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Review

Expert consensus on the combined investigation of ulnar neuropathy at the elbow using electrodiagnostic tests and nerve ultrasound

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HIGHLIGHTS

- Expert consensus was sought to guide clinicians on the investigation of ulnar neuropathy at the elbow (UNE) using EDX and US.
- The experts agreed that all investigations of UNE should include both nerve conduction studies and US.
- US should include assessment of cross-sectional area and nerve mobility at the elbow, and imaging of the entire ulnar nerve.

ABSTRACT

The addition of ultrasound (US) to electrodiagnostic (EDX) tests can significantly enhance the accuracy of testing for ulnar neuropathy at the elbow (UNE). We aimed to obtain expert consensus to guide clinicians on the combined use of EDX and US in UNE investigation.

Consensus was achieved using the Delphi method. Two consecutive anonymised questionnaires were submitted to 15 experts, who were asked to choose their level of agreement with each statement. Consensus was pre-defined as $\geq$ 80% rating agreement.

The experts concluded that all investigations of UNE should include both nerve conduction studies and US. There was consensus that US should include cross-sectional area measurement and assessment of nerve mobility at the elbow, and that the entire ulnar nerve should be imaged.

This study defined expert opinion on the 'core' techniques that should be used routinely in the UNE investigation using EDX and US. Areas with lack of consensus highlighted some controversial issues in the current use of these diagnostic modalities and the need for future research.

This document is an initial step to guide clinicians on the combined investigation of UNE using EDX and US, to be regularly updated as new research emerges.

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Contents

1. Introduction

Ultrasound (US) has emerged over the last few decades as a diagnostic tool with the potential to significantly enhance the accuracy of testing for common mononeuropathies by adding morphological information regarding nerve and surrounding structures. Morphological information cannot be obtained with electrodiagnostic (EDX) testing.

The neurophysiological investigation of ulnar neuropathy at the elbow (UNE) using traditional EDX methods can be challenging. Unlike the investigation for carpal tunnel syndrome, EDX testing for UNE often fails to produce a diagnosis (estimated sensitivity ranging from 38 to 89% (AANEM 1999a), to achieve localization, or to provide information that may guide the choice of treatment (Beekman et al, 2004a, 2011; Pelosi and Mulroy, 2019). The addition of US can help to fill some of these gaps (Alrajeh and Preston, 2018; Beekman et al, 2004a, 2011; Ellegaard et al., 2015; Omejec and Podnar 2015; Pelosi et al, 2018, 2021; Pelosi and Mulroy, 2019; van Veen et al, 2015). Despite the increasing popularity of US, only a relatively small number of laboratories worldwide have systematically incorporated it into their neurodiagnostic clinical practice. Furthermore, clear consensus on how this should be done is lacking. This study aimed to create expert consensus for the combined investigation of UNE using both EDX and US, and to provide a guide to clinicians evaluating patients with suspected UNE.

2. Methods

An international panel of experts was recruited for this study. Experts were defined as having both clinical experience and research publications on diagnostic testing in UNE.

We initially intended to create practice guidelines. However, the literature review made clear that definitive research-based evidence required to formulate practice parameters and guidelines for the combined investigation of UNE is lacking. We therefore unanimously agreed that an 'expert consensus' was the appropriate approach.

Consensus was sought using the Delphi method procedures. Since the 1960s, health services have increasingly used the Delphi method to develop consensus guidelines or standards in areas where research-based evidence is inconclusive or absent. The method also suits panels with geographically dispersed membership precluding effective in-person communication (Cantrill et al, 1996; Linstone and Turoff, 2011).

The Delphi method is a multistage technique, with each stage building on the previous one. First, the panel of judges (experts) is surveyed anonymously on a specific topic. Survey answers are then statistically analysed and results fed back to the panel. This process is repeated until a consensus is reached. Two to 4 surveys are most commonly needed. The first questionnaire is usually based on a review of the scientific literature, although other approaches have also been used (Cantrill et al, 1996).

The surveys were prepared by two authors (LP and MSC) through electronic correspondence. The first survey was based on a literature review regarding the ability of EDX and US to address questions of UNE: (a) diagnosis, (b) localization, (c) disease severity and (d) information that may facilitate management. A summary of the literature review was sent to all the authors for review and comment before the first questionnaire was prepared. Details of the literature search and summary are in the Appendix A.

The surveys were sent electronically to all the group members. For each statement, members were asked to choose their level of agreement on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) and to add any comments they may have regarding their choice. No instructions were given on what to base their answers on. The expert's answers were returned to the lead investigator (LP) and initially not shared with the other group members.

The frequency of the ratings of the first survey were calculated. The ratings on the top two levels (strongly agree and agree) were combined to indicate the overall frequency of agreement (for example, strongly agree 50% and agree 10% = 60% total agreement), and the ratings on the bottom two levels (disagree and strongly

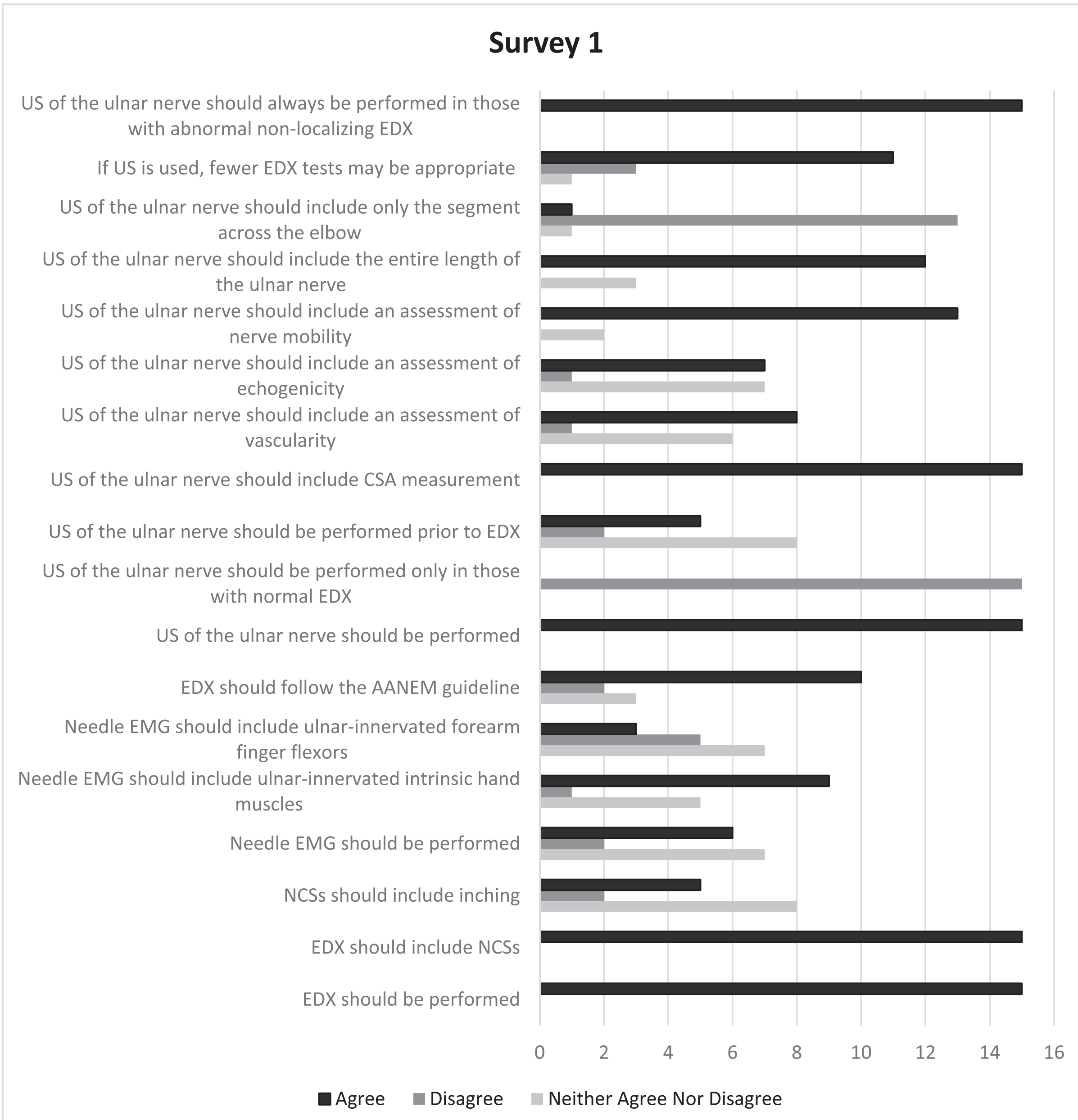

Fig. 1. Ratings by 15 experts on each statement of survey 1. EDX = electrodiagnostic; NCSs = nerve conduction studies; US = ultrasound.

disagree) were similarly combined to estimate the overall frequency of disagreement with the statement.

'Group consensus' on each statement was pre-defined as ≥80% rating frequency (i.e. ≥80% agreement or 80% disagreement or 80% neither agree nor disagree) and, 'No group consensus' as <80%.

The results and all the anonymised comments from the first survey were re-circulated for further comments and formed the basis of a second survey. The experts were also invited to suggest any additional questions that could be submitted to the panel in the following survey. Answers to the second survey were analysed using the same method as for the first survey. Results and comments from the second survey were again re-circulated.

Following the results of surveys 1 and 2, the experts were invited to participate in an open debate via e-mail on the most controversial issues.

A summary of the statements for which 'group consensus' was achieved and a separate summary of the statements for which there was 'no group consensus' were prepared by the same two authors who created the surveys (LP and MSC) and circulated to all the other panel members for review and final approval.

3. Results

3.1. Expert recruitment

Seventeen experts were approached, of whom 15 agreed to participate. Nine countries from four continents were represented: Australia (1); Hungary (1); Italy (2); New Zealand (1); Slovenia (1); South Korea (1); The Netherlands (4); United Kingdom (1); United States (3).

3.2. Surveys

Eighteen statements were included in the first survey (Fig. 1) and nine in the second (Fig. 2). There was a 100% response rate for both surveys. Rating frequencies for each statement in surveys 1 and 2 are shown in Figs. 1 and 2, respectively. Table 1 summarises the statements with 'group consensus' (≥80% ratings) and Table 2 the statements with 'no group consensus' (<80% ratings).

4. Discussion

Increasing awareness of the utility of US in the investigation of mononeuropathies has led to greater use in clinical neurophysiologic practice. While this stands to improve patient care, its application has been non-systematic due to a lack of clear consensus on best practices.

The first questionnaire was carefully based on a literature search and review, which aimed to establish the state of current knowledge on what each method (EDX and US) offers and how the two methods can most effectively work together in order to maximize the efficiency of the neurophysiological investigation without duplication (see the Appendix A for a review of the pertinent literature).

The expert panel unanimously agreed that EDX and US together are more informative than either modality alone. The experts concluded that both methods (EDX and US) should be used routinely where the relevant expertise and equipment are available. The addition of US to the neurophysiological investigation of UNE should therefore not only be restricted to situations in which EDX is non-localizing or inconclusive.

The techniques for EDX and US used in different laboratories worldwide are variable. This study defined what the experts think are the 'core' techniques within each method that should be used routinely in the combined investigation. The panel agreed that EDX testing should always include sensory and motor nerve conduction studies, using the physician's preferred method for these procedures. Interestingly, the surveys uncovered some controversial issues in the current use of available EDX techniques, with particular regard to the routine use of motor "short segment" or "inching" and needle EMG. A relatively small majority of experts follow the AANEM guidelines, which recommend inching and EMG as part of a second line of tests offering possible benefit, "*If ulnar motor conduction studies with stimulation at the wrist, above and below the elbow recording from the abductor digiti quinti are inconclusive*" (AANEM, 1999b). However, amongst the experts, some also recommended routine use of the inching technique and/or needle EMG. Our surveys established that a consensus on whether or not these EDX techniques should be used routinely (in the combined investigation with both EDX and US) cannot be

Table 1
Group consensus (≥80% ratings).

1.	EDX and US together are more informative than either modality alone
2.	Both modalities should be performed in all investigations of UNE
3.	EDX testing should always include nerve conduction studies
4.	US of the ulnar nerve should include CSA measurement
5.	US of the ulnar nerve should include an assessment of nerve mobility
6.	US of the ulnar nerve should include the entire length of the ulnar nerve

CSA = cross-sectional area; EDX = electrodiagnostic; UNE = ulnar neuropathy at the elbow; US = ultrasound.

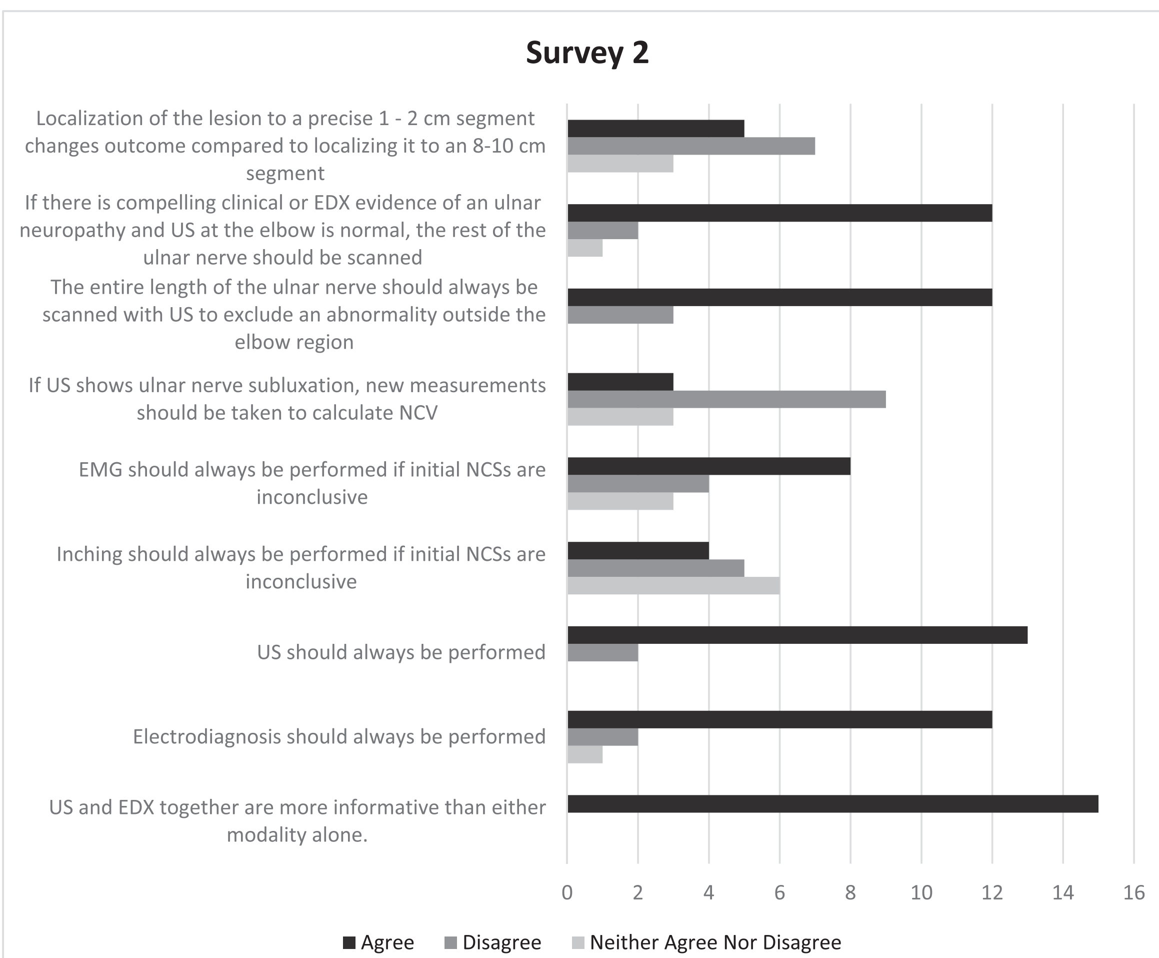

Fig. 2. Ratings by 15 experts on each statement of survey 2. EDX = electrodiagnostic; NCSs = nerve conduction studies; NCV = nerve conduction velocity; US = ultrasound.

achieved at this stage and the decision should be left at the operator's discretion. This may change if new research emerges.

For US, measuring the nerve cross- sectional area (CSA) at the elbow should always be performed, and the measurement should be obtained *at least* at the site where the nerve is largest (CSAmax). Other techniques, like the swelling ratio or flattening ratio may be performed at the examiner's discretion to reinforce the CSA findings, if needed. There has been increasing interest in recent years in US assessment of nerve vascularity and echogenicity. Our panel concluded that these are promising emerging techniques, but further evidence is needed before specifying their optimal use in clinical practice.

The panel also agreed that the entire ulnar nerve from wrist to axilla should be imaged, both to exclude an abnormality (any change in morphology or echogenicity of the nerve, or the appearance of any abnormal musculoskeletal structure near the nerve) outside the elbow region in UNE and to look for an abnormality elsewhere when nerve ultrasound at the elbow is normal. CSA measurements need only be taken where visually apparent changes in nerve morphology or echo-intensity are observed.

Ultrasound examination at the elbow should always include an assessment of nerve (sub)luxation and dislocation with elbow flexion.

There was 'no group consensus' on which modality to use first and whether or not fewer EDX tests may be appropriate if US is used. So, these should be at the discretion of the examiner.

The Delphi method has limitations. The consensus reflects the opinion of one particular group only, while the way in which level of consensus is defined and the optimum number and type of experts or sampling size are selected is arbitrary. Our group was uni-disciplinary, consisting exclusively of physicians who had published research on EDX and US in UNE, who were pioneers of nerve ultraosund and familiar with the use of both EDX and US in their clinical practice.

This document should be regarded as an initial step, to be regularly updated as new research emerges. Our results highlight the need for future research to be conducted in a prospective and systematic manner. Few articles in our literature search met the STARD criteria for diagnostic accuracy or clinical utility (Bossuyt et al, 2012; Cohen et al, 2016, 2017). Future research should compare the EDX and US findings with intra-operative findings (in surgical cases), treatment outcomes (whether surgical or conservative), and with systematic clinical follow-up (both short-term and long-term).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Literature search and review

1. Literature search

The literature search focused on studies that included both EDX and US.

Two experts (LP and MSC) did an independent advanced search of full original papers (no case reports or reviews) on Medline using PubMed over the 2000-2020 period, with 'ultrasound', 'ultrasonography' or 'sonography' AND 'ulnar neuropathy' or 'cubital tunnel syndrome', limiting the search to 'English', 'human', 'journal' and 'adults 19+'. The search was then narrowed down first based upon the titles of the papers and then further narrowed using the STARD for Abstract criteria (Cohen et al, 2016, 2017).

The literature review aimed at establishing current knowledge of the ability of each technique to address questions of: (a) diagnosis, (b) lesion location, (c) disease severity and (d) any information that may facilitate management.

From each article, we noted all the data on:

(a) diagnostic accuracy of EDX and US, including methodological and non-methodological factors that may affect diagnostic accuracy in clinical practice
(b) the ability of EDX and US to localize the lesion at the elbow and, more precisely, to which elbow segment
(c) aspects of each technique that provide a reliable quantification of disease severity
(d) any other information that each technique can potentially provide to assist in management decisions.

Additional studies of US methodology and emerging techniques were searched and reviewed by a third expert (DC).

2. Paper selection

Twenty papers were included in the final selection (Alrajeh and Preston, 2018; Bayrak et al, 2010; Beekman et al, 2004a, 2004b; Boom and Visser, 2012; Cheng et al, 2016; Ellegaard et al, 2013; Ghanei et al, 2015; Gruber et al, 2010; Omejec et al, 2015, 2016; Omejec and Podnar, 2015, 2018, 2020; Pelosi et al, 2018; Pelosi and Mulroy, 2019; Scheidl et al, 2013; Simon et al, 2015; Tagliafico et al, 2010; van Veen et al, 2015) (Supplementary table).

3. Paper review

3.1. Diagnostic accuracy

3.1.1. Diagnostic sensitivity

Five studies assessed the sensitivity of EDX and US using the clinical diagnosis of UNE as the reference standard.

Sensitivity in these studies ranged from 47 to 89% and, 54 to 84% for EDX and US, respectively. The lower scores of 47% and 54% were from a study that included a large proportion of patients with very mild clinical severity (sensory symptoms only) (Pelosi and Mulroy, 2019). Without the very mild group from this study, the lower ranges of sensitivity increase to 63% and 71% for EDX and US, respectively. The mean sensitivity across all studies, including a total of 373 arms, was 75% for EDX and 79% for US.

Four out of five studies that compared the US nerve CSA (3 studies) or diameter (one study) to the 10 cm (across-elbow segment) EDX, found higher sensitivity for US (Beekman et al, 2004a; Ellegaard et al, 2013; Pelosi and Mulroy 2019; van Veen et al, 2015) and one out of five studies found higher sensitivity for EDX (Omejec et al, 2015). In the latter study, EDX sensitivity was significantly higher when the 2 cm inching method was used. In a following study which is not included in this selection (as no US was done), Omejec and Podnar (2016) suggested that, alternatively, with a single additional stimulation, two 4 cm segments across the elbow can be assessed, which increases sensitivity (relative to the 10 cm across-elbow segment) and enables accurate UNE localization.

In all studies, the diagnostic yield increased (up to 91% on average) by using both techniques in comparison to either technique alone.

Table 2
No group consensus (<80% ratings).

60% to 80% consensus:
If US is used, fewer EDX tests may be appropriate
EDX testing should follow the AANEM guideline
Needle EMG should include ulnar-innervated intrinsic hand muscles
If US shows ulnar nerve subluxation, new measurements should be taken to calculate nerve conduction velocity (60% disagreed)
< 60% consensus:
Nerve conduction studies should include inching
Inching should always be performed if initial nerve conduction studies are inconclusive
Localization of the lesion to a precise 1–2 cm segment changes outcome compared to localizing it to an 8–10 cm segment across the elbow
Needle EMG should be performed
EMG should always be performed if initial nerve conduction studies are inconclusive
US of the ulnar nerve should include an assessment of vascularity
US of the ulnar nerve should include an assessment of echogenicity
Needle EMG should include ulnar-innervated forearm finger flexors
US of the ulnar nerve should be performed prior to EDX testing

EDX = electrodiagnostic; EMG = electromyography; US = ultrasound.

3.1.2. Diagnostic specificity

Diagnostic specificity when using both techniques was reported in two studies. It was the same (82%) for EDX and US in one study (Omejec et al, 2015) and, better for EDX (87% vs 73%) in another (van Veen et al, 2015).

3.1.3. Factors affecting diagnostic accuracy

1. Disease severity

The likelihood of finding abnormal tests increased with the severity of the clinical deficits. In two studies that specifically looked at the effect of disease severity, the sensitivity of both EDX and US to detect an abnormality was excellent (100%) in clinically severe and poor in clinically very mild or, to a lesser extent also mild, ulnar neuropathies (Pelosi and Mulroy, 2019; Omejec and Podnar, 2020). However, EDX localization and, therefore, diagnosis of UNE is not possible if the compound muscle action potential (CMAP) is absent or, it may be not possible if the CMAP amplitude is markedly reduced and the CMAP morphology abnormal.

2. Methodology

For EDX, inching (using locally collected reference ranges per 2 cm segment) was superior to the 10 cm-segment for both diagnosing and precisely localizing UNE (Omejec et al, 2015; Omejec and Podnar, 2020), which is also consistent with previous studies not included in this review.

Other aspects of EDX methodology that affect sensitivity have been dealt with in previous reviews and statements (AANEM).

For US, CSAmax at the elbow has been found to be more sensitive than the CSA swelling ratio (Omejec and Podnar, 2015).

The sensitivities of CSA and nerve diameter have not been systematically compared. CSA is more commonly used. Nerve constriction as assessed with US has been reported in one study and was found in about half of the patients with UNE at the humero-ulnar aponeurotic arcade (Omejec and Podnar, 2015).

3.2. Localization

There is general agreement in the literature that a proportion of UNEs cannot be localized by EDX and, that US is particularly valuable in this situation. The question of US utility in ulnar neuropathy with abnormal non-localizing EDX was specifically addressed in two studies, which reported 100% sensitivity of US for localization. Most of these were UNE (Alrajeh and Preston 2018; Pelosi et al, 2018).

It has been suggested that the neurophysiological investigation could further facilitate management decision by providing a more accurate localization of the UNE, specifically by distinguishing the lesions at the humero-ulnar aponeurotic arcade from those at the retro-condylar groove. In one study, the former were approximately five times less common, but more likely to require surgical intervention (Omejec and Podnar 2015). The same authors found that localization using the 2 cm inching technique was superior to US in UNE with conduction block, which are mainly lesions at the retro-condylar groove. On the other hand, US was superior to inching in localizing axonal UNEs, whether at retro-condylar groove or humero-ulnar aponeurotic arcade, and severe UNEs (Omejec and Podnar, 2015, 2020). UNE localizations by EDX and/or US were also validated using intraoperative neurophysiological studies (Omejec et al, 2016).

The largest nerve thickening was at the site of the lowest nerve conduction velocity in one study (Omejec and Podnar 2015). By contrast, in another study, the region of slowing on inching matched the segment corresponding to CSAmax in only 29.4% of nerves, whereas there were significant correlations between the latency recorded from epicondyle to 2.5 cm distal to epicondyle and the CSAs at the adjacent segments (Simon et al, 2015).

3.3. Assessment of disease severity

It is generally assumed that the amplitude of the sensory and motor action potentials to distal stimulation provides a good estimate of the severity of axonal loss. Needle EMG may provide additional information on the severity of chronic denervation and disease activity, which could be particularly relevant to the management of chronic UNEs.

The CSA or nerve diameter was larger in axonal UNEs than in UNEs associated primarily with demyelinating EDX features or conduction block (Beekman et al, 2004b; Omejec and Podnar 2015; Scheidl et al, 2013).

A negative correlation has been reported between CSAmax or nerve diameter and the amplitude of the CMAP (Beekman et al, 2004a; Scheidl et al, 2013).

A recent study reported a positive correlation between clinical severity and CSAmax at the elbow. However, there was a significant overlap between the mild and moderate clinical groups, suggesting that CSAmax cannot be used to adequately assess disease severity in individual patients (Pelosi and Mulroy, 2019).

3.4. Additional information that could be relevant to management

As mentioned above, evidence of nerve constriction has only been reported in one study and was found in only about half of the patients with UNE at the humero-ulnar aponeurotic arcade (Omejec and Podnar, 2015).

We did not perform a systematic analysis of the incidence of anomalous muscles/masses/ganglia or other potential causes of nerve compression at the elbow that could be detected by US, but US is expected to be superior to EDX in this respect.

One of the 20 selected studies reported that nerve hypermobility occurred significantly more often in UNEs that were clinically very mild or mild than in clinically severe UNEs (Pelosi and Mulroy, 2019). However, a systematic analysis of the literature on nerve mobility and its implications has not been done in this review.

3.5. Other ultrasound techniques

For US investigation of UNE, the US measurement of the CSA-max or nerve diameter at the elbow is the well-known parameter. This measurement is sensitive and relatively easy to perform. However, other measurements and approach of nerve evaluation have been reported. First, the CSA comparison of two different sites of the nerve (swelling ratio), obtained by a ratio of the CSAs may be informative for the depiction of the nerve suffering (Bayrak et al, 2010). The ratio between the maximum and minimum diameters of the ulnar nerve at elbow (flattening ratio), considering its transverse scan, can also be used (Gruber et al, 2010). This measurement can be obtained by a usual nerve scan and considers two linear measures (the diameters) instead of a surface (nerve area).

Intraneural vascularization can be demonstrated by power-Doppler imaging. Increased vascularization may be associated with more severe UNE. This approach should always be combined with the CSA evaluation, but it minimally increases the diagnostic sensitivity (Cheng et al, 2016). Nerve echogencity may deserve attention also. In general, hypoechogenicity is more pronounced in an injured nerve (Tagliafico et al, 2010). Semiquantitative scales of computer-based quantification of echogenicity have been proposed (Boom and Visser, 2012; Ghanei et al, 2015). This information, when combined with nerve size, may increase the sensitivity and specificity for UNE diagnosis. The quantitative assessment of nerve echogenicity is promising but there are some important technical limitations to overcome.

The described approaches are supported by a relatively low number of studies and are not common in clinical practice. These methods have to be associated with the usual CSA evaluation to increase the diagnostic power of US.

4. Summary and comments on the literature review

In summary, the literature review showed the following:

The most widely used EDX method was measuring the motor conduction velocity at the elbow over a 10 cm segment. It is the 'first-line' method in the most widely followed guidelines on EDX parameters for diagnosing UNE (AANEM 1999b). Inching was the EDX parameter with the highest sensitivity (Omejec et al, 2015; 2020).

The most studied and most commonly used US parameter for the diagnosis of UNE was the nerve CSA at the elbow. Nerve diameter was also used. The sensitivities of CSA and nerve diameter have not been systematically compared. Other US measurements that have been proposed include 'swelling ratio' (Bayrak et al, 2010), 'nerve flattening' (Gruber et al, 2010) and, more recently, vascularity (Cheng et al, 2016) and echogenicity (Boom and Visser, 2012; Ghanei et al, 2010; Tagliafico et al, 2010). These methods may have diagnostic potential, but additional evidence is needed for clinical application.

US sensitivity to diagnose UNE was slightly superior to the EDX method that is most widely used (measuring the motor conduction velocity at the elbow over a 10 cm segment) in a majority of the studies selected (Beekman et al, 2004a; Ellegaard et al, 2013; Pelosi and Mulroy, 2019; van Veen et al, 2015). Two studies from one laboratory, in which US was compared to the inching method, reported higher sensitivity for the latter (Omejec et al, 2015; Omejec and Podnar 2020).

A proportion of UNEs, which are most often axonal, cannot be localized by EDX, but are all localized by US (Alrajeh and Preston, 2018; Pelosi et al, 2018).

With either EDX or US, the likelihood of diagnosing UNE is modest when the clinical deficits are mild or very mild and high when the deficits are severe (Omejec and Podnar, 2020; Pelosi and Mulroy, 2019). The addition of the second method is most valuable to increase the diagnostic yield in mild and very mild UNEs and, US is most valuable to diagnose UNE in severe non-localizing cases on EDX (Pelosi and Mulroy, 2019).

In all studies reviewed, diagnostic yield increased significantly (up to 91% on average) by using both EDX and US techniques in comparison to either technique alone (Beekman et al, 2004a; Ellegaard et al, 2013; Omejec and Podnar 2015; Pelosi and Mulroy, 2019; van Veen et al, 2015).

Both inching and US nerve CSA can help to precisely localize the lesion, specifically by distinguishing between nerve lesion under the humero-ulnar aponeurotic arcade from those at the retro-condylar groove. It has been suggested that this distinction may guide the choice of treatment (Omejec and Podnar, 2015, 2018), but this has yet to be definitely proven. Precise localization is not always achievable. US is superior to inching in situations when the CMAP is absent or too abnormal to allow precise measurement of latency (Omejec and Podnar, 2015, 2020).

Pre-existing literature on EDX established that the amplitude of the CMAPs provides a good estimate of axonal loss, which in turn, is a good estimate of disease severity. This remains the best method for assessing UNE severity. Some studies have shown a positive correlation between nerve CSA and axonal loss and/or clinical severity (Beekman et al, 2004a; Omejec and Podnar 2015; Pelosi and Mulroy, 2019; Scheidl et al, 2013). Further investigations, however, are required to determine the US ability to quantify disease severity.

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.04.018.

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