EVIDENCE-BASED GUIDELINE: NEUROMUSCULAR ULTRASOUND FOR THE DIAGNOSIS OF CARPAL TUNNEL SYNDROME

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ABSTRACT: *Introduction*: The purpose of this study was to develop an evidence-based guideline for the use of neuromuscular ultrasound in the diagnosis of carpal tunnel syndrome (CTS). *Methods*: Two questions were asked: (1) What is the accuracy of median nerve cross-sectional area enlargement 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? A systematic review was performed, and studies were classified according to American Academy of Neurology criteria for rating articles of diagnostic accuracy (question 1) and for screening articles (question 2). *Results*: Neuromuscular ultrasound measurement of median nerve cross-sectional area at the wrist is accurate and may be offered as a diagnostic test for CTS (Level A). Neuromuscular ultrasound probably adds value to electrodiagnostic studies when diagnosing CTS and should be considered in screening for structural abnormalities at the wrist in those with CTS (Level B).

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Carpal tunnel syndrome (CTS) is a combination of signs and symptoms resulting from mononeuropathy of the median nerve as it passes through the rigid carpal tunnel in the wrist.[1] It is a common condition that affects 2.7% of the general population and results in health-care costs exceeding $500 million annually in the USA.[2,3] CTS is typically diagnosed by history and physical examination, and electrodiagnostic studies (nerve conduction studies and sometimes electromyography) are used to confirm the presence of a median mononeuropathy. Electrodiagnostic studies have limitations; they are uncomfortable and do not directly assess the anatomy of the median nerve and its surrounding structures.

Over the past 20 years, neuromuscular ultrasound has been introduced into electrodiagnostic laboratories as a complement to nerve conduction studies and electromyography for the diagnosis of a variety of nerve and muscle conditions.[4] CTS is the condition most commonly studied with neuromuscular ultrasound, and individuals with CTS have displayed ultrasonographic evidence of focal enlargement of the median nerve at the wrist.[5] In addition, neuromuscular ultrasound can identify causes of median mononeuropathy at the wrist and structural anomalies that could not be detected with electrodiagnostic studies alone, such as compressive cysts, tumors, and vessels.[5]

This evidence-based guideline was designed to address 2 critical questions regarding the use of neuromuscular ultrasound for the diagnosis of CTS. First, what is the accuracy of median nerve cross-sectional area enlargement, as measured with ultrasound, for the diagnosis of CTS? Second, what added value, if any, does neuromuscular ultrasound provide over electrodiagnostic studies alone for the diagnosis of CTS?

DESCRIPTION OF THE ANALYTIC PROCESS

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) convened an expert panel of physicians specializing in neurology, physical medicine and rehabilitation, and radiology, selected to represent a broad range of expertise related to neuromuscular ultrasound and CTS. Some panel participants reported using

Abbreviations: AAN, American Academy of Neurology; AANEM, American Association of Neuromuscular and Electrodiagnostic Medicine; CTS, carpal tunnel syndrome; NCS, nerve conduction studies

Key words: carpal tunnel syndrome; median nerve; mononeuropathy; nerve conduction studies; ultrasound

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neuromuscular ultrasound frequently for clinical and research purposes, and others reported never using the technology. All panel participants had expertise in the clinical and electrodiagnostic assessment of CTS.

In May 2011, PubMed was used to search Medline to identify all potential abstracts. The search terms "carpal tunnel syndrome *OR* median nerve *OR* median neuropathy" were combined with the terms "ultrasound *OR* ultrasonography *OR* sonogram *OR* sonography." This produced 724 articles from 1990 to May 2011. This was narrowed to 641 articles by including "English-only" and "human-only" studies. The titles of those articles were reviewed for relevance, which yielded 240 articles, and each abstract was then reviewed by at least 2 investigators. This resulted in 121 articles for full manuscript review. After each article was reviewed in its entirety by 2 investigators, 67 were identified as relevant for this guideline. In order to be considered relevant, the article had to describe the use of ultrasound to image the wrist in individuals suspected of having CTS.

The 67 relevant articles were rated by at least 2 investigators according to criteria set by the American Academy of Neurology (AAN).[6] Articles pertaining to the accuracy of median nerve cross-sectional area measurements for the diagnosis of CTS (45 articles) were assessed using the AAN criteria for rating an article on diagnostic accuracy, and articles pertaining to neuromuscular ultrasound as a screening tool to identify anatomic explanations for CTS were assessed using AAN criteria for rating a screening article (23 articles). One article was assessed for both diagnostic accuracy and as a screening article. Both rating systems are included in the Appendices.

Studies with the highest levels of evidence (Class I and II) are discussed in the text and summarized in the evidence tables. At each step in the process, disagreements were arbitrated by a third investigator.

ANALYSIS OF THE EVIDENCE

Accuracy of Neuromuscular Ultrasound. Forty-five relevant articles pertaining to the accuracy of neuromuscular ultrasound in the diagnosis of CTS were identified. Four were graded as Class I and 2 as Class II. Of the 27 that were Class III, 18 received this rating because they had spectrum bias (in all cases healthy volunteers served as the control group); 6 received this rating because the ultrasonographer was not blinded to clinical or other diagnostic information; and 3 had both spectrum bias and lack of blinding.[7–33] Spectrum bias occurs when cases and controls are potentially at opposite ends of the disease spectrum, which may artificially enhance the diagnostic accuracy of a test. For example, the articles with spectrum bias reviewed in this study used healthy volunteers as controls rather than a control population more representative of individuals referred for possible CTS in a typical clinical practice. If not explicitly stated in the article that blinding of the ultrasonographer occurred, the corresponding author was e-mailed to clarify this issue, and if no response was received it was categorized as having not been blinded. In general, the Class III articles demonstrated high diagnostic accuracy of ultrasound for the diagnosis of CTS, similar to the Class I and II articles. Of the 12 articles graded as Class IV, 8 received this rating because they did not report enough measures of diagnostic accuracy (sensitivity and specificity, or a likelihood ratio) and 4 because the control group selection was not acceptable.[34–45] In all 4 cases in which the control group selection was unacceptable, the control group included individuals with symptoms consistent with CTS but normal nerve conduction studies. Although it is important to study individuals with this type of conflicting clinical data (incongruent symptoms and nerve conduction studies), it is the authors' opinion that it is problematic to use such individuals as a control group when assessing the accuracy of a diagnostic test.

Four articles were identified that met Class I level of evidence (Table 1), meaning that the studies were prospective (cohort studies), were blinded, were free of spectrum bias, used appropriate reference standards, and included measures of diagnostic accuracy.[46–49] Three of the studies defined individuals as having CTS if they had both consistent clinical symptoms and abnormal nerve conduction studies, whereas Altinok et al. defined CTS as those with a consistent clinical presentation and improvement in symptoms after 3 months of non-surgical treatment. Three studies used wrists contralateral to the wrist with CTS as the controls (as long as the participant was asymptomatic on that side and the nerve conduction studies were normal on that side),[46,47] and Altinok et al. recruited controls from outpatients presenting to the same clinic for causes unrelated to CTS. The presence of different case definitions for CTS is not problematic. In fact, in a condition such as CTS, in which the "gold standard" for diagnosis is debated, it is beneficial in evidence-based guidelines to have studies in which the reference standards for diagnosis were established using different methods. Similarly, it is beneficial to have different control groups, and the authors thought the 2 different control groups (contralateral unaffected hands and individuals referred to the clinic for non-CTS indications) were clinically appropriate

Table 1. Class I level of evidence studies* of the accuracy of neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome.

Year	First author	Reference standard	Number with CTS	Number without CTS	Sensitivity	Specificity	Accuracy	Area cut-off
2004	T. Altinok	Clinical + improvement	40	40	65.0%	92.5%	78.9%	9 mm^2
		and NCS	NA	NA	100%	92.5%	NA	9 mm^2
2004	S.M. Wong	Clinical + NCS	64	33	82.8%	72.7%	79.3%	10 mm^2
2005	H.-R. Ziswiler	Clinical + NCS	78	23	82.0%	87.0%	83.4%	10 mm^2
2010	A. Mohammadi	Clinical + NCS	132	32	97.0%	98.0%	97.2%	8.5 mm^2

NA, not available (data presented in the article did not include this value or permit calculation of this value); NCS, nerve conduction studies.
**To meet Class I level of evidence these studies are prospective, are blinded, are free of spectrum bias, have appropriate reference standards, and include measures of diagnostic accuracy.*

and minimized spectrum bias. The use of contralateral unaffected wrists also raised the question of whether there was statistical independence between the control wrists and the wrists with CTS. This cannot be definitively answered without the original data. However, if they were not independent, that would make the control and affected wrists more similar, which would likely result in an underestimation of the diagnostic accuracy of the test.

The four Class I studies used slightly different median nerve cross-sectional area cut-offs to diagnose CTS (ranging from 8.5 to 10 mm^2), and all studies used the direct tracing method to measure median nerve area. Ziswiler et al. measured the median nerve at the site of maximal enlargement at the wrist, and the other 3 studies measured the nerve at, or just proximal to, the level of the pisiform bone. Our guideline development panel considered studies with diagnostic accuracy >70% to be acceptable and supportive of neuromuscular ultrasound for the diagnosis of CTS (accuracy = sensitivity × prevalence + specificity × (1 − prevalence)). The sensitivity of median nerve cross-sectional area for the diagnosis of CTS ranged from 65% to 97%, specificity from 72.7% to 98%, and accuracy from 79% to 97%. Interestingly, Altinok et al. also analyzed their data using nerve conduction studies in addition to clinical diagnosis, and this more strict case definition of CTS resulted in an increase in the sensitivity of neuromuscular ultrasound from 65% to 100%.

Two Class II articles were identified (Table 2), and they met the same criteria as the Class I articles, except they involved retrospective data collection (case–control studies).[50,51] Nakamichi and Tachibana used only clinical criteria to classify participants as CTS or controls, and the control subjects were recruited from a health fair. The median nerve cross-sectional area was calculated by tracing the nerve at 3 sites within the carpal tunnel and taking the mean of those measurements, with 12 mm^2 selected as the cut-off for the diagnosis of CTS. The study by Klauser et al. is unique among the 6 Class I and II articles in that it only examined those with bifid median nerves within the carpal tunnel. The area of each portion of the nerve was traced and then added together, and a single cut-off of 12 mm^2 was used. They also reported improved accuracy when the difference between the median nerve area measured at the wrist and proximal forearm was calculated, with a difference of 4 mm^2 or greater used to diagnose CTS.

Conclusion. Based on consistent Class I and Class II evidence, neuromuscular ultrasound measurement of median nerve cross-sectional area at the wrist is established as accurate for the diagnosis of CTS.

Recommendation: If available, neuromuscular ultrasound measurement of median nerve cross-sectional area at the wrist may be offered as an accurate diagnostic test for CTS (Level A).

Clinical Context. As is the case with all ultrasonographic imaging, neuromuscular ultrasound of the median nerve at the wrist should be performed and interpreted by clinicians experienced with the technique. Scanning protocols and reference values for median nerve cross-sectional area at the

Table 2. Class II level of evidence studies* of the accuracy of neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome.

Year	First author	Reference standard	Number with CTS	Number without CTS	Sensitivity	Specificity	Accuracy	Area cut-off
2002	K. Nakamichi	Clinical	414	408	67.0%	97.0%	82.0%	12 mm^2
2011†	A.S. Klauser	Clinical + NCS	53	28	83.0%	50.0%	71.5%	12 mm^2
					92.5%	96.4%	93.9%	Δ4 $mm^{2‡}$

**To meet Class II level of evidence these studies are retrospective, are blinded, are free of spectrum bias, and include measures of diagnostic accuracy.*
†*This study only evaluated those with bifid median nerves.*
‡*This is the difference in median nerve area at the wrist compared to the forearm.*

Table 3. Class II level of evidence studies* of the added value of neuromuscular ultrasound in the diagnosis of carpal tunnel syndrome.

Year	First author	Number with CTS	Percentage and type of abnormal structures
1993	K. Nakamichi	20	25% with unilateral CTS (by clinical and NCS criteria) have *occult ganglia* in the carpal tunnel
2000	E. Iannicelli	294	2% with CTS have a *bifid median nerve*
2008	I.K. Bayrak	320	13% with CTS have a *bifid median nerve* 6% with CTS have a *persistent median artery*
2011	L. Padua	35	17% with CTS have a *finding that changes therapeutic approach* 9% have a *bifid median nerve* 9% have a *persistent median artery* 6% have *tenosynovitis* 3% have *accessory muscles*

**To meet Class II level of evidence these studies draw from a statistical and non-referral clinic-based sample of patients, evaluate all CTS patients prior to surgery, and conduct neuromuscular ultrasound on all study participants.*

wrist should be established by each laboratory prior to using neuromuscular ultrasound for the diagnosis of CTS.

Added Value of Neuromuscular Ultrasound. Twenty-three articles were identified that potentially demonstrated the added value of neuromuscular ultrasound as a diagnostic tool when used in combination with electrodiagnostic studies. Four were graded as Class II (Table 3), and the rest were classified as Class IV (all of these were case reports and case series). None were graded as Class I, because no studies drew from a population-based sample of patients. None were Class III, because all the studies that were not case reports or case series met Class II criteria.

The 4 articles that met Class II criteria described studies that drew from a statistical and non-referral clinic-based sample of patients, evaluated all CTS patients prior to surgery, and included neuromuscular ultrasound on all study participants.[7,52–54] Three of these articles described the detection of bifid median nerves at the wrist, and 2–13% of those with CTS had a bifid nerve.[7,53,54] Two studies described the detection of persistent median arteries, which occurred in 9–13% of those with CTS.[7,54] The study by Padua et al. also described the detection of tenosynovitis (6%) and accessory muscles within the wrist (3%) in those with CTS. The study by Nakamichi and Tachibana was unique in that it assessed the affected wrists in those with unilateral CTS (meaning the contralateral side was normal by clinical and nerve conduction criteria). Neuromuscular ultrasound detected occult ganglia causing median mononeuropathy in 25% of the CTS-affected wrists in this population.

All 19 of the Class IV articles were case reports or case series in which neuromuscular ultrasound was used to identify abnormal structures causing median mononeuropathy at the wrist. These structures included traumatic neuromas, Schwannomas, lipofibromatous hamartomas, ganglion cysts, thrombosed persistent median arteries, an abscess, and compressive gouty tophus.[55–73]

Conclusion. Based on Class II evidence, neuromuscular ultrasound of the wrist probably adds value to electrodiagnostic studies when assessing CTS as it can detect structural abnormalities.

Recommendation: If available, neuromuscular ultrasound should be considered to screen for structural abnormalities at the wrist in those with CTS (Level B).

Clinical Context. Screening for structural abnormalities at the wrist that cause CTS is likely to be of higher yield in those with atypical CTS. This was demonstrated by Nakamichi and Tachibana, who found a high rate of occult ganglia only in those with unilateral CTS. This is an atypical presentation, as most patients have bilateral CTS (defined by symptoms, nerve conduction studies, or both).[52] Other atypical presentations of CTS include sudden onset and onset in the setting of trauma. Although ultrasound can identify structural abnormalities, it is possible these abnormalities may not always be the underlying cause of the median mononeuropathy. In addition, the prevalence of such abnormalities in the general population is not known, so the sensitivity and specificity of ultrasound for the identification of these structures cannot be calculated based on currently available data. The wide prevalence range for bifid median nerves (2–13%) may be secondary to ultrasound device resolution (earlier studies identified fewer bifid nerves), ultrasound technique and site of imaging within the wrist, or patient population. The presence of structures such as persistent median arteries and accessory muscles is clearly of therapeutic interest, as it may alter the choice of interventional approach (either injection or

surgery). Knowledge of a bifid median nerve and other anatomic variants is also of interest in planning the treatment of CTS,[53] and identification of such variants prior to invasive intervention can even assist later in the assessment of failed intervention. In addition, the presence of a bifid median nerve may be an independent risk factor for the development of CTS.[7]

CLINICAL CONTEXT SUMMARY FOR ALL EVIDENCE

A single neuromuscular ultrasound evaluation of the wrist in those with CTS allows for assessment of both median nerve cross-sectional area and the presence of structural abnormalities, and this complements well the information obtained during an electrodiagnostic study (which is the gold standard for diagnosis of CTS). Some variability exists in the devices, scanning protocols, and reference ranges for the diagnosis of CTS when using neuromuscular ultrasound, but this is to be expected. As a comparison, similar variability exists in electrodiagnostic techniques. It is anticipated that with continued experience with neuromuscular ultrasound techniques, more uniformity will occur as consensus develops regarding optimal use of the technology. It should also be noted that many studies have proposed other neuromuscular ultrasound parameters that can be used to assist in the diagnosis of CTS, but these were not assessed in this guideline. These include median nerve flattening ratios; measures of median nerve mobility, echogenicity, and vascularity; and measures of flexor retinaculum bowing.

RECOMMENDATIONS FOR FUTURE RESEARCH

1 A standardized protocol for using neuromuscular ultrasound in the diagnosis of CTS should be developed. This should include definition of the optimal site of median nerve cross-sectional area measurement, standardization of nerve outlining technique, and further refinement of reference values.
2 Further research and evidence-based guidelines should assess the usefulness of other neuromuscular ultrasound parameters for the diagnosis of CTS, such as median nerve flattening, mobility, echogenicity, vascularity, and bowing of the flexor retinaculum.
3 Large population-based studies that enroll consecutive patients with CTS should be performed to assess for all structural abnormalities that may be causative or change therapeutic approach, which will help further determine the added benefit of neuromuscular ultrasound in the diagnosis of CTS.
4 Finally, large studies should be performed to determine whether neuromuscular ultrasound changes treatment strategies and outcomes in those with CTS when compared with those in which CTS is established using only electrodiagnostic studies. This type of study should also allow for cost–benefit analyses of neuromuscular ultrasound in the diagnosis of CTS.

DISCLAIMER

This statement has been provided as an educational service of the AANEM. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care of a particular neurological problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodology. The AANEM recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guidelines into perspective with current practice habits and challenges. No formal practice recommendation should be inferred.

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APPENDIX 1: AAN CLASSIFICATION OF THE EVIDENCE FOR RATING OF A DIAGNOSTIC ARTICLE[6]

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case–control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared with a broad spectrum of controls, or a cohort study with a broad spectrum of persons with the suspected condition where the data were collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case–control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

APPENDIX 2: AAN CLASSIFICATION OF THE EVIDENCE FOR RATING OF A SCREENING ARTICLE[6]

Class I: A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class II: A statistical, non-referral clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class III: A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

APPENDIX 3: CLASSIFICATION OF RECOMMENDATIONS

The four possible recommendation classifications include:

- A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in specified population. (Level A rating requires at least 2 consistent Class I studies.) [In exceptional cases, 1 convincing Class I study may suffice for an "A" recommendation if: (1) all criteria are met; and (2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.]
- B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least 1 Class I study or 2 consistent Class II studies.)
- C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least 1 Class II study or 2 consistent Class III studies.)
- U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

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