used to assist with the diagnosis of hereditary neuropathies. Among the genetic neuropathies, Charcot-Marie-Tooth type 1A (CMT1A) is one of the most prevalent subtypes. It is an autosomal dominant inherited demyelinating motor and sensory polyneuropathy caused by duplication of the *PMP22* gene. In patients with genetically confirmed CMT1A, ultrasound revealed uniformed nerves enlargement, with significantly increased CSA of the nerve roots, brachial plexus, and peripheral nerves, compared with those in healthy subjects and patients with CMT type 2.[76,88] Ultrasound may be particularly helpful in CMT type 1 patients with hypertrophic nerves and absent CMAP response due to distal muscle atrophy, or an inability to tolerate nerve conduction study due to the need for high stimulation intensity.[76,88] An increase in nerve CSA is also seen disproportionately in children with CMT1A[89] and other demyelinating CMT subtypes.[90,91]

In addition, hereditary neuropathy with liability to pressure palsy (HNPP) due to a deletion of the *PMP22* gene is associated with focal nerve enlargement at common entrapment sites,[92] whereas non-inflammatory axonal neuropathies generally show normal nerve sizes.[93,94] Loewenbrück et al further proposed the use of diagnostic ultrasound models to discriminate between demyelinating and axonal forms of CMT; they reported high sensitivity (84%-100%) and specificity (86%-100%) with ultrasound, especially for the axonal CMT subtypes.[95,96] Therefore, a combination of clinical exam, electrodiagnostic study, and nerve ultrasound may provide important clues for targeted gene testing.

Similarly, nerve ultrasound has been used to elucidate peripheral nerve involvement in Friedreich ataxia, autosomal dominant spinocerebellar ataxia, plus other cerebellar ataxia with neuropathy syndromes.[97–99]

Diagnosis of Other Neuropathies

As summarized below, nerve ultrasound can aid in confirming the diagnosis of inflammatory neuropathies, nerve tumors, and traumatic nerve injuries; it can also be used in the evaluation of small fiber polyneuropathy.[100] A polyneuropathy screen generally includes an examination of standard ultrasound muscles, with the addition of distal muscles such as the peroneus tertius, first dorsal interosseous, and other clinically affected muscles (see Figure 1C), as well as ultrasound scanning of common peripheral (median, ulnar, fibular, and tibial) nerves, plus proximal brachial plexus and nerve roots as clinically indicated.

Acquired Inflammatory Neuropathies

Acute (AIDP) or chronic (CIDP) inflammatory demyelinating polyneuropathy is associated with patchy enlargement of the peripheral nerves and nerve roots that can be visualized by ultrasound.[76,101,102] In one study of AIDP, multifocal nerve enlargements with increased CSA were seen within 3 weeks after the onset of symptoms, with sonographic improvement after treatment 3 months later.[103] Another recent study provided class II evidence that a compact nerve ultrasound protocol with scanning of bilateral median nerves and brachial plexus has high positive and NPV (100% and 98%, respectively) for discriminating CIDP, Lewis-Sumner syndrome, and MMN from other clinical mimics.[104] Thus nerve ultrasound may be used in conjunction with the clinical exam and electrophysiology to distinguish between different types of acquired demyelinating neuropathies and to optimize treatment plans.

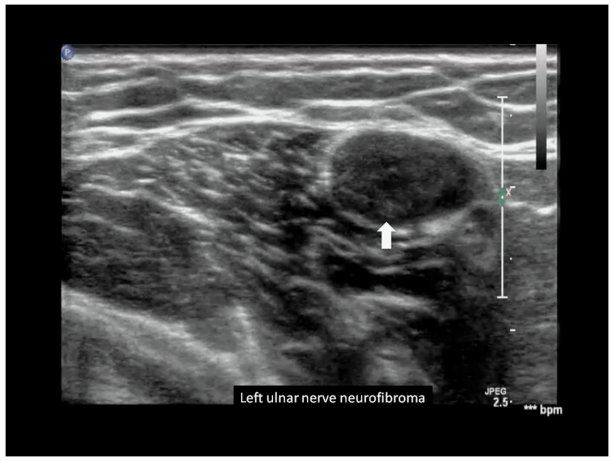

Figure 13: *Left ulnar nerve with neurofibroma, marked by the arrow.*

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Table 2: Examples of diagnostic values of ultrasound in specific neuromuscular disorders

Type of neuromuscular disease (NMD)	Age range (in years)	Number of patients	Methods of ultrasound assessment	Sensitivity	Specificity	Comments
General screen						
Pillen et al (2003)[20]	0.5-14	36	Quantitative, muscle EI and MT	92%	90%	Quantitative muscle US can detect NMD in children
Pillen et al (2006)[23]	0-18	76	Visual vs. quantitative	71% 87%	92% 67%	Quantitative method is more objective and accurate
Pillen et al (2007)[21]	0-18	150	Quantitative Overall Neurogenic Myopathic	 71% 67% NA	 91% 94% NA	Sensitivity is lower in children <3 years, with 25% false-negative rate
Brockmann et al (2007)[30]	0-18	134	Semi-quantitative Overall Myopathic Neurogenic	 81% 67% 77%	 96% 92% 98%	Overall sensitivity, specificity, and accuracy was lower in children ≤3 years old, and in mitochondrial diseases
Brandsma et al (2014)[26]	0-7	100	Visual, muscle echodensity and homogeneity	85%	75%	Overall higher specificity in experienced observer (86% vs. 69%)
ICU-acquired weakness (ICU-AW) Witteveen et al (2017)[68]	Median 60	71	Quantitative, MT, EI, homogeneity, nerve size, and CSA	3%-46%	67%-97%	A single neuromuscular US exam is not able to reliably diagnose ICU-AW in ICU patients early in the disease
Myopathy						
Muscular dystrophies, all Heckmatt et al (1988)[125]	0-18	66	Semi-quantitative	76%	NA	US is a valuable screening test in children with NMD Higher false negatives in preclinical cases
DMD Weng et al (2017)[123]	2-24	47	Quantitative, US Nakagami imaging of lower limb muscles	76%	95%	Changes in the Nakagami parameter correlated with severity and functional decline in boys with DMD
Myotonic disorders Abraham et al (2018)[126]	17-60	16	Quantitative thenar muscles relaxation time	88%	100%	A cut-off of >0.9 was used for myotonia detection; relaxation time did not correlate with severity
Congenital myopathies Heckmatt et al (1988)[125]	0-9	7	Semi-quantitative	57%	NA	In myopathy the muscle thickness is usually preserved
Metabolic myopathies, all Heckmatt et al (1988)[125]	0.5-14	4	Semi-quantitative	50%	NA	US can show selective muscle involvement within the quadriceps
Mitochondrial myopathies Pillen et al (2006)[23]	1-15	53	Quantitative	25%-46%	85%-100%	US is not ideal as a screening test for young children with metabolic myopathies
Acid-maltase deficiency Hwang et al (2017)[49]	0.1-2.5	35	Semi-quantitative	100%	84%	US is a good screening tool for newborns with suspected Pompe disease
Inflammatory myopathies Reimers et al (1993)[127]	21-82	70	Visual and quantitative	83%	NA	US improved clinical assessment for myositis
Inclusion body myositis (IBM) Noto et al (2014)[128]	68-79	18	Quantitative, forearm FDP-FCU EI contrast	100%	NA	Selective involvement of FDP in sporadic IBM
Neuropathy						
Polyneuropathy (PN): CMT Heckmatt et al (1988)[125]	2-16	8	Semi-quantitative	63%	NA	Distal lower extremities muscles more affected in CMT

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Table 2. *Continued*

Type of neuromuscular disease (NMD)	Age range (in years)	Number of patients	Methods of ultrasound assessment	Sensitivity	Specificity	Comments
Loewenbrück et al (2017), CMT[96]	Mean					US diagnostic models showed high accuracy for both demyelinating and axonal subtypes of CMT
(a) Axonal	58.1	25	Quantitative	100%	100%	
(b) Demyelinating	50.1	60	Nerve US	84%	86%	
Loewenbrück et al (2016)[95]	Mean					US had lower sensitivity than NCS for acquired PN, but comparable specificity. US is comparable to NCS for CMT
(a) Acquired PN	68.4	36	Quantitative	56%	93%	
(b) CMT	43.0	53	Nerve US	65%	100%	
CIDP, LSS, and multifocal motor neuropathy Goedee et al (2017)[104]	Mean 58 54 56	 44 CIDP 9 LSS 22 MMN	Quantitative nerve CSA and echogenicity	83%-95%	98%-100%	Class II evidence that sonographic enlargement of proximal median nerve and brachial plexus can accurately identify patients with CIDP, LSS, and MMN
Vasculitic syndrome, Goedee et al (2016)[110]	Mean 65	16	Quantitative nerve CSA	94%	88%	Nerve enlargement proximal to compression sites with brachial plexus sparing seen
Focal neuropathy						
Carpal tunnel syndrome (CTS) Cartwright et al (2012)[10]	Systemic review	Systemic review	Quantitative nerve CSA	65%-97%	73%-98%	US of median nerve cross-sectional area is helpful in diagnosing CTS (Level A)
Ažman et al (2017)[81]	Mean 54	 86	 Quantitative nerve CSA	93%	91%	Inlet-outlet CSA is useful in confirming diagnosis of CTS
Meralgia Paresthetica Suh et al (2013)[84]	17-69	23	Quantitative nerve CSA	96%	96%	US is useful in the diagnosis of meralgia paresthetica, based on the CSA of LFCN
Thoracic outlet syndrome (TOS) Arányi et al (2016)[85]	19-74	20	Quantitative nerve CSA	95%	NA	Wedge-sickle sign seen with fibromuscular bands in most patients with neurogenic TOS
Phrenic neuropathy Boon et al (2014)[70]	33-84	66	Quantitative diaphragm thickness	93%	100%	US accurately identified patients with diaphragmatic respiratory failure (Class II)
Other focal PN Zaidman et al (2013)[19]	1-78	53	Quantitative nerve CSA	93%	86%	US detected focal lesions more frequently than MRI
Schwennicke et al (1998)[129]	19-75	204	Quantitative	72%	NA	US abnormalities appeared 10 days after nerve injury
Motor neuron disease						
SMA Heckmatt et al (1988)[125]	0-17	27	Semi-quantitative	70%	NA	Atrophy is prominent in SMA and other neurogenic disease
Amyotrophic lateral sclerosis						
Arts et al (2012)[38]	23-79	59	Quantitative, fasciculations	96%	84%	US is a promising screening tool for ALS vs. ALS mimics
Grimm et al (2015)[42]	18-90	80	Quantitative US US plus EMG	88% 96%	NA NA	US plus EMG improved the diagnostic certainty of ALS
Johansson et al (2017)[37]	Mean 65	 58	 Quantitative, fasciculations	73%	85%-100%	US detected more muscles with fasciculations in ALS
Tsuji et al (2017)[41]	Mean 71	36	Qualitative, fasciculations	92%	100%	Fasciculation US score from 9 muscles is useful in ALS

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Table 2. *Continued*

Type of neuromuscular disease (NMD)	Age range (in years)	Number of patients	Methods of ultrasound assessment	Sensitivity	Specificity	Comments
ALS vs. MMN Grimm et al (2015)[43]	Mean 65.6 55.6	17 ALS 8 MMN	Quantitative Nerve US	87%	94%	Enlarged nerves/roots in 4 or more areas serve to differentiate MMN from ALS
Loewenbrück et al (2016)[44]	Mean 53.6 65.1	5 MMN 8 ALS	Quantitative Nerve CSA	100%	92%	Nerve US is highly accurate in differentiating between ALS and MMN

ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyneuropathy; CMT = Charcot-Marie-Tooth disease; CSA = cross-sectional area; DMD = Duchenne muscular dystrophy; EI=echointensity; EMG = electromyography; FCU = flexor carpi ulnaris; FDP = flexor digitorum profundus; IBM = inclusion body myositis; ICU = intensive care unit; LFCN = lateral femoral cutaneous nerve; LSS = Lewis-Sumner Syndrome; MMN = multifocal motor neuropathy; MT = muscle thickness; NA = not available; NCS = nerve conduction study; PN = polyneuropathy; SMA = spinal muscular atrophy; US = ultrasound.

In neuralgic amyotrophy, nerve inflammation with enlarged CSA can be seen involving the brachial plexus as well as peripheral nerves in the distal upper arm.[105–108] Focal nerve enlargement can also at times be demonstrated by ultrasound in other axonal inflammatory disorders such as sarcoid neuropathy[109] and neuropathy associated with vasculitis syndromes.[110]

Neurofibromatosis and Neurolymphomatosis

Ultrasound has been used to detect early or subclinical peripheral nerve involvement in neurofibromatosis type 1 (NF1) and 2 (NF2). Affected nerves show focal areas of gross hypoechoic enlargement of the various fascicles. Isolated focal enlargement constitute a localized neurofibroma, while multiple serpentine-like affected fascicles are seen in a plexiform neurofibroma. The abnormalities often extend over long segments of the main limb nerves and can also occur in skin nerve branches (Figure 13).[111–113]

As well, in a recent case report of three adults with lymphoma and clinical evidence of focal neuropathy, nerve ultrasound was helpful in identifying lymphomatous peripheral nerve infiltration or neurolymphomatosis that was subsequently confirmed by biopsy.[114] Therefore, ultrasound may be beneficial for peripheral nerve tumor surveillance in patients with neurofibromatosis and possibly neurolymphomatosis.[115]

Traumatic Nerve Injuries

Ultrasound has also been used to assess patients with focal nerve injuries, including infants with obstetrical brachial plexopathy and adults with acquired peripheral nerve or brachial plexus trauma.[116–117] Pillen et al[118] recently showed that the cervical roots, brachial plexus, and proximal nerves can be visualized by ultrasound as early as the neonatal period, and reference data are available from their standardized nerve ultrasound protocol. As well, Smith et al[119] reported on the utility of ultrasound for patients with combat-related peripheral nerve injuries, in addition to standard clinical, EMG, and MRI exams. In their study, ultrasound was superior to electrodiagnostic test in the ability to clearly demonstrate the specific site of focal nerve involvement among four adults post gunshot or blasts injuries with non-excitable nerve responses; the location was later confirmed by surgical inspection.[119]

Injections for Entrapment Neuropathies

Ultrasound provides clear anatomic landmarks for steroids injections as part of the treatment for entrapment neuropathies;[120] in addition, it can be used to determine the clinical response to treatment. Lee et al found a significant reduction in the median nerve CSA starting 1-week post injection for CTS; changes in ultrasound parameters correlated with patient-reported improvement in pain scores.[121]

Diagnostic Values of Ultrasound in Neuromuscular Disorders

A summary of the diagnostic values for ultrasound in specific myopathies, neuropathies, and motor neuron disorders is provided in Table 2. In experienced hands, ultrasound is a sensitive and specific tool for the detection of many neuromuscular disorders, and it can also be used as a screening tool among children with suspected peripheral nervous system diseases. It is not well suited as a general screening test for metabolic myopathies, and the utility of ultrasound may be reduced in young children under 3 years of age.[23,30] Alternative methods using texture analysis and acoustic structural quantification of sonographic images may further increase the diagnostic utility of ultrasound for many patients with neuromuscular diseases.[122,123]

Conclusion

This review has focused on the clinical applications of nerve and muscle ultrasound. It has shown that neuromuscular ultrasound can provide added diagnostic values in both adult and pediatric neurology practice. Ultrasound can be used as a point-of-care and patient-friendly screening tool for many peripheral nervous system disorders, and it may obviate the need for more invasive testing. It is expected that over the next 5-10 years, neuromuscular ultrasound will play a definitive role in the diagnostic workup for many of these patients.

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Disclosures

The authors have nothing to disclose.

Statement of Authorship

JKM analyzed the literature and drafted the manuscript; NvA performed the literature search, critically revised the manuscript for content and provided the images.

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