Indications for neuromuscular ultrasound: Expert opinion and review of the literature


*Department of Neurology at Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC, USA
†Department of Rehabilitation Medicine, National Institutes of Health, Bethesda, MD 20892, USA
‡Departments of Neurology and Clinical Neurophysiology, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands
§Department of Neurology, Neuromuscular Division, Duke University School of Medicine, Durham, NC, USA
¶Don Carlo Gnocchi ONLUS Foundation, Piazzale Rodolfo Morandi, 6, 20121 Milan, Italy
∥Department of Geriatrics, Neurosciences and Orthopaedics, Università Cattolica del Sacro Cuore, Rome, Italy
¶¶Department of Physical Medicine and Rehabilitation, The Ohio State University, Columbus, OH, USA
####Department of Physical Medicine and Rehabilitation, OhioHealth Riverside Methodist Hospital, Columbus, OH, USA
####Department of Neurology, University Hospitals, Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA
#####Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA
######Hans Berger Department of Neurology, Jena University Hospital, Jena 07747, Germany
#######Department of Neurology and Clinical Neurophysiology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands
########Department of Physical Medicine & Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt
##########Department of Neurology, Yong Loo Lin School of Medicine, National University Singapore, Singapore
###########Department of Neurology, Kantonsspital Lucerne, Switzerland
###########Department of Neurology, Inselpital Bern, Switzerland
###########Department of Physical Medicine and Rehabilitation, Korea University Guro Hospital, Seoul, Republic of Korea
###########Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea
###########Division of Neurology, Department of Medicine, The Ottawa Hospital and University of Ottawa, Canada
###########Department of Clinical Neurophysiology, East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK
###########Department of Neurology, University Hospital Tuebingen, Tuebingen, Germany
###########Division of Neuromuscular Medicine, Department of Neurology, Washington University in St. Louis, 660 S. Euclid Ave, Box 8111, St. Louis, MO 63110, USA

**Article info**

Article history:
Accepted 2 September 2018
Available online xxxx
Keywords:
Neuropathy
Myopathy
Motor neuron disease
Electromyography
Nerve conduction studies
Diaphragm

**Abstract**

Over the last two decades, dozens of applications have emerged for ultrasonography in neuromuscular disorders. We wanted to measure its impact on practice in laboratories where the technique is in frequent use.

After identifying experts in neuromuscular ultrasound and electrodiagnosis, we assessed their use of ultrasonography for different indications and their expectations for its future evolution. We then

**Highlights**

- Experts routinely use ultrasound to evaluate both common and rare disorders of nerve and muscle.
- Accumulated evidence now puts diagnostic neuromuscular ultrasound on par with EMG and NCS.
- Medical centers must acquire ultrasound equipment to keep electrodiagnostic laboratories current.


1388-2457/© 2018 Published by Elsevier B.V. on behalf of International Federation of Clinical Neurophysiology.
identified the earliest papers to provide convincing evidence of the utility of ultrasound for particular indications and analyzed the relationship of their date of publication with expert usage. We found that experts use ultrasonography often for inflammatory, hereditary, traumatic, compressive and neoplastic neuropathies, and somewhat less often for neuronopathies and myopathies. Usage significantly correlated with the timing of key publications in the field. We review these findings and the extensive evidence supporting the value of neuromuscular ultrasound. Advancement of the field of clinical neurophysiology depends on widespread translation of these findings.

© 2018 Published by Elsevier B.V. on behalf of International Federation of Clinical Neurophysiology.
1. Introduction

For much of the last fifty years, there has been remarkable uniformity in electrodiagnostic practice. Aside from the rare patient who might need referral to a specialized center for a single fiber EMG study, patients have been able to receive consistent diagnostic evaluations with comparable results regardless of the size of the laboratory or its geographic location. However, now a number of laboratories provide advanced ultrasound imaging in addition to standard electrophysiological assessment of nerve and muscle, a trend that appears to be accelerating, and this is creating an unprecedented gap between ultrasound enhanced and standard clinical neurophysiology practice.

Over 25,000 papers have now been published in PubMed on diagnostic ultrasound of nerve and/or muscle. It accurately establishes a diagnosis for a wide variety of neuromuscular disorders (Hobson-Webb et al., 2018, Pillen et al., 2016, Cartwright et al., 2012). Furthermore, the technique has also changed the way we think and speak. In the past it was common parlance to say that the nerves in chronic entrapment syndromes were “pinched,” but now we have all seen how they can be focally or diffusely enlarged, subject to dynamic compression or internally distorted (Tagliafico, 2016). The purpose of this study was to conduct a survey of experts to see how neuromuscular ultrasound is changing electrodiagnosis, its scope of applications, and to determine to what extent ultrasound should be considered optional versus necessary in a modern clinical neurophysiology practice. It also looked to see how closely the date of publications on new indications for ultrasound correlated with actual use of the technique, and finally, it reviewed the literature, to present the evidence on the use of ultrasound for neuromuscular indications.

2. Methods

2.1. Expert panel

Members of the expert panel were drawn from suggestions of former journal editors and members of the governance of the International Federation of Clinical Neurophysiology. They were selected from three specialties that routinely practice electrodagnostic medicine: Neurology, Clinical Neurophysiology, and Physical Medicine and Rehabilitation (PMR). Invitations were sent to 22 identified individual experts of whom 19 agreed to participate; 2 who chose not to participate were no longer actively involved with neuromuscular ultrasound and the third felt that expert status had yet to be reached. There were 8 neurologists, 6 clinical neurophysiologists, and 5 PMR physicians. All participants met the following criteria: (a) significant practical experience with the technique; (b) participation in national and international courses teaching neuromuscular ultrasound; and (c) multiple publications in the fields of both electrodagnostic medicine and neuromuscular ultrasound (mean = 57 publications per expert, including 5 textbooks). The panel represented 9 different countries on 4 continents. Since the survey was in part designed to assess the integration of ultrasound into electrodagnostic practice, experts in neuromuscular ultrasound whose primary specialty was radiology or rheumatology were not included, although their contributions to the field are cited throughout.

2.2. Questionnaire

The questionnaire was designed to estimate the frequency that experts use ultrasound for different indications in their practice and how often they used ultrasound prior to electrodagnostic testing. Additional questions were directed at how experts saw the future of the technology, how they characterized its diagnostic usefulness, and what aspects of instrumentation they found most helpful in their current practice. All the participant experts were given the opportunity to provide feedback on the questions prior to completing the survey.

2.3. Survey analysis

The survey on indications was intentionally worded with terms that assessed relative frequency of use. It focused on current usage—not intended usage in the future. Participants were asked if they had patients referred for the indication specified and if so, had they used ultrasound always, often, sometimes, or never in evaluating such patients. Subsequently, the same indications were reviewed to evaluate the expert’s use of ultrasound as the initial diagnostic evaluation prior to electromyography (EMG) and nerve conduction studies (NCS), again, always, often, sometimes or never. For the purposes of analysis and data display, somewhat arbitrary units were assigned (always = 100%, often = 70%; sometimes = 30%, never = 0%). For the portions of the survey assessing instrumentation impact and future expectations for the field, questions also used qualitative terms. The assigned percentage values for these terms is indicated in the figure legends, to help assist in information display. For future expectations, the maximal likelihood score achievable was adjusted to 90%, to indicate the inherent limitations of prediction.

It is recognized that this approach to data display and analysis is non-quantitative, but it was designed to provide a reasonably accurate way to compare the relative usage of ultrasound across...
multiple indications. Similarly, users of clinical rating scales sometimes assign percentages to ordinal data to express relative severity of a disorder or relative change with treatment for primarily descriptive purposes. The experts were not allowed to discuss with one another or see the results of others’ questionnaires until after all the data were collated and only one questionnaire was completed per laboratory. Also, the experts, while completing the survey, were unaware of the intention to compare their responses to the timing of the published literature. A few items had a fair to large number of experts who had not encountered that particular indication (e.g. lepromatous neuropathy), and asterisks in the figures highlight these items.

2.4. Literature review

The review of the literature, for papers cited in the discussion, focused primarily on indications for neuromuscular ultrasound. These were selected based on clinical judgment of their relevance to the field and the strength of the evidence contained. Once compiled, the discussion and citations were circulated among the experts and they were encouraged to provide additional or alternate references if they thought they provided equivalent or stronger evidence than those chosen, or if they addressed other unique aspects of the indication. When available, evidence based reviews were included. All the expert participants reviewed a draft of the manuscript and provided input at the draft stage and all were in agreement with the final draft of the manuscript.

2.5. Additional analysis of index papers

We were curious to see if there was a relationship between the timing of particularly informative papers published on specific indications for neuromuscular ultrasound and their application in practice by this group of experts. For each specific indication for nerve disorders, the literature was searched for the earliest meaningful publication, and the frequency of neuromuscular ultrasound use was correlated with this date. Not all indications had definitive publications, mostly because certain categories were too non-specific (specifically: palpable masses, phobic patients, variant anatomy, ‘other’ entrapment neuropathies, thoracic outlet syndrome, and ‘other’ axonal neuropathies); but of the 30 nerve indications, surveyed, 24 items were specific enough to have identifiable single, early influential publications. These were determined first by searching Google Scholar (“sonography” of the specific indication) and evaluating the top papers listed. The paper that was earliest, with the highest ranking, and that was sufficiently specific (e.g. mentioned the indication in the title or characterized findings in a series of patients on that indication) was chosen. This approach identified 18 of the 24 index papers, 12 (50%) of which were ranked #1 or #2 in Google Scholar, and another 6 (25%) of which were ranked between #3–6. This method did not identify index papers for the other 6 indications (multiple unrelated papers occupied the top ten citations). Those were selected by reviewing all papers in PubMed (“sonography of X”) and choosing the earliest descriptive series of patients that was published on the topic that was sufficiently specific. One paper is a case report in press because no earlier publications are available. Once collated, the group of experts was given a chance to see if there were alternative papers, particularly if from earlier years, that were superior or equivalent to the paper cited. For more details, see Appendix. An evaluation of indications for ultrasound in muscle disorders was not conducted because referrals for primary muscle disease make up only a small fraction of referrals in electrodiagnostic practice.

Once this data was collected, years since publication of the identified key indication paper and frequency of ultrasound use by the expert panel was analyzed to determine if a correlation was present. We hypothesized that the indications with longer intervals since publication of the index paper would correlate with more experts using ultrasound for the given indication.

3. Results

3.1. Indications

Experts use ultrasound for a large number of indications the majority of the time (Figs. 1–5). This ranges from about half of the time for inflammatory myopathies, to significantly more than half the time for diaphragm paresis, motor neuron disease, chronic inflammatory and hypertrophic neuropathies, suspected masses or tumors, brachial plexopathy, entrapment and traumatic neuropathies, unexplained muscle atrophy, and those phobic or unable to tolerate electrodiagnostic studies. Of the items queried, cervical radiculopathy had the least usage, and the technique was used less than half the time in common axonal neuropathies, diabetic amyotrophy, camptocormia, cranial neuropathy, and Guillain Barre syndrome.

Of interest, the association between years since the seminal publication on an indication and the frequency of use of ultrasound showed a moderate correlation with R = 0.56 and robust significance p = 0.004 (Fig. 6).

3.2. Ultrasound first

Ultrasound first is a catchphrase and approach that refers to the use of ultrasound as an initial study to facilitate diagnosis. For neuromuscular ultrasound this sometimes refers to use in the clinic to evaluate patients with complex and undiagnosed muscular dystrophy to guide the choice of subsequent gene tests (Bönnemann et al., 2014). In this survey, we queried experts regarding the frequency with which they have used ultrasound before performing either EMG or NCS studies for patients referred to their laboratory (Figs. 1–5). We found that at least some of the surveyed experts have used ultrasound first for virtually all the indications listed, and the majority of experts believe that ultrasound first will become routine for a select group of disorders in the future.

3.3. Usefulness of ultrasound components and future expectations for the field

One participant did not complete this portion of the survey, and several participants did not answer one or two of the questions in it because they were unsure how to respond. Therefore, each question in Figs. 7–9 indicates the number of respondents per item and the distribution of those responses.

The most useful aspects of neuromuscular ultrasound, according to the experts, are that it helps define anatomy, discovers unexpected findings, and complements electrodiagnostic testing (Fig. 7). Experts also find modest to moderate added value in the ability of ultrasound to assess nerve movement, image real-time blood flow in nerve and muscle, and display fascicular anatomy. Of available ultrasound instrumentation, the experts find high-resolution transducers and color and power Doppler imaging to be of considerable benefit in daily practice (Fig. 8). Experts find moderate benefit from extended field of view ultrasound and quantitative gray scale analysis. Contrast agents, speckle tracking, elastography, and 3-D ultrasound are considered of limited benefit at this time, but it should be noted that these are new technologies that are not widely available and have yet to be thoroughly studied (Gasparotti et al., 2017; Goutman et al., 2017; Motomiya et al., 2017; Dikici et al., 2017; Kwon et al., 2014).
The experts uniformly agree on the high likelihood that more laboratories will adopt neuromuscular ultrasound, it will become a key element in training residents and fellows, its role in neuromuscular research will continue to expand, and the technology will continue to improve (Fig. 9). Further, the consensus was strongly positive for every future application assessed.

4. Discussion

Experts who are already highly skilled in electrodiagnosis use neuromuscular ultrasound frequently for multiple indications. Once adopted for one indication, its usage quickly spreads across multiple indications. The discussion is designed to (A) summarize...
NERVE DISORDERS: Focal

- Tarsal tunnel syndrome (NC=0) [31%]
- Fibular neuropathy at the knee (NC=0) [29%]
- Ulnar neuropathy at the elbow (NC=0) [31%]
- Carpal tunnel syndrome (NC=0) [37%]
- Other entrapment neuropathy (NC=1) [29%]
- Traumatic neuropathy (NC=1) [29%]

Never | Ultrasound Ever | Ultrasound First | Always
--- | --- | --- | ---
0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100%

Fig. 3. This figure uses the same display strategies outlined in Fig. 1 but for another group of indications.

NERVE DISORDERS: Polynuropathy, primarily demyelinating

- CIDP (NC=1) [19%]
- Multifocal motor neuropathy (NC=1) [19%]
- CMT (NC=1) [26%]
- HNPP (NC=0) [23%]
- Guillain Barre syndrome (NC=0) [9%]

Never | Ultrasound Ever | Ultrasound First | Always
--- | --- | --- | ---
0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100%

Fig. 4. This figure uses the same display strategies as outlined in Fig. 1, for a different group of indications.

NERVE DISORDERS: Motor or sensory neuronopathy or axonal polynuropathy

- ALS/motor neuron disease (NC=0) [23%]
- Non-diabetic axonal neuropathy (NC=0) [4%]
- Diabetic polyneuropathy (NC=0) [7%]
- Sensory neuropathy (NC=1) [6%]
- Toxic neuropathy (NC=0) [8%]

Never | Ultrasound Ever | Ultrasound First | Always
--- | --- | --- | ---
0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100%

Fig. 5. This figure uses the same display strategies as outlined in Fig. 1. These indications are labeled as situational, as they are not tied to a specific diagnosis.

the evidence supporting the indications for neuromuscular ultrasound (Section 5), (B) address the likelihood of the continued evolution and value of neuromuscular ultrasound (Section 6) and (C) characterize the translational implications of these findings (Section 7). The first of these, Section 5, is, by necessity, the longest as it surveys the breadth of existing literature on neuromuscular ultrasound (note, less than 1% of the available literature is cited.)

5. The rationale underlying indications for neuromuscular ultrasound: A review

This section highlights the published evidence to date on the variety of indications or the use of neuromuscular ultrasound. Many of the indications are related and most of the pathologic changes described for nerve and muscle (e.g. muscle atrophy, nerve enlargement, and altered echogenicity) are common to multiple disorders. The selection of citations was designed to help the interested reader find a few representative papers for each indication; an exhaustive review is beyond the scope of this paper. Those engaging in a more in depth search of these topics will find that the numbers of studies on neuromuscular ultrasound, the absence of conflicting evidence and the consistency of findings further attests to its usefulness.

5.1. Generalized muscle disorders:

The first indication ever discovered for neuromuscular ultrasound was for primary muscle diseases. (Heckmatt and Dubowitz, 1980). The Heckmatt grading scale (Heckmatt et al., 1982), which rates echointensity of the muscle and the visibility of the signal of the subjacent bone into 4 levels, is still used for grading ultrasound images of muscle involvement in a variety of myopathic and neurogenic disorders. Quantitative assessment is also possible (Scholten et al., 2003). The changes on ultrasound (and on MRI and CT) primarily reflect the gradual atrophy and loss of healthy myocytes and their replacement by fat and fibrous tissue (Reimers et al., 1993a; Pillen et al., 2009). It was noted early on that ultrasound was relatively insensitive in distinguishing end stage muscle disease from end stage neurogenic disorders, and that the interpretation of muscle ultrasound often takes place in the context of broader clinical and laboratory assessments.

5.1.1. Inclusion body myositis (52%/16%)

The percentages shown are the estimated use frequency from Figs. 1–5, first showing the usage of ultrasound for the disorder (52%), and second showing the usage of ultrasound first (prior to other electrodiagnostic studies) (16%).

Inclusion body myositis is one of the few common muscle disorders with a characteristic signature on ultrasound in which the flexor digitorum profundus is significantly more echogenic and atrophic than the adjacent flexor carpi ulnaris. A single ultrasound image of these adjacent muscles highlights this striking disparity (Vu and Cartwright 2016, Noto et al., 2014). In the majority of cases a similar disparity has been noted in the lower limb, with increased echogenicity in the gastrocnemius compared to the soleus muscle (Nodera et al., 2016). In ALS or polymyositis, disorders commonly confused with inclusion body myositis, adjacent muscles are almost always equally involved. It is not known to what extent other less common myopathies may show a pattern similar to that seen in inclusion body myositis, but this is a topic under active study. In affected patients, the distinguishing ultrasound findings, which can be acquired quickly without discomfort, help narrow the differential diagnosis and limit the number of additional electrodiagnostic studies needed to establish a diagnosis.

5.1.2. Other inflammatory myopathies: dermatomyositis (51%/11%) and polymyositis (45%/11%)

In the acute phase, polymyositis and dermatomyositis are characterized by normal or increased muscle thickness, sometimes with evidence of fasciitis manifest as increased fascial thickness,
increased blood flow on color Doppler or reduced echointensity. Tissue enlargement and hypoechogenicity in these disorders may result from increased blood flow, which can sometimes be identified with increased power Doppler signal as well (Yoshida et al., 2016, Bhansing et al., 2015, Habers et al., 2015). With chronicity, the muscle becomes more echogenic and atrophy develops with decreased blood flow (Reimers et al., 1993a; 1993b). Because the clinical examination, muscle biopsy, EMG and serum CK are typically quite informative in polymyositis and dermatomyositis, the role for ultrasound is discretionary. The appearance of subcutaneous edema (early) and calcification (late) in affected patients can provide additional helpful information regarding the acuteness or chronicity of the disorder.

5.1.3. Muscular dystrophy (44%/11%)

Although neuromuscular ultrasound findings in muscular dystrophy can be prominent (Heckmatt and Dubowitz, 1980, Heckmatt et al., 1982), the added value of ultrasound imaging in the more common muscular dystrophies is modest as diagnosis can often be made clinically and confirmed with blood tests. Dynamic imaging of dystrophic muscle can also be of value in that the relaxation time of percussed muscle can be used in the assessment of myotonia (Abraham et al., 2018). For less common muscular dystrophies, the distribution of imaging findings among different muscles can help in the selection of the most appropriate genetic study (Bönnemann et al., 2014; Zukosky et al., 2015; Brockman et al., 2007). For example, in Bethlem myopathy muscle ultrasound reveals increased echointensity in the center of the rectus femoris (the central shadow sign) (Pillen et al., 2008, Bönnemann et al., 2003). Unlike MRI or CT, which require scheduling and may involve radiation or sedation, ultrasound can be performed at the point of care, speeding up the evaluation and reducing risk and cost. In patients with only mild weakness, ultrasound can be used to identify muscles with high yield for EMG or biopsy (Heckmatt and Dubowitz, 1987; Lindequist et al., 1990).

Fig. 7. This figure demonstrates the self-reported assessment of how much each of the aspects of ultrasound imaging contributes to its diagnostic impact in practice. In parentheses is the absolute number of responses for each category by the 18 experts: Not at all = 0%, somewhat = 30%, A moderate amount = 70%, a great deal = 90%. Note that the highest possible score using this grading system would be 90%. Note that one participant did not address the survey questions in Figs. 7–9, and a few participants did not answer one or two of the questions because they were unsure as to how to best respond.

Fig. 8. This figure demonstrates the self-reported assessment by the experts of how much each of the instrumentation features added to the diagnostic value of ultrasound imaging. In parentheses is the absolute number of responses for each category: None = 0%, very little = 10%, somewhat = 30%, a moderate amount = 70%, or a great deal = 90%. Note that the highest possible score would be 90% using this grading system. (See Fig. 7 legend for additional details).
5.2. Muscle disorders, localized

5.2.1. Diaphragm paresis (66%/40%)

The experts most frequently use muscle ultrasound for the evaluation of diaphragm paresis. In large part this relates to the challenges posed by electrodiagnostic study of this muscle. The diaphragm does not lend itself to belly-tendon electrode placement for nerve conduction studies and co-stimulation artifact from the brachial plexus can further complicate interpretation. Further, needle electromyography (EMG) of the diaphragm poses a risk of pneumothorax, which can be life threatening in a patient with pre-existing respiratory dysfunction. Few electrodiagnostic laboratories routinely perform diaphragm studies.

Ultrasound is sensitive and accurate for diagnosing diaphragm paresis (Boon et al., 2014). It provides a non-invasive view of diaphragm muscle thickness and echogenicity at rest and with maximal activation, and allows for reliable side-to-side comparison. It is superior to fluoroscopic evaluation for detecting paresis (Boon et al., 2014). Furthermore, ultrasound is helpful for EMG studies in that it can be used to guide needle placement or to estimate the depth and location of the diaphragm, thus substantially reducing the risk of complications (Boon et al., 2008; Harper et al., 2013; Shahgholi et al., 2014). It is a technique which may be used as the first and/or only test for assessing diaphragm function in a clinical neurophysiology laboratory.

Recent papers suggest a role for ultrasound in evaluating patients in the intensive care unit prior to extubation and for assessing the potential benefit of diaphragmatic pacing (Zambron et al., 2017; Sklasky et al., 2015). Given the vital importance of diaphragm function, further ultrasound indications are likely to evolve (Harlaar et al., 2018).

5.2.2. Selective muscle atrophy (61%/30%)

Occasionally patients present with unexplained muscle atrophy. Ultrasound can quantify the degree of atrophy, and based on the echogenicity of the muscle, it can provide information regarding its chronicity. Ultrasound screening can provide additional useful information regarding involvement of other affected muscles as well, often providing insight into its cause. In extreme cases of profound atrophy the affected muscle may be electrically silent, showing neither insertional activity nor motor unit potentials (Walker and Macdonald, 2012). Ultrasound is often used by experts to evaluate unexplained focal muscle atrophy because it helps the design of subsequent electrophysiologic studies and may facilitate pattern analysis of additional affected and unaffected muscles before performing extensive electromyography. Ultrasound can also help guide needle placement in an atrophic muscle to ensure that the needle is not inserted into an uninvolved deeper muscle or other vital structure (Boon et al., 2014).

5.2.3. Intramuscular cysticercosis (50%/0%)** (Two asterisks mean that less than half the experts have seen patients with this indication, one asterisk means that 6–9 of the experts have not seen it)

This is a rare disorder, and few of the experts have seen cases where this disorder was suspected. Ultrasound reveals a cystic structure in muscle, sometimes also demonstrating a calcified sclerotic (Nagaraju et al., 2015, Kanhere et al., 2015, Chaudhary, 2014), which in the proper clinical setting is highly suggestive of the diagnosis. Because electrodagnosis is uninformative in this disorder, neuromuscular ultrasound is of particular value.

5.2.4. Ultrasound guidance of chemodenervation (41%/24%)

Ultrasound is a proven tool for guiding local anesthetic injections and soft tissue biopsies, so it is not surprising that ultrasound is also effective for guiding botulinum toxin injections (Alter et al., 2013; Alter and Karp 2017). The impact of ultrasound has been documented to result in better outcomes in spasticity and dystonia for botulinum toxin injections (Picelli et al., 2012, Walter et al., 2018) and when combined with e-stimulation, for phenol injections as well (Matsumoto et al., 2017). Of interest, subspecialists in PMR, familiar with ultrasound guidance for joint injections, tended to be more likely users of this technique than clinical neurophysiologists or neurologists in this survey. Ultrasound guidance of botulinum toxin also proves helpful in patients who have complications from misplaced EMG needle guided injections (Hong et al., 2012). Ultrasound can assist in identifying the cricothyroid membrane or muscle in patients requiring botulinum toxin for voice disorders and spastic dysphonia (Siddiqui et al., 2015, Yang et al., 2015). For subjects in whom muscle localization is challenging, ultrasound is attractive for injection guidance because it can be used along with EMG needle guidance and electrical stimulation.
5.2.5. Camptocormia (38%/24%)  
Camptocormia refers to a syndrome in which patients have an unusual bent-spine posture when upright which remits on becoming supine. Although rare, it can be seen in association with Parkinson’s disease or neuromuscular disorders (Ghosh and Milone, 2015), its causes are disparate, either resulting from dystonic contraction of trunk flexors or from a myopathy affecting spine extensors (Sakai et al., 2017, Bertram and Colosimo, 2016, Bertram et al., 2015). Ultrasound is helpful in distinguishing these causes as it can identify hypertrophy of flexor muscles if they are dystonic and atrophy and increased echogenicity of extensor muscles if they are myopathic. Since the myopathy that causes camptocormia is often atypical, using multiple modes of diagnostic evaluation (i.e. imaging and EMG) is often helpful in confirming its presence and assisting with proper biopsy guidance. Correct diagnosis of dystonic camptocormia can help determine if a trial of DBS or botulinum toxin might be appropriate, treatments that would be unhelpful or pose risks if the disorder is caused by myopathy.

5.3. Nerve disorders

5.3.1. Regional or multifocal (primarily axonal) nerve disorders  
5.3.1.1. Nerve tumor or neuroma (89%/47%) (Beggs et al., 1999—index paper). Although electrodiagnosis can localize pathology to a segment of nerve, it is insensitive for characterizing pathology within this segment. Neuromuscular ultrasound is capable of identifying tumors or neuromas, which may even occur at common entrapment sites (Telleman et al., 2017a, 2017b, Zhang et al., 2016, Tahiri et al., 2013, Gruber et al., 2007 Hobson Webb and Walker 2004, Beggs et al., 1999). Although not explored in this survey, recent studies have demonstrated the potential usefulness of intra-operative ultrasound in guiding surgical management of nerve tumors as well (Simon et al., 2014; Jose et al., 2014). Ultrasound can help distinguish affected from unaffected fascicles in such cases, and can also be useful for screening multilocular tumors as seen in neurofibromatosis (Winter et al., 2017; Telleman et al., 2018b, 2017a, 2017b).

5.3.1.2. Nerve torsion (81%/26%)* (Aryanyi et al., 2015—index paper). Of recent interest, has been the reported association of brachial neuritis with nerve torsion, particularly in the radial nerve, which may develop acutely or chronically in association with brachial neuritis (Pan et al., 2014; Arányi et al., 2017, 2015; Shi et al., 2018; Samarawickrama et al., 2016a). Ultrasound reveals focal acute constrictions or fascicular entwinement within a nerve which appear as beading. Although electrodiagnostic studies can identify severe axonal injury, only imaging studies such as ultrasound can identify the signature features of this disorder which may prompt urgent surgical evaluation.

5.3.1.3. Thoracic outlet syndrome (75%/23%) (no index paper identified). The challenge of establishing a diagnosis and identifying patients likely to respond to surgery for thoracic outlet syndrome is well known (Ferrante and Ferrante, 2017; Strakowski, 2013; Simmons, 2013). Ultrasound offers several clues to its presence, including the ability to identify cervical ribs or fibrous bands that may impinge on the brachial plexus, and the ability to identify focal swelling of nerve trunks or roots (Arányi et al., 2016, Mangruikar et al., 2008). It also has a unique value for dynamic assessment of potentially compressing muscles, such as the scalenes and pectoralis minor with provocative clinical maneuvers (Sücher 2012). Although well studied in other disorders of the brachial plexus, neuromuscular ultrasound in neurogenic thoracic outlet syndrome has yet to be systematically studied, in part due to the lack of a gold standard for its diagnosis.

5.3.1.4. Neurolymphomatosis (73%/33%)* (Vijayan et al., 2015—index paper). Cases of neurolymphomatosis have been seen by only a few of the surveyed experts. It may present as either polineuropathy or mononeuropathy with either diffuse of focal enlargement of nerves (Vijayan et al., 2015). A significant increase in intraneural blood flow may be seen on power Doppler imaging which facilitates diagnosis of this rare disorder (Walker and Cartwright 2015).

5.3.1.5. Brachial plexopathy (72%/24%) (Martinoli et al., 2002a—index paper). Electrodiagnostic evaluation of plexus lesions is limited in that short segment motor or sensory nerve conduction studies are difficult and distal nerve conduction studies and needle EMG are suboptimal for precise localization. In contrast, ultrasound can provide exquisite detail of the brachial plexus and its many branches as well as related structures in the neck that can contribute to nerve compression (Martinoli et al., 2002a, Baute et al., 2018). However, the brachial plexus is a challenging area in which to develop expertise in neuromuscular ultrasound (Somashekar, 2016, Smith et al., 2016). MR imaging is an alternative, albeit one with possibly lower sensitivity and specificity (Zaidman et al., 2013a).

5.3.1.6. Neurofibroma (71%/48%) (Telleman et al., 2017a; 2017b—index papers). Recent reports have suggested a potentially promising role for identifying and following neurofibromas in patients with neurofibromatosis, tumors which may undergo malignant transformation (Telleman et al., 2018b, 2017a; Winter et al., 2017). The low cost and ease of use of ultrasound make it ideal as a screening tool, but further studies are needed to determine how it can best be used in managing patients.

5.3.1.7. Lepromatous neuropathy (66%/26%)* (Martinoli et al., 2000—index paper). Few of the experts have seen cases of lepromatous neuropathy as it is rare in their geographic areas of practice. However, ultrasound can be quite helpful in diagnosis with nerve enlargement sometimes most prominent in the ulnar nerve just proximal to the medial epicondyle, often with increased vascularity. (Bathala et al., 2017, 2012; Jain et al., 2016; Martinoli. 2000). From a public health perspective, the portability of ultrasound devices, which can be battery or solar powered, makes them particularly attractive for screening individuals in areas without access to modern infrastructure who may be at increased risk for leprosy or cysticercosis.

5.3.1.8. Brachial neuritis (63%/21%) (Arányi et al., 2015—index paper). Imaging in brachial neuritis has been quite informative. Both by MR and ultrasound, this disorder can cause torsion or multifocal abnormalities in peripheral nerves at multiple levels throughout the upper limb (Arányi et al., 2017, 2015; Gruber et al., 2017; Abraham et al., 2016; Lieba-Samal et al., 2016; Van Allen 2017). In addition, the identification of focal enlargement of limb nerves or individual proximal nerve fascicles by ultrasound provides evidence of this disorder. Such findings, in patients with signs of anterior interosseous (or other focal) neuropathy but with a history suggestive of brachial neuritis, can help avoid the need for surgical exploration for suspected entrapment. Ultrasound can also identify patients for surgical intervention should they show evidence of nerve torsion with distal loss of function.

5.3.1.9. Diabetic amyotrophy (28%/4%) (An et al., 2018—index paper). Clinical evaluation and electrodiagnostic testing are usually definitive in diabetic amyotrophy. However, ultrasound can be of value in evaluating muscle involvement and chronicity. A recent case suggests that proximal lower limb motor and sensory nerves may show focal changes on ultrasound extending beyond the expected radiculoplexus distribution, but more studies are
needed (An et al., 2018). The deep location of the lumbosacral plexus makes it inaccessible to routine ultrasound imaging; here MRI is the preferred technique.

5.3.1.10. Cranial neuropathy (22%/6%) (Cartwright et al., 2009—index paper). Cranial neuropathies are an emerging area of investigation by ultrasound in part because of the recent improvements in ultrasound resolution and in part because of the challenge of evaluating cranial nerves with electrophysiology (Smith, 2018, Stino and Smith, 2018). Cranial nerves 1, 3, 4, 5, 6, 8, 9 are difficult to visualize on ultrasound (Tawfik et al., 2015). The optic nerve is readily imaged, but caution should be taken to ensure that power settings on the instrument (and use of color flow imaging) are limited to avoid inadvertent injury to the eye. As it is often considered part of the CNS, it is not discussed further in this review (Tawfik et al., 2017). However, the extent to which ultrasound can visualize cranial nerves is limited, and with increasing experience with the technique new indications may evolve.

5.3.1.11. Cervical radiculopathy (12%/6%) (Kim et al., 2015—index paper). A few publications have suggested that ultrasound can identify nerve enlargement in cervical spinal nerves just as they exit the neural foramen in radiculopathy (Takeuchi et al., 2017; Metin Ökmen et al., 2018; Kim et al., 2015), but further studies are needed. Expert use of ultrasound is limited in this area, but expertise in imaging the spinal nerves in a common disorder such as cervical radiculopathy could have additional value in helping electrodiagnosticians acquire skill in brachial plexus imaging.

5.3.2. Focal nerve disorders

Ultrasound is helpful in entrapment neuropathies in a variety of ways. It provides anatomic confirmation of focal neuropathy which is particularly useful when electrophysiological studies are borderline or non-localizing. It also can identify unexpected anatomic lesions that can cause nerve compression, such as cysts, foreign bodies or tumors, which may be electrophysiologically indistinguishable from common entrapment. Ultrasound also provides additional physiologic information, such as nerve vascularity and mobility that may be of help in evaluating pathophysiological mechanisms (Park et al., 2018; Dejacso et al., 2013).

5.3.2.1. Tarsal tunnel syndrome (89%/31%) (Nagaoka et al., 2005—index paper). Some studies suggest electrodagnostic techniques have relatively poor accuracy for identifying tibial neuropathy at the tarsal tunnel (Doneddu et al., 2017). Ultrasound can be used to identify anatomic structures in the tarsal tunnel that could predispose to neuropathy such as lipomas, varicosities, ganglion cysts or tenosynovitis. In addition, it provides a direct evaluation of the size and fасicular anatomy of the tibial nerve (Nagaoka et al., 2005, Tawfik et al., 2016). A recent review concludes that imaging may be more informative than electrodagnostic in this disorder likely accounting for expert interest in the technique (Doneddu et al., 2017; Iborra et al., 2018). In one recently reported series, ultrasound was abnormal in all cases of electrodagnostically verified tarsal tunnel syndrome (Samarawickrama et al., 2016b).

5.3.2.2. Fibular neuropathy (88%/29%) (Visser 2006—index paper). Fibular neuropathy at the knee provides a compelling rationale for the use of ultrasound for diagnosis because ultrasound sometimes demonstrates a surgically correctible intraneural ganglion cyst (Spinner et al., 2008). This finding is more common in patients lacking another cause for the disorder such as leg crossing, squatting or weight loss (Visser 2006, Cartwright and Walker 2013, Visser et al., 2013). Electrophysiological findings alone cannot exclude the presence of such a cyst, and given the higher resolution of ultrasound than MRI, ultrasound appears more sensitive for their detection (Wilson et al., 2017). The common fibular nerve can also be severely injured from knee dislocations and other trauma in that region. The anatomic correlation provided by ultrasound in these types of injuries includes nerve stretch, compression from hematoma, transection, projectile penetration or muscle tear and can assist with proper diagnosis and management (Zywiel et al., 2011, Marciniak 2013, Grant et al., 2015). Ultrasound can also help identify variant fibular nerve anatomy that may complicate interpretation of nerve conduction studies (Luchetta et al., 2011).

5.3.2.3. Ulnar neuropathy at the elbow (84%/31%) (Beekman et al., 2004—index paper). Ultrasound also provides a particularly useful assessment of the ulnar nerve at the elbow (Yoon et al., 2010; Yoon et al., 2008, Beekman et al. 2004a). Nerve conduction studies are less sensitive for diagnosing this disorder than carpal tunnel syndrome. One complicating factor is subluxation or dislocation of the ulnar nerve over the medial epicondyle with elbow flexion in some individuals. In such cases, the measurement of the expected course of the ulnar nerve around the elbow overestimates the true length of the nerve, which leads to a nerve conduction velocity calculation that may miss true slowing (Childress, 1975; Kim et al., 2005, 2008). Recent papers have suggested that dislocation, in which the nerve completely pivots around the medial epicondyle may be protective, whereas, subluxation, where it rises up on the medial epicondyle, but does not dislocate, may place the nerve just deep to the skin adjacent to the medial epicondyle where it is vulnerable to pressure at the elbow (Leis et al., 2017). However, the extent to which subluxation actually puts the nerve at risk is debated. (Van Den Berg et al., 2013). Ultrasound imaging, with a bit of practice, provides a more precise assessment of this type of nerve movement than palpation, particularly in obese patients or in those who have had previous ulnar nerve surgery. It also can be used to assess the influence of the medial triceps brachii muscles on subluxation and compression of the nerve (Jacobson et al., 2001).

Reference values for the ulnar nerve show consistency across multiple studies (Fink et al., 2017; Terayama et al., 2018). Of additional interest, ultrasound can help pinpoint the lesion to the retroepicondylar groove (sulcus olecrani), most often seen in desk workers, or the humerolunar arcade (cubital tunnel proper) below the attachment of the flexor carpi ulnaris muscle just distal to the elbow, more commonly seen in manual workers (Omejec and Podnar, 2016). Ultrasound is effective for detection of anatomic variations such as an anconeus epitrochlearis muscle that can predispose to nerve compression, particularly in younger individuals (Lee et al., 2016; De Maeseneer et al., 2015). Further, ultrasound is helpful in identifying ulnar nerve pathology in symptomatic patients in whom electrodiagnosis is normal (Yoon et al., 2010) and, in conjunction with nerve conduction studies, may also help predict the results of surgical intervention (Beekman et al., 2004b). Ultrasound also is useful for assessing post-surgical problems, as it can identify undesired positioning of the nerve, excessive mobility or subluxation, kinking, persistent focal notching and post-surgical scarring (Gruber et al., 2015, Duetzmann et al., 2017). Ultrasound imaging also can help identify focal nerve compression at the retroepicondylar groove (sulcus olecrani) or the humerolunar arcade (cubital tunnel proper) below the attachment of the flexor carpi ulnaris muscle just distal to the elbow, as well as identify other causes of ulnar mononeuropathy such as a previous ulnar nerve surgery (Leis et al., 2017). Ultrasound can also help identify variant fibular nerve anatomy that may complicate interpretation of nerve conduction studies (Luchetta et al., 2011). Ultrasound imaging can also help identify focal nerve compression at the retroepicondylar groove (sulcus olecrani) or the humerolunar arcade (cubital tunnel proper) below the attachment of the flexor carpi ulnaris muscle just distal to the elbow, as well as identify other causes of ulnar mononeuropathy such as a previous ulnar nerve surgery (Leis et al., 2017). Ultrasound can also help identify variant fibular nerve anatomy that may complicate interpretation of nerve conduction studies (Luchetta et al., 2011).
Further investigation of how ultrasound can enhance management and outcomes is needed (Cartwright et al., 2015).

5.3.2.4. Carpal tunnel syndrome (82%/37%) (Buchberger et al., 1991—index paper). Neuromuscular ultrasound is supported by level A recommendation for the diagnosis of carpal tunnel syndrome (Cartwright et al., 2012). Further, neither NCS nor ultrasound have been shown convincingly to be diagnostically superior to one another; rather they are essentially of equivalent value. Of interest, up to 25% of false negative ultrasound studies in CTS may result from isolated enlargement of the median nerve in the distal carpal tunnel or palm instead of the wrist, and this should be taken into account in any future studies comparing the two approaches (Paliwal et al., 2014; Csillik et al., 2016). Ultrasound evaluation of the median nerve in suspected carpal tunnel syndrome should include, at a minimum, distal and proximal portions of the nerve in the hand; blood flow imaging may also be of benefit (Karahan et al., 2018).

Ultrasound imaging of the median nerve in CTS adds value to NCS in several ways. First, it provides anatomic evidence of focal enlargement that is independent of electrophysiological findings. Second, it provides a structural baseline for subsequent studies, complementing the physiological baseline provided by NCS should patients need to be restudied for treatment failure. For example, ultrasound can identify focal pathology in the recurrent branch of the median nerve a structure sometimes injured during surgery (Smith et al., 2017; Kiefer et al., 2017). Third, it sometimes identifies unexpected causes or contributing factors not evident by electrodiagnosis including tumor, accessory muscles, or thrombosis of a persistent median artery (DeFranco et al., 2014; Walker et al., 2012; Rzpecka-Wejs et al., 2012; Padua et al., 2006). Fourth, it can identify variants, such as Martin-Gruber anastomosis, which can complicate interpretation of nerve conduction studies (Gans and van Alfen, 2017). Fifth, ultrasound of carpal tunnel syndrome, the best understood, easiest to image, and most frequently encountered focal neuropathy, helps practitioners hone and maintain ultrasound imaging skills in identifying neuromuscular pathology. These include changes in echogenicity and nerve shape that accompany entrapment, atypical nerve branching, persistent median artery, anomalous tendon, nerve and muscle anatomy, loss of normal nerve sliding and movement relative to the tendons with wrist/finger flexion and extension, increased nerve vascularity, and neuorgenic atrophy and hyerechogenicity in muscles innervated by the median nerve.

5.3.2.5. Other entrapment neuropathy (81%/29%) (no index paper identifiable). When relatively uncommon entrapments are suspected, most of the experts find ultrasound of benefit in part because unexpected anatomic pathology is likely to be more often found in such disorders. Furthermore, in many less common neuropathies, short segment nerve conduction studies are not always possible. In such cases, ultrasound could be used to enhance near nerve studies, should they be desired (Deimel et al., 2013). Patients anxious to find the cause of their symptoms, particularly if electrodiagnostic studies are negative, are often reassured by ultrasound, even if it too yields negative results. Of note, this survey did not specifically address the use of ultrasound in meralgia paresthetica, posterior interosseous neuropathy, or other disorders of smaller nerves, specific indications for which there is increasing evidence of its value. (Walker, 2017; Kim et al., 2017; Hung et al., 2016; Moritz et al., 2013; Diemel et al., 2013; Aravindakannan and Wilder-Smith, 2012; Kim et al., 2012). Of particular interest is “double crush” syndromes in which ultrasound can rapidly screen for a second focal neuropathy in a patient with compression at a distal or proximal site of the same nerve (Dietz et al., 2016; Erra et al., 2016; Lee et al., 2016). Also not addressed in this report, are uses of ultrasound for evaluating bowel and bladder dysfunction an area of active ongoing research (Tagliafico et al., 2014).

5.3.2.6. Traumatic neuropathy (81%/29%) (Cartwright et al., 2007—index paper). Perhaps the most persuasive outcomes evidence for the use of neuromuscular ultrasound is in suspected traumatic neuropathy (Renna et al., 2012; Chin et al., 2017; Burks et al., 2017; Lauretti et al., 2015). In these cases, ultrasound modifies the diagnosis and treatment plan in up to 58% of studies (Padua et al., 2013, 2012). Discoverable pathology ranges from transection, to scar tissue formation, to bony entrapment of nerves in fractures or callous. Transection is of particular importance, as electrodiagnostic studies alone cannot distinguish between transection and acute complete neuropahty or chronic complete axonotmesis (Bianchi et al., 2014; Walker, 2017; Cartwright et al., 2007). Delaying surgery, even by a few weeks, to repair transection results in worse outcomes so the ability to detect transection early is of prognostic significance. Furthermore, ultrasound can help identify nerve lesions distant from the trauma site, for example posterior interosseous neuropathy may develop in patients with radial nerve compression from humeral fractures (Erra et al., 2016). Finally, ultrasound may help in management and prognostication after traumatic neuroma (Coraci et al., 2015). Distinguishing lesioned from unlesioned fascicles and extraneuronal from intraneuronal scarring, fibrosis or hematoma can help guide surgical intervention. Not surprisingly, a majority of the experts frequently use ultrasound in suspected nerve trauma.

5.4. Generalized primarily demyelinating nerve disorders

5.4.1. Charcot Marie Tooth (CMT) (76%/25%) (Martinoli et al., 2002b—index paper)

Ultrasound demonstrates striking, diffuse, nerve enlargement in CMT type 1, the most common form of hereditary hypertrophic neuropathy. The abnormality is present from a very young age, is more prominent proximally, and is associated with significant enlargement of individual nerve fascicles (Telleman et al., 2018a; Yiu et al., 2015; Martinoli et al., 2002b). A quick ultrasound scan, even of one or two nerves is highly informative, and can be used to screen family members of affected patients. Given the harm that chemotherapy can cause in such patients, a quick and painless screening tool for patients suspected of having the disorder is of value. Of note, the absence of profound nerve enlargement does not exclude axonal forms of CMT, but nerves may be moderately enlarged in these disorders as well (Padua et al., 2018; Schreiber et al., 2013). A recent report also suggests that nerve enlargement may be seen in children with Dejerine-Sottas disease (Hobbelman et al., 2018), and is prominent in CMT1B (Cartwright et al., 2009).

5.4.2. Chronic inflammatory demyelinating polyneuropathy (CIDP) (83%/19%) and multifocal motor neuropathy (MMN) (76%/19%) (Sugimoto et al., 2013; Zaidman et al., 2013b—index papers for CIDP; Beekman et al., 2005 index paper for MMN)

These two disorders are discussed together because a number of recent neuromuscular ultrasound papers include both disorders. In both, ultrasound typically demonstrates significant, multifocal nerve enlargement particularly in the proximal median and ulnar nerves and brachial plexus, not always associated with clinical dysfunction in the same distribution. Several grading scales and protocols for determining abnormality have been proposed (Grimm et al., 2016a; Kerasnoudis et al., 2016; Padua et al., 2014; Jang et al., 2014) and perhaps the simplest of these is most attractive (Goeede et al., 2017). Given the risk and expense of treating CIDP and MMN with steroids, IVIG, or chemotherapeutic agents it makes sense to use both imaging and electrophysiology to establish a diagnosis. Furthermore, ultrasound may help differentiate suba-
5.4.3. Hereditary neuropathy with liability to pressure palsies (HNPP) (68%/23%) (Beekman et al., 2002—index paper)

Hereditary neuropathy with liability to pressure palsies (HNPP) also demonstrates striking multifocal nerve enlargement by ultrasound, but unlike CIDP or MMN, the distribution of findings in HNPP is selective to sites of enhanced anatomic vulnerability (Padua et al., 2018).

5.4.4. Guillain Barre syndrome/acute inflammatory demyelinating polyneuropathy (AIDP) (54%/9%) (Zaidman et al., 2009—index paper)

Electrophysiologic testing early in GBS shows a number of specific and informative findings for diagnosis (Alberti et al., 2011). Of interest, ultrasound may also show changes, even early in the disease course or in variant forms, with enlargement in proximal spinal nerves (Berciano et al., 2017, 2014; Mori et al., 2016, Razalli et al., 2016, Grimm et al., 2016b, 2014a, Gallardo et al., 2015). This is of interest, since delayed motor root conduction latencies are also an early finding in this disorder (Temucin and Nurku 2011). In the future, experts may choose to use ultrasound more frequently in the evaluation of Guillain Barre Syndrome if studies show it can inform prognosis.

5.5. Generalized primarily axon/motor neuron loss disorders

5.5.1. Motor neuron disease and amyotrophic lateral sclerosis (ALS) (77%/23%) (Arts et al., 2008—index paper)

Ultrasound is a particularly sensitive tool for detecting fasciculations in muscle (Walker et al., 1990). Now that the Awaji criteria include fasciculations as part of the diagnostic criteria for amyotrophic lateral sclerosis (ALS), adding ultrasound to the clinical exam has proven to be useful for establishing this diagnosis in patients (Grimm et al., 2015, Boekestein et al., 2012, Misawa et al., 2011, O’gorman et al., 2017). Ultrasound can also be used to assess the split hand index, using echointensity ratios of the thenar and hypothenar muscles (Seok et al., 2018). For those seeking electrodiagnostic confirmation of ALS, ultrasound, by identifying promising muscles for EMG sampling, can reduce the number of muscles that need to be tested for diagnosis (Caires 2017). Of note, recent studies have suggested that fasciculations may be the earliest manifestation of amyotrophic lateral sclerosis, and that as this disease spreads to uninvolved limbs, fasciculations may be the heralding feature. It is possible therefore, that fasciculations could also serve as a biomarker of the disorder (de Carvahalo et al., 2017; Eisen and Vuic, 2013).

Nerve ultrasound in ALS may also be of diagnostic benefit because motor nerves tend to be slightly smaller than normal. This is likely due to gradual motor axonal loss (Schreiber et al., 2016; Cartwright et al., 2011). Multifocal motor neuropathy (MMN), which can be confused clinically with motor neuron disease, often shows enlargement of nerves, and as such, the presence of nerve enlargement may be a useful additional discriminating factor in distinguishing between MMN and ALS (Jongbloed et al., 2016).

Spinal muscular atrophy, a now treatable disorder, also shows characteristic changes on ultrasound, with hyperechoic, atrophic muscles and a correspondingly hyperechoic layer of subcutaneous fat. The striking contrast between the hyperechoic fat and hyperechoic muscle provides a useful yardstick for assessing its presence (Wu et al., 2010). Given that this is a disorder primarily of infants and children, the availability of a non-invasive tool for its diagnosis, makes it of particular value. A recent study has suggested that ultrasound detected atrophy and echogenicity may be useful biomarkers of SMA progression (Ng et al., 2015).

Ultrasound is also informative in patients who have old or remote polio, in that it shows a striking increase in echogenicity, and often fasciculations, in muscles that were once affected by the disorder (Walker et al., 1990).

5.5.2. Non-diabetic axonal polyneuropathy (32%/4%); diabetic polyneuropathy (27%/7%); toxic neuropathy (17%/8%) (Other—non-diabetic polyneuropathy—no index paper identifiable; diabetic polyneuropathy Severensson et al., 2007—index paper; toxic neuropathy Briani et al., 2013—index paper).

Experts find relatively limited usefulness for ultrasound in diabetic and axonal neuropathies (Telleman et al., 2018a). Recent publications have shown mild generalized enlargement of nerves in diabetic neuropathy, and occasional enlargement of nerves in some toxic neuropathies (Breiner et al., 2017; Stone et al., 2014; Briani et al., 2013). The few reports on neuromuscular ultrasound in zoster neuropathy, vasculitic neuropathy, and trans-thyretin amyloidosis suggest it may have a helpful role (Podner et al., 2017; Nodera et al., 2006; Zubair et al., 2017; Salvagallo et al., 2017). For example, in suspected vasculitic neuropathy, ultrasound may help in selection of affected nerve segments for biopsy (Grimm et al., 2014b). Further investigation of these and other predominantly axonal neuropathies (e.g. HIV neuropathy, for which ultrasound findings have not been reported) may identify specific patterns of nerve changes apparent by ultrasound.

5.5.3. Sensory neuronopathy (22%/6%) (Pelosi et al., 2017—index paper)

While nerves typically enlarge and become hypoechoic in most neuropathies (Walker 2017), recent studies have shown that in some sensory neuropathies, particularly cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), nerve thinning can be seen (Pelosi et al., 2018, 2017). Ultrasound in Friedreich’s ataxia, another, somewhat more complicated and possibly mixed form of sensory neuronopathy, shows that some nerves may show enlargement in this disorder, so additional work is needed (Mulroy et al., 2017). In Wartenberg’s migrant sensory neuritis, an idiopathic, patchy, pure sensory neuropathy ultrasound reveals diffuse multifocal nerve enlargement which includes pure sensory and mixed nerves (Herraets et al., 2017). At this time, most experts are not routinely using ultrasound to evaluate pure sensory disorders, but further investigation seems promising.

5.6. Situational indications:

5.6.1. Palpable masses (86%/47%)

It is not uncommon for patients to describe palpable lumps or bumps during an electrodiagnostic evaluation. Ultrasound is quite helpful in these cases. It can demonstrate to the patient that nothing is apparent by ultrasound which can be quite reassuring; alternatively, it can identify lesions which sometimes are not apparent by clinical examination. Common palpable findings include benign enlarged lymph nodes, lipomas and ganglion cysts. However ultrasound can identify a wide variety of other pathologic changes including scar tissue, neuromas, tumors, calcifications, aneurysms, arteritis, aberrant muscles or tendons, musculoskeletal disorders and bony malformations. The sonoacoustic properties of unexpected peripheral masses may also be useful in discriminating between various peripheral nerve associated tumors and changes on color Doppler may even help in the diagnosis temporal arteritis (Ryu et al., 2015, Nescher et al., 2002). The neuromuscular sonog-
A recent report suggests that extra-neural findings are not uncommon in routine neuromuscular ultrasound examinations (Bignotti et al., 2018).

5.6.2. Variant anatomy (76%/34%)

Variant anatomy can sometimes be anticipated, for example, in patients with congenital malformations, severe trauma, or who have undergone reconstructive surgery or nerve transposition. In others, anatomic variation is discovered during their laboratory evaluation. In either case, ultrasound can be of value in helping to guide EMG and NCS studies for nerves or muscles in unusual locations and for evaluating pathology secondary to the variant anatomy (Zhu et al., 2011; Erra et al., 2013; Enhesari et al., 2014; Cesmebasi et al., 2015b; Gans et al., 2017; Grigoriu et al., 2015). For example, persistent median arteries can thrombose causing acute symptoms suggestive of carpal tunnel syndrome or nerves can be entrapped in instrumentation used to secure displaced fractures (Walker et al., 2013; Peer et al., 2001). Identifying variant anatomy also may help guide interventions around vital structures. Ultrasound can also be used to identify anatomic variants suggested by unusual NCS findings such as Martin-Gruber anastomoses or accessory fibular nerves (Gans and van Alfen, 2017; Luchetta et al., 2011).

5.6.3. Phobic patients or patients unable to tolerate electrodiagnosis (67%/67%)

A small percentage of patients referred for electrodiagnostic testing are unable to tolerate the procedure. Small children and infants present special challenges in this regard and an unknown number are never referred for testing even when it might be appropriate. At the request of the parents, sedation is sometimes used which has other risks and drawbacks. As a third component of the neuromuscular evaluation, ultrasound offers an intermediate step in the evaluation of such individuals. It assesses nerves and muscles in a patient friendly manner, which in itself, may be sufficient for diagnosis in some disorders or suitably informative to obviate the need for EMG or nerve conduction studies. For example, there is evidence that ultrasound, by assessing the echointensity ratio of differentially innervated muscles, may be helpful in quantitating the extent of axonal loss in distal hand muscles without the discomfort of EMG (Kim et al., 2016). Sometimes, after performing an ultrasound, enough trust is built with the examiner to allow for limited additional electrodiagnostic studies. Ultrasound may also help in determining if there is a need for other types of testing.

6. The value of neuromuscular ultrasound and the likelihood of its continued evolution:

6.1. Validity and limitations of the expert survey

This study has several limitations. It should be reiterated that the self-reporting component regarding expert usage is nonquantitative and the translation of terms such as ‘sometimes, often and frequent’ can vary across different individuals. It is further possible that participant enthusiasm for ultrasound may have biased the results. Hidden bias in a survey of this type cannot be completely excluded, although a number of steps were taken to avoid or minimize it. The geographic and specialty representation among the experts is well balanced and there was, reassuringly, a consensus among the experts on the selection of representative publications cited in this report. The survey involves self-reporting and recall instead of a monitored retrospective analysis of all studies performed, and it is possible that inaccuracies resulted from this approach; however, given the variation in responses from participant to participant, and significant variations in practice suggest that there was no universal trend in over or underreporting ultrasound usage. It should be noted, however, that the overall relationship between the publication date of evidence and the actual usage of ultrasound (Fig. 6) suggests that expert practice is responsive to the published literature and thus, less likely to be reflective of internal or systematic bias.

Another limitation of the manuscript is that it does not address the skill level required to perform neuromuscular ultrasound, nor the requisite sophistication of ultrasound equipment to address certain conditions. Similarly, appropriate requirements for instrumentation for each indication have yet to be defined, but this reflects the evolving nature and standardization of ultrasound devices. The time required for physicians in electrodiagnostic practice to acquire expert ultrasound imaging and interpretation skills is unknown because many of the experts learned ultrasound through the inefficient process of trial and error. However, the degree to which thoughtful instruction can speed up learning is significant in that reliable large muscle ultrasound measurement skills can be acquired with less than one hour’s training, and reliable upper extremity nerve imaging skills can be acquired in two months of residency training in an electrodiagnostic laboratory with ultrasound equipment (Zaidman et al., 2014a; Garcia-Santibanez et al., 2018).

Other possible limitations of neuromuscular ultrasound undressed in this manuscript include the overlap in presentation of musculoskeletal (MSK) disorders with neuromuscular disorders. Not all physicians skilled in neuromuscular ultrasound can evaluate for MSK disorders. It is also possible that ultrasound could contribute to the costs of neurodiagnostic evaluations. However, once expertise in neuromuscular ultrasound and an instrument are acquired, the marginal cost of ultrasound is quite modest. An analysis of the cost of ultrasound in practice is beyond the scope of this review, but preliminary work suggests ultrasound is cost-effective (Cartwright et al., 2015).

6.2. Is there reason to expect that MRI will supersedes ultrasound as a complementary routine test for neuromuscular evaluation?

The experts were not specifically asked this question, but the investment in ultrasound and optimism for its future clearly indicates that this is not felt to be likely. To date, for the few published comparisons of MRI with neuromuscular ultrasound, ultrasound has proven to be an equal or somewhat superior diagnostic technique (Bignotti et al., 2017; Smith et al., 2016; Jannsen et al., 2014; Zaidman et al., 2013a; Gabmarota et al., 2007). This is not surprising as ultrasound has significantly better resolution than MRI (Cartwright et al., 2017, Gamberota et al., 2007), and the computer driven technology that has contributed to improved MR resolution over the last few decades is similar to the technology that continues to improve ultrasound resolution. The lower cost, portability, and availability without scheduling of ultrasound are fixed advantages of the technique. Nonetheless, MRI offers specific advantages including contrast enhancement, tractography and access to nerves throughout the body—information unavailable through ultrasound making MRI a valuable tool for research, validation of ultrasound findings and direct evaluation of patients. Of note, ultrasound and MRI measurements of nerve size correlate quite well (Pitarokoili et al., 2018).

6.3. Relative growth of electrodiagnostic and ultrasound imaging technology

Although ultrasound and electrodiagnosis both evolved from oscilloscope technology (Walker, 2007), electrodiagnostic technol-
ogy is in an evolutionary plateau at this time and is relatively unchanged in the last few decades. Motor unit quantitation has improved with newer programs, but the impact of computerized EMG analysis has been, at best, modest. In contrast, ultrasound has evolved considerably and this survey shows a unanimous expert consensus as to continued improvements in ultrasound technology. Furthermore, instrumentation is becoming more adaptable, with remarkable miniaturization of some ultrasound devices, some now the size of a cellular telephone. Image resolution continues to improve with modifications in transducers and signal analysis, and over the last few decades, the entry level cost of an effective instrument has dropped considerably. Currently, at least two companies have developed combined ultrasound/EMG instruments that can simultaneously display ultrasound and EMG data. Standard options on ultrasound instruments have also increased, with extended field of view, 3-D and 4-D imaging, elastography, and other advanced programs becoming more available on smaller instruments. Ultra-high frequency transducers have been developed that offer unprecedented visualization of superficial peripheral nerves and surrounding structures (Cartwright et al., 2017). Training in neuromuscular ultrasound is now much more widespread than a decade ago. The evolution of ultrasound is accelerating and recognition of this trend has led to training medical students and residents in clinical applications of ultrasound, and in a few countries, neuromuscular ultrasound certification programs are active or in development. There is also rapidly growing interest in the use of ultrasound guidance for enhancing existing techniques such as steroid injections, diagnostic anesthetic blocks and pre-operative localization of nerves, as well as in the development of new techniques such as needle fenestration for carpal tunnel syndrome, hydrodissection of entrapped nerves and regenerative procedures (Hanna et al., 2017, Tudose et al., 2017, Cass, 2016, Strakowski, 2016, Tagliafico et al., 2016, McShane et al., 2012). Expertise with ultrasound is a prerequisite for would-be innovators in these areas and for those testing the clinical value of new approaches.

6.4. Added value of instrumentation and ultrasound in practice

The majority of the focus of neuromuscular ultrasound over the last few decades has been on resolving the anatomy of nerves, muscles, blood vessels and the surrounding tissues (Figs. 7 and 8). Experts have thus placed the highest value, in their current equipment, on the high resolution transducers and color flow imaging—the features most helpful for assessing anatomy, complementing electrodiagnostic findings, and in identifying unexpected pathology. Quantitative gray scale analysis and extended field of view, techniques which can further assist in anatomic resolution are rated next most helpful. Contrast agents, speckle tracking, elastography and 3D ultrasound are more recent innovations in ultrasound technology that have been the subject of relatively few publications, and not all experts have access to these innovations. Understandably, they are rated less important at this time, as the potential usefulness of these technologies has not been fully explored. Given the added time required to use these techniques and the greater complexity involved in assessing physiology compared to anatomy (e.g. changes in anatomy over time), it can be assumed that their integration into routine practice will take longer than the immediate benefits of high-resolution transducers and blood flow assessment.

6.5. Future expectations for neuromuscular ultrasound

The most compelling results of the survey relate to the unanimity of opinion by experts on the continued expansion for indications and use of neuromuscular ultrasound in the future. None of the experts foresee curtailment of their use of the technology and all foresee a high likelihood for more indications, better quality instruments, more research, and better diagnosis. All see it as a part of routine clinical neurophysiology training and practice in the future. Also, given the increasing use of ultrasound in medical schools, it seems likely that prospective residents and fellows will expect training programs to be able to instruct them in neuromuscular ultrasound. Point of care ultrasound is becoming an integral part of many medical specialties as well. The experts are optimistic about increasing pediatric indications for neuromuscular ultrasound and the use of ultrasound first for certain indications. The only area where there is significantly less agreement by experts is the likelihood of lower cost-ultrasound instruments.

6.6. The nature of the current evidence

The rate of discovery of new indications for neuromuscular ultrasound, the endurance of previously discovered indications, the continued evolution of instrumentation, its non-invasiveness, and the growing use of ultrasound for different neuromuscular disorders by experts in electrodiagnostic medicine makes a compelling case for imaging in clinical neurophysiology laboratories. We encourage rigorous attention to design in future studies of neuromuscular ultrasound to help facilitate its acceptance by those outside the field of electrodiagnosis. Similarly, readers interested in formal levels of evidence are encouraged to explore the literature and report their findings. However, for those readers who practice electrodiagnosis and who wish to form an independent opinion on the usefulness of neuromuscular ultrasound, we suggest that they borrow an instrument and simply look for themselves.

7. Translational implications

For decades, electrodiagnostic medicine has been based on a fairly equal assignment of importance to EMG and NCS in the evaluation of patients referred for a neuromuscular evaluation. This is because the need for one or both procedures cannot be determined until an expert in the laboratory sees the patient and initial test results are available. A laboratory that only performed one of these tests would be of limited value.

Neuromuscular ultrasound has now become, in addition to EMG and NCS, a third component of a neurodiagnostic evaluation. This is because the need for any combination of EMG, NCS or ultrasound cannot be determined until an expert sees the patient and some preliminary test results are available (Tables 1 and 2). What makes the interplay of the three studies of interest is that some information provided by EMG and NCS cannot be replicated by ultrasound including selective motor versus sensory impairment in the same nerve, sensory localization with respect to the dorsal root ganglion, and some aspects of prognosis and severity. On the other hand, ultrasound diagnoses common entrapment neuropathies with an accuracy comparable to that of electrodiagnosis, localizes other nerve problems when NCS alone cannot (e.g. when responses are absent, when inching is not possible, or when nerve dysfunction is not severe enough to be detected electrically). Furthermore, ultrasound provides information beyond localization unavailable by EMG or NCS regarding the presence or absence of intrinsic or extrinsic nerve pathology (e.g. tumors, cysts etc.) or chronic muscle disease and it provides this information quickly, safely, and without discomfort.

7.1. Re-envisioning electrodiagnosis

Fifty years ago, the approach in an electrodiagnostic laboratory was to perform all possibly helpful diagnostic studies at the initial
develop protocols for sequencing these three types of studies to NCS across testing centers will eventually lead practitioners to able. The inclusion of neuromuscular ultrasound with EMG and regard, painlessly adding information that is otherwise unobtain-
in Tables 1 and 2, neuromuscular ultrasound is instrumental in this useful for guiding patient care. As discussed above and as shown approach to diagnosis in a patient with suspected neuromuscular etiology of genetic and antibody tests. Over this time period, the may now undergo a wide vari-
instead of muscle biopsy to fur-
then, testing alternatives have evolved. Instead of spinal myelogra-
5. Evaluates diaphragm function and provides guidance, if needed, for EMG needle insertion.
6. Muscle ultrasound, by using echointensity ratios, may provide insight into relative axonal loss in distal muscles.
7. Helps identify variant nerve anatomy that complicates interpretation of nerve conduction studies (Martin-Gruber or accessory fibular nerve).

Table 1
Added value of ultrasound in focal neuropathy.

(A) Suspected focal neuropathy already localized by electrodiagnosis (EDX)
1. Confirms or further refines localization (e.g. in long segments, such as median nerve in the forearm).
2. Excludes unexpected intrinsic or extrinsic anatomic pathology (e.g. ganglion cyst in fibular neuropathy at the knee, or focal nerve tumor/neuroma).
3. May be used to exclude a second entrapment of the nerve at a distal or proximal site (e.g. double crush).
4. Establishment of anatomic baseline for future comparison in anticipation of medical or surgical treatment.
5. Muscle ultrasound, by using echointensity ratios, may provide insight into relative axonal loss in distal muscles.

(B) Suspected focal neuropathy unable to be further localized by EDX (absent motor/sensory responses)
1. Localizes the lesion to a specific site along the nerve.
2. In the presence of trauma, confirms nerve continuity or identiﬁes transection and assesses for hematoma, bone injury, or other contributing factors.

(C) Suspected focal neuropathy with borderline EDX
1. Can help support or refute the presence of focal nerve pathology.
2. May identify distortion of the ulnar nerve with elbow ﬂexion, which may account for false negative NCS ﬁndings.
3. May identify a proximal fascicular lesion masquerading as a distal entrapment as in brachial neuritis.

Table 2
Added value in other neuromuscular disorders.

(A) Suspected polyneuropathy (before or after EDX)
1. Helps support or refute the presence of hypertrophic polyneuropathies (CMT, MMN, CIDP, HNPP, and AIDP).
2. Distinguishes CMT and HNPP from CIDP and MMN.
3. Increased power Doppler signal may identify leptomeningeal neuroma or neuromyelomatosus.
4. Evaluates distal muscle atrophy/increased echogenicity indicative of a chronic neurogenic process.
5. Demonstrates nerve thinning in CANVAS or enlargement in Wartenberg’s migrant sensory neuritis.

(B) Suspected motor neuron disease: prior to EMG
1. Identiﬁcation of fasciculations to help diagnose ALS using modiﬁed Awaji criteria, or to enhance muscle selection for EMG examination.
2. Distinction, based on location, size and frequency, of benign from pathological fasciculations.
3. May provide evidence, using relative muscle echointensity and thickness, of split-hand syndrome which may be seen in ALS.
4. The absence of enlarged nerves (and the presence of slightly smaller nerves) may help distinguish motor neuron disease from MMN.
5. Evaluates diaphragm function and provides guidance, if needed, for EMG needle insertion.
6. Quantitative muscle ultrasound may help distinguish central and peripheral etiologies in infants and small children, and helps guide choice of further testing.

(D) Other
1. Evaluates nerve and muscle in those unable to tolerate EDX.
2. Identifies calcification and/or cysts indicative of prior inﬂammation, hemorrhage or infection.
3. May be used to guide chemodenervation, steroid injections, near nerve needle placement, or phenol injections, or nerve biopsy.
4. May be used to map the course of nerves (e.g. spinal accessory) prior to surgical intervention to prevent injury.

Abbreviations, CMT = Charcot Marie Tooth, MMN (Multifocal motor neuropathy), CIDP = chronic inﬂammatory demyelinating polyneuropathy, HNPP = Hereditary neuropathy with liability to pressure palsy, AIDP = acute inﬂammatory demyelinating polyneuropathy. CANVAS = cerebellar ataxia, neuropathy, vestibular areﬂexia syndrome). EMG = electromyography.

encounter because patients were often reluctant to return and because, at that time, alternative studies of the peripheral nervous system were typically invasive and not always informative. Since then, testing alternatives have evolved. Instead of spinal myelogra-
4. The absence of enlarged nerves (and the presence of slightly smaller nerves) may help distinguish motor neuron disease from MMN.

Those interested in staying current in clinical neurophysiology need to first acquire a high-resolution ultrasound device and then develop skill in its use. At this time, many laboratories do not have access to ultrasound; for example, in Canada at this time there are fewer than 10 centers in the country with ultrasound access. This is no longer tenable and it is the responsibility of hospitals and academic medical centers to promptly address this issue. The second step does not require immediate mastery of all potential applications, but rather, it need only begin with one individual mastering one indication along with one nerve segment and relevant muscles. Once this is done, the technique can gradually spread to more nerve segments, muscles, indications and members in a laboratory. For each of the experts surveyed, the technique was mastered one nerve, one muscle, and one indication at a time, and now, there are ample courses and literature to guide newcomers to acquire expertise relatively quickly. The gap in best practices between experts to optimize clinical helpfulness and diagnostic yield (Te Riele et al. 2017).

and most practitioners in the field of peripheral clinical neurophysiology hinder optimal care and the advancement of the field. Acquiring an ultrasound instrument and the skills needed to use it must be a top priority for all electrodiagnostic laboratories.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Declarations of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2018.09.013.

References


