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Carpal tunnel syndrome, nerve conduction studies and ultrasonography: A literature review

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Abstract
Objective: The purpose of this literature review was to determine the role of nerve conduction studies and ultrasonography in the diagnosis of carpal tunnel syndrome.
Methods: A search of the current literature was performed, leading to the inclusion of 17 suitable papers for analysis. The outcomes of these papers were used to outline a better understanding of the role of ultrasonography in the diagnosis of carpal tunnel syndrome when compared to the gold standard of nerve conduction studies.
Results/Discussions: Clinical and neurophysiological examinations are important in diagnosing CTS. At this stage NCS are still the gold standard diagnostic tool in the diagnosis of CTS, however information must be applied appropriately to the clinical scenario at hand.
Conclusion: Nerve conduction studies remain the gold standard for the diagnosis of carpal tunnel syndrome; however there are many new studies emerging that demonstrate the benefits of ultrasonography in the diagnosis of CTS, importantly when considering cost effectiveness, availability, and accuracy.

Keywords: carpal tunnel syndrome (CTS), ultrasonography

Introduction
Chronic wrist pain is an affliction that affects many people, both athletes and non-athletes and is a common referral for the Orthopaedic Surgeon. While there are many potential diagnoses, Carpal Tunnel Syndrome (CTS) is one of the most common problems that people are affected by. Sufferers often complain of either wrist pain or paraesthesia of areas supplied by the median nerve when it becomes compressed under the flexor retinaculum and chronic sufferers can have atrophy of the thenar muscles. It can also occur secondary to other causes such as trauma, arthritis, paratenosynovitis and pregnancy [1]. While clinical diagnosis utilises several key tests (such as Tinel's and Phalen's) nerve conduction studies (NCS) have been and are still commonly used. Despite this the literature still states there is no gold standard and recently other investigations such as Ultrasonography (US) have been used to investigate the syndrome. Consequently the aim of this review is to evaluate the literature regarding CTS, NCS and Sonography.

Methods
A search of the Ovid Medline database was performed. The search terms used were "Carpal Tunnel Syndrome", "Nerve Conduction" and "Ultrasound" with the results being limited to "English", "last five years", "humans" and "full text only". This produced 341 suitable results that were subsequently reviewed by one reviewer to include suitable studies. Excluded studies were those where CTS was not the main pathology, where diagnostic approach was not investigated as well as confounding variables. Additionally study types such as case reports, conference abstracts, editorials and comments were also excluded. As a result 17 papers were deemed suitable. Additionally three further guidelines were included as they provided recommendations and guidelines from three premier bodies in the field of carpal tunnel syndrome.

Critical Analysis and Discussion
There have been several pieces of literature that discuss CTS, NCS and ultrasonography. The papers review each investigatory method separately or comparatively and as an aid to diagnosing carpal tunnel syndrome.
Prior to reviewing the major pieces of literature it is important to have an understanding of nerve conduction studies and electromyography. Huynh and Kiernan provided an article on clinical neurophysiology and NCS. Clinical neurophysiology is the collective term for NCS and needle electromyography. It is used to identify lesion sites, the pathophysiology of certain degenerative neurological disorders, mono-neuropathies and more diffuse processes. It uses pairs of electrodes to identify electrical amplitudes, latency (milliseconds), duration of response (milliseconds), and conduction velocity of nerve fibres. It can also use late responses to assess proximal nerve segments such as plexus or roots. The key points that Huynh and Kiernan suggested in addition to above, is that NCS are safe and generally well-tolerated, however their interpretation is highly context specific and must be applied to the clinical picture [2].
The American Academy of Orthopaedic Surgeons' clinical practice guidelines on the diagnosis of CTS are the most extensive published guidelines. Published in 2007 it is an extensive review of the literature that draws on the evidence available to provide recommendations in the diagnosis of CTS. The guidelines provide three main recommendations (figure 1) that are assigned a "Level of Evidence" and "Grade of Recommendation". Of these recommendations, none have level I evidence with level V the most common. Additionally,

none of the studies obtained a grading of A with Grade C the most common [3]. While this publication provides various practice points with a structured and thorough systematic review there are also some flaws. As a significant number of exclusion criteria are present, the number of excluded studies (381) far outweighs the included (99). Another point of discussion is that despite stating that a revision is aimed for 2010, there is still no published update of the document.

Two other documents from two peak bodies aim to further illuminate the diagnosis of CTS. A shared publication between the American Academy of Electrodiagnostic Medicine, American Academy of Neurology and American Academy of Physical Medicine and Rehabilitation aimed to provide practice points for electrodiagnostic studies in CTS. The review aimed to build on previous literature reviews in 2000 and 1993 by providing recommendations based on the findings of the previous reviews. The key clinical questions included determined were:

1. In patients clinically suspected of having CTS, what are the best EDX studies to confirm the diagnosis?
2. How can future clinical research studies be improved to evaluate the usefulness of laboratory studies, including EDX studies, to confirm the diagnosis of CTS?

This document provided a transparent description of the review processers and reviewers. The reviewers were a task force of senior clinicians with an interest in CTS and EDX. The review process used the same six literature inclusion criteria to replicate the search process of previous reviews. From this 11 methods of EDX were found (A-K) (see appendix 2) with their pooled sensitivities and specificities documented. Future research was recommended to be prospective, have a clinical diagnosis of CTS as well as have standardised date collection protocol [4].

The final academy publication is also the most recent having been published in 2012. The AANEM conducted a literature review to provide an evidence-based guideline for Neuromuscular Ultrasound in diagnosing CTS. The questions asked of the studies reviewed were the following:

1. What the accuracy of median nerve cross-sectional area enlargement is as measured with ultrasound for the diagnosis of CTS?
2. What added value, if any, does neuromuscular ultrasound provide over electrodiagnostic studies alone for the diagnosis of CTS?

The review was undertaken by a panel of experts following a search of the literature that revealed 67 articles of relevance. The studies with level of evidence I and II were reviewed and discussed. The accuracy of ultrasound was assessed in 45 of the 67 studies. Of these only four studies were either class I or II while the others below due to apparent bias or lack of reporting quality. The class I studies used median nerve cross-sectional areas (MNCSA) between 8.5-10mm^2. The expert panel thought diagnostic accuracy>70% to be accepted as supportive of ultrasound. Results demonstrated sensitivity of US for diagnosis of CTS between 65-97%, specificity from 72.7-98% and accuracy from 79-97%. The review stated that based on the class I and II evidence, MNCSA is accurate for the diagnosis of CTS. For studies that addressed the added value of ultrasound four class II and 19 class IV studies were found. The class II studies evaluated CTS patients prior to surgery where the class IV studies were case reports that used to US to identify abnormal structures at the wrist. The review concluded that neuromuscular US probably adds to electrodiagnostic studies in CTS as it can aid the identification of abnormal structures [5].

While there have been significant consensus positions and reviews by the major medical associations that manage CTS, there are a number of other articles that highlight and review the accurate diagnosis of CTS. These papers often review the adjunct investigations used to aid in the diagnosis. A 2014 Australian publication suggested that currently there was no agreed-upon reference test and that diagnosis was done either clinically, electro diagnostically or both. Factors that were associated with abnormal NCS were increasing age, positive examination and high physician confidence in the diagnosis. One study in the review found that NCS changed the pre-test management plan by 19% based on the outcome where two other reviews found no statistically significantly changes in post-test probability of CTS when NCS was added as well as no difference in symptom resolution[6]. Further studies evaluated US and found that specificity and sensitivity were 63% and 66% where NCS had 83% and 78% respectively[7]. Despite this NCS should still be applied appropriately. An earlier prospective study of 40 patients had previously suggested NCS did not add to the diagnosis when symptoms and signs confirm CTS but merely delayed the diagnosis (by 10 weeks on average in this study). This was measured by initial NCS and initial and repeat surveys following injection of 8mg of Depo-medrone. It found that 70% of the patients benefited from injection and that even those with borderline/normal NCS and vague signs (32 patients), 66% still benefitted from injection [6].

Clinical and neurophysiological examinations are important in diagnosing CTS. In 181 patients referred to a neurologist for wrist pain and paraesthesia, only 37 were positive on clinical diagnosis and 31 were both positive on both clinical and neurophysiology. The study found NCS to have a sensitivity of 0.51 and specificity of 0.95 and suggested it were better to exclude CTS than accurately diagnose [8]. Higher sensitivities of NCS have been reported previously in the Takai Journal of Experimental and Clinical Medicine. A 2014 study reviewed five “Standard” nerve conduction studies as well as two “guideline” and “option” measurements. In 168 hands (104 CTS and 64 control) all measurements bar median motor distal latency measured sensitivities >83% in CTS hands and >67% in the milder subgroup. All measured specificities were >95%. It concluded that all the standard tests have comparable sensitivities and that the “option” second lumbricals-interossei latency should be recommended as “standard” [9]. Another concern for NCS is the question of grading severity that has been subsequently addressed in a 2013 article. While grading may be able to provide valuable guidance for management it is also misleading as latencies and other recorded data do not correlate to clinical symptoms. Additionally laboratories each have different reference values making it harder to have a standardised value [10]. Sucher also proposed a 3-level grading system as a baseline that may be able to be built on in the future.

However the information gathered from NCS must be applied with the clinical picture. This is due to CTS being a clinical syndrome, not an electrodiagnostic finding. In clinical cases of CTS with negative NCS the publication suggested that the (a) condition is too mild with few fibres affected; (b) symptoms present due to intermittent reversible ischaemia; (c) testing occurs after re-innervation of the sensory nerve action potential. The practical value in electrodiagnostic studies is to confirm no other condition exists and that whether a conduction block and/or axonal death are present. Neuromuscular US is a useful aid to diagnosis. It offers multiple measurements however the most reliable is MNCSA at tunnel inlet, and at the tunnel outlet [11] as enlarged nerve size is considered an objective sign of oedema. Further methods were wrist-forearm ratios as well as dynamic studies[12]. This was further supported by a 2013 study that compared multiple points for US in the wrist and forearm in a prospective study of 115 wrists. It found that MNCSA at its maximal shape offered a reproducible tool for CTS diagnosis and thresholds of 9.8-13.8mm^2 yielded sensitivity and specificity of 92% [13]. Other suggested methods by a paper published in 2015 included the difference (Δ-CSA) and ratio (R-CSA) between MNCSA at the carpal tunnel level and the pronator quadratus. Threshold values were useful in predicting CTS compared to NCS as well as determining moderate-severe disease [14]. A 2014 article suggested using the flattening ratio of the median nerve during certain movements of the hand (tendon gliding exercises) such as when moving from straight hand position to hook position and hook position to fist position. It also found significantly increased MNCSA in the CTS affected group compared to the normal group. However this study did not form any definitive conclusion regarding FR or MNCSA and thus does not contribute an overall opinion [15].

A 2015 review of the role of ultrasound in diagnosing CTS in Rheumatology further supports ultrasounds use as a diagnostic tool. Comparing US with NCS it stated that sensitivity and specificity were comparable. While it could not assess function, ultrasound of the wrist adds value to the diagnosis of CTS by allowing visualisation of the flexor retinaculum and underlying structures to detect abnormalities [16]. Wrist US can also be used as a guide for non-operative treatment (Steroid injection). Additionally, it is able to monitor disease progression as well as being more available and accessible [17]. A 2012 article also suggests that U/S is a more cost-effective strategy for CTS diagnosis than EDX alone, although it is important to state this is in an American health setting [18]. It has also been shown that US has a role to play in the diagnosis symptomatic patients with negative electrodiagnostic tests, especially in early CTS [19]. An earlier study also found similar results however used further subgroup analysis. It used 68 patients (102 wrists) with CTS against a control group of 36 (68 wrists). Within the 102 wrists, 74 also underwent NCS with 62 positive results. In the CTS group patients had a MNCSA of 12.7mm^2 and 11.4mm^2 (direct vs. indirect) whereas the healthy controls had values of 7.0mm^2 and 6.8mm^2 respectively. Subgroup analyses revealed that the CTS group with positive NCS actually had larger values (13.7 and 12.6mm^2). The direct method used a continuous boundary trace within the nerve's echogenic boundary where the indirect used the transverse and antero-posterior measurements [20].

Similarly, a 2014 article also supported U/S a diagnostic tool as an alternative for CTS diagnosis. In this prospective study, 90 patients and 180 wrists were assessed. Of these, 120 wrists were electrophysiologically confirmed as CTS and 60 non-diseased. Ultrasound was then used to measure across three levels; proximal to tunnel inlet, at the tunnel inlet and outlet, and flexor retinaculum thickness (FRT). Comparisons were then made between U/S and NCS. The authors found that in CTS diseased hands. The mean MNCSA were 13.31 and non-disease 8.57 mm. A threshold of 9.15 mm^2 MNCSA at tunnel inlet was found to be the most diagnostically accurate, with 99.2% and 88.3% sensitivity and specificity respectively [21].

As previously stated above, there are many studies that demonstrate U/S as comparable in terms of sensitivity and specificity to NCS in the diagnosis of CTS. However, there is a range of MNCSAs being reported for diagnosis of CTS. It has been hypothesised that this may be due to differences between study groups, such as age and ethnicity and other biometric factors. Fu *et al*. thus suggests that to account for this individual variability, a ratio between inlet CSA and outlet CSA should be utilised. The authors found that IOR improves the diagnostic accuracy for diagnosis of CTS, with specificity of 93% and sensitivity of 91% with the optimal diagnostic cut off value of 1.3 [22].

Another subgroup of CTS patients exists where NCS is normal. A 2014 study also assessed MNCSA and Flexor Retinaculum Thickness (FRT) in 35 patients (60 wrists) with clinical CTS but normal NCS against a control of 20 patients (40 hands). Using cut-off values obtained from the control group of 9.5mm^2 for MNCSA and 0.8mm for FRT it found similar measurements as previously mentioned studies with MNCSA increased in 48.6% and FRT in 34.3% of patients. While supportive of ultrasound as an adjunct this was quite a small study, with patients already pre-screened by specialists and with co-existing conditions excluded [23]. Similarly, a 2014 case report found two cases, a 41-year-old male and 38-year-old Asian female who despite chronic CTS symptoms had repeated normal NCS. On ultrasound the male was found to have a MNCSA of 13mm^2 and the female had 22mm^2 and 20mm^2 (Carpal tunnel entry and exit). The cause of this was theorized to be a "pattern reversal" from ischaemia-reperfusion injury of the synovial connective tissue surrounding the median nerve [24]. While supportive of the found literature, little significance can be taken due to the lack of strength of a case report.

Further studies have aimed to analyse investigation for CTS in multiple other ways. A 2014 article reviewed ultrasound as a prognostic factor for carpal tunnel decompression. This observational study had a large patient population, reviewing all the patients who attended a dedicated CTS clinic between 2007-2011. Patients completed the Boston CTS-specific Symptom Severity Scale (SSS) and Functional Status Scale (FSS) both at time of NCS and at follow-up as well as a simple 1-5 scale and the Canterbury Severity Scale (CSS) at the NCS. At the time of data extraction 150 hands were available with US results and five were excluded. From this study 86% of the remaining cases described "much improved" or "cured". Uni-variate analysis revealed no clear correlation

between surgery and change in SSS or FSS. Multi-variate analysis however found several factors that increased the likelihood of success such as higher BMI, non-manual worker, right side surgery, higher neurophysiological grade, and larger CSA. This is one of the few studies to not confirm small or large CSA measurements as positive predictive factors for surgical outcome [25]. Further methods that have been reviewed are median nerve longitudinal displacement, MN area as well as perimeter measurement using both dynamic and static US. A 2015 article found that patients with CTS had decreased MN longitudinal displacement, as well as increased MN area and perimeter in a prospective study of 155 patients. It also found that changes identified were more convincing when CTS was deemed severe and that US demonstrated a sensitivity of 70-71% and specificity of 80-84% [26].

The role of Doppler U/S in assessing intraneural blood flow has also been explored, with a review of 7 articles being established by an article in 2014. There are numerous hypotheses in the pathophysiology of CTS, with one being nerve ischaemia second to compression [27]. The review established the median sensitivity of Doppler being 72% (41 – 95%) and median specificity of 88% (71 – 100%). The review finds that intraneural blood flow across the 7 studies reviewed never being demonstrated in healthy individuals. Thus, detection of median nerve intraneural blood flow may indicate pathology. The exact pathophysiological mechanism is unclear, as increased intraneural flow is also detected in ulnar neuropathy and leprosy. As with other forms of U/S, Doppler is operator dependant [28] requiring sufficient expertise in the medium. It is thus difficult to determine the diagnostic value of Doppler U/S in diagnosis of CTS, as EDX studies and MNCSA seem to be more diagnostically accurate [29].

Conclusion

Nerve conduction studies and ultrasonography are both useful tools in the diagnosis of carpal tunnel syndrome. Both modalities have multiple studies reviewing the benefits and detriments of each approach. Nerve conduction studies have much support in the literature, however ultrasonography, especially the use of median nerve cross sectional area, has a growing body of literature supporting it as a diagnostic aid for CTS. As more clinicians utilise ultrasonography as a diagnostic tool due to its lower cost and wider availability hopefully further research will support ultrasonography being adopted as a primary tool for diagnosis. At this stage NCS are still the gold standard diagnostic tool in the diagnosis of CTS, however information must be applied appropriately to the clinical scenario at hand.

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