NEUROMUSCULAR ULTRASOUND FOR THE EVALUATION OF
AMYOTROPIC LATERAL SCLEROSIS

By

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LIST OF ABBREVIATIONS

ALS: amyotrophic lateral sclerosis
ALSFRS-R: revised ALS functional rating scale
EI: echo intensity
EMG: electromyography
FVC: forced vital capacity
MIP: maximal inspiratory pressure
MND: motor neuron disease
MUNE: motor unit number estimation
SMA: spinal muscular atrophy
SOD1: superoxide dismutase 1
TDP-43: TAR DNA-binding protein 43
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NEUROMUSCULAR ULTRASOUND DEFINITIONS

**Anechoic:** An absence of returning echoes, resulting in an image that is black.

**Echogenicity:** The degree to which a structure reflects echoes back toward the transducer. Increased echogenicity results in brighter images.

**Echointensity:** A quantitative assessment of echogenicity or brightness, typically presented as a single mean value obtained using gray-scale analysis of a region of interest.

**Echotexture:** The perceived texture of the image created after processing of the returning echoes recorded by the transducer.

**Gray-scale analysis:** A quantitative technique used to assess black and white pictures, such as ultrasound images, in which each pixel is assigned a value from 0 (black) to 255 (white) based on the shade of the gray in the pixel.

**Hyperechoic:** Increased echo signal, which results in a brighter image.

**Hypoechoic:** Decreased echo signal, which results in a darker image.
ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that causes progressive loss of motor neurons, which results in weakness, respiratory compromise, and typically death within 5 years of disease onset. The diagnosis is often delayed up to a year from the time of onset because it is a clinical diagnosis and there are few tests available to assist in the diagnostic evaluation. Neuromuscular ultrasound is an emerging tool for the diagnosis of a variety of conditions, but it has not been studied extensively in individuals with ALS. This study was designed to determine if neuromuscular ultrasound could detect changes in peripheral nerves and muscles of individuals with ALS, which could then be used to assist in diagnosis. Several neuromuscular ultrasound parameters were compared between 20 individuals with ALS and 20 age and gender matched controls. The cross-sectional area of the median nerve in the mid-arm was smaller in the ALS group than controls (10.5 mm$^2$ vs. 12.7 mm$^2$, p = 0.0023), and the ALS group also had a thinner biceps/brachialis muscle complex than controls (2.1 cm vs. 2.9 cm, p = 0.0007). These findings show that neuromuscular ultrasound can detect nerve and muscle atrophy in ALS, so it should be further explored prospectively as a diagnostic tool and possible disease biomarker.
Amyotrophic lateral sclerosis (ALS), which is also known as Lou Gehrig’s disease in the United States and Charcot’s or motor neuron disease (MND) in Europe, is a condition in which motor neurons in the brain and spinal cord progressively die, which results in limb weakness, dysarthria, dysphagia, dyspnea, and eventually respiratory compromise and death. Onset can occur at any age after the second decade of life, but prevalence escalates with increasing age and the peak age of onset is about 74 years old. The incidence in the United States and Europe ranges between 1.5 and 2.7 cases per 100,000 per year, and the incidence may be lower amongst African, Asian, and Hispanic ethnicities compared to whites. It occurs more often in men than women, and other identified factors that slightly increase the risk of developing ALS include cigarette smoking, United States military service, manual labor, athleticism, and trauma. The clinical presentation is variable, with asymmetric limb-onset weakness occurring in about 80% of cases, bulbar onset in nearly 20%, and diaphragmatic onset in fewer than 1%. Because both upper motor neurons (in the brain and spinal cord) and lower motor neurons (starting in the spinal cord and extending outward) are lost, the pattern of clinical manifestations is relatively unique and often involves progressive spasticity in addition to atrophy and weakness. There is no cure for ALS, and the glutamate inhibitor riluzole, which results in an increased life expectancy of just a few months, is the only approved medical treatment. Supportive care and interventions such as percutaneous
endoscopic gastrostomy feeding tubes and non-invasive ventilation have resulted in mild increases in life expectancy for those with ALS, but the mean time of death is still 3-4 years from disease onset.\textsuperscript{13,14}

The etiology of ALS remains unknown. Approximately 90\% of cases are sporadic and 10\% are familial, with the majority of inherited cases following an autosomal dominant pattern. Until recently, the most commonly identified form of familial ALS was caused by mutations in the superoxide dismutase 1 (SOD1) gene.\textsuperscript{15} While SOD1 mutations remain a cause in about 25\% of familial ALS cases, very recent data indicate that a hexanucleotide repeat expansion on chromosome 9p21 causes 46.0\% of familial ALS in a Finnish population. In addition, this gene is also linked to 21.1\% of sporadic ALS in the same population.\textsuperscript{16} While the complete pathophysiology of ALS remains unknown, these recent genetic discoveries indicate that a large portion of ALS cases are characterized by TAR DNA-binding protein (TDP-43) positive inclusions throughout the nervous system.\textsuperscript{17} It has also been shown that mutations in the gene encoding the protein ubiquitin 2 result in defects in the protein degradation pathway, which causes abnormal protein aggregation and perhaps explains a common mechanism for familial and sporadic ALS.\textsuperscript{18} Putting these recent genetic discoveries together has led to the intriguing theory that perhaps ALS results from the accumulation of toxic RNA, which interferes with normal cellular metabolism.\textsuperscript{16} Other implicated pathophysiologic mechanisms include glutamate excitotoxicity, glial cell mediated processes, mitochondrial dysfunction, growth factor deficiencies, and others.\textsuperscript{19}
Diagnosing ALS

Despite advances in understanding the pathophysiology of ALS, there remains no biochemical assay for the disease and establishing the diagnosis still requires a detailed history and physical examination. For clinical and research purposes, diagnostic criteria have been established through expert consensus, with the most commonly used criteria being the revised El-Escorial clinical criteria and the Awaji electrodiagnostic criteria (Figure 1.1).\textsuperscript{20, 21} These criteria are rooted in the basic premise that ALS causes death of upper and lower motor neurons, which spreads to contiguous spinal segments. This results in lower motor neuron findings of weakness, atrophy, fasciculations, and denervation potentials seen with electromyography (EMG), and upper motor neuron findings of spasticity, brisk reflexes, and the presence of normally absent pathologic reflexes. Exclusion of other conditions that mimic ALS is also an important aspect of the diagnostic process, and electrodiagnostic techniques (nerve conduction studies and EMG) help confirm denervation and reinnervation and exclude sensory nerve involvement and demyelination, which are uncommon in ALS.\textsuperscript{22} Taking all this information together, the diagnosis of ALS is usually clear to clinicians experienced with the disease, but it can be quite confusing to primary care physicians, non-neurologist specialists, and even neurologists not accustomed to seeing individuals with ALS.\textsuperscript{23} This results in a mean delay in diagnosis between 9 and 16 months, which can limit treatment options, decrease enrollment in clinical trials, increase patient and family distress and anxiety, and perhaps even close a window of time when motor neuron function is impaired but not irreversibly damaged, as has been suggested by animal and human research.\textsuperscript{24-26}
Figure 1.1. The revised El-Escorial and Awaji criteria are shown above. The Awaji criteria consider fasciculations to be evidence of lower motor neuron involvement and gives electrodiagnostic evidence of lower motor neuron dysfunction the same weight as clinical evidence.27 (LMN, lower motor neuron; UMN, upper motor neuron).
Development of other diagnostic tools is needed in ALS to help clinicians and researchers diagnose the condition earlier and more accurately.\textsuperscript{25} Even clinicians with extensive ALS experience encounter patients in which the diagnosis is not clear until months have elapsed and the disease has progressed as expected, so new diagnostic tools are actively being sought by those who treat and study this disease.

\textbf{Surrogate Markers of Disease Progression in ALS}

Several markers have been proposed for tracking disease progression in ALS and some are used routinely in clinical care and treatment trials (Table 1.2).\textsuperscript{28} The revised ALS Functional Rating Scale (ALSFRS-R) is a valid and reliable tool consisting of questions pertaining to daily function.\textsuperscript{29} It has high construct validity and is used in almost all clinical trials, although it may lack sensitivity for detecting progression that does not result in changes in activities of daily living. Forced vital capacity (FVC), maximal inspiratory pressure (MIP), and other measures of respiratory insufficiency are also used routinely in clinical and research settings, but these surrogate markers of disease progression also lack sensitivity, particularly in those who have not yet experienced respiratory involvement.\textsuperscript{30} Finally, motor unit number estimation (MUNE) is an electrodiagnostic technique that provides objective data of motor unit loss.\textsuperscript{31} It is reliable and demonstrates rates of decline in ALS that compare favorably to other biomarkers, but it is uncomfortable and its use has only been demonstrated in a small subset of muscles. In addition, MUNE can be time consuming and is not used in routine clinical practice.
Table 1.1. Current and potential biomarkers for diagnosis and tracking of disease progression in ALS.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Used Routinely?</th>
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<tbody>
<tr>
<td>ALS Functional Rating Scale</td>
<td>Yes</td>
</tr>
<tr>
<td>Forced Vital Capacity/Maximal Inspiratory Pressure</td>
<td>Yes</td>
</tr>
<tr>
<td>Electrodiagnostic Studies：&lt;br&gt;Motor unit number estimation</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurophysiological index</td>
<td>No</td>
</tr>
<tr>
<td>Electrical impedance myography</td>
<td>No</td>
</tr>
<tr>
<td>Phrenic nerve compound muscle action potential</td>
<td>No</td>
</tr>
<tr>
<td>Cerebrospinal fluid analyses：&lt;br&gt;TDP-43</td>
<td>No</td>
</tr>
<tr>
<td>Tau protein</td>
<td>No</td>
</tr>
<tr>
<td>S100beta</td>
<td>No</td>
</tr>
<tr>
<td>sCD14</td>
<td>No</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>No</td>
</tr>
<tr>
<td>Plasma analyses：&lt;br&gt;L-ferritin</td>
<td>No</td>
</tr>
<tr>
<td>Monocyte chemoattractant</td>
<td>No</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony stimulating factor</td>
<td>No</td>
</tr>
<tr>
<td>Magnetic resonance image techniques：&lt;br&gt;Diffusion weighted image</td>
<td>No</td>
</tr>
<tr>
<td>Diffusion tensor imaging</td>
<td>No</td>
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</table>

Other surrogate markers of disease progression have been developed for following individuals with ALS (Table 1.2), but the ALSFRS, FVC, and MUNE are employed most often, and a combination of these markers are typically used in clinical trials as they have complementary characteristics. Ideally, future biomarkers for ALS will be reliable, sensitive (even to pre-clinical changes), painless, quick, applicable to different muscle groups that may be affected (and different sub-types of ALS), and responsive to meaningful changes in disease progression. Such biomarkers will increase the accuracy and decrease the length of clinical trials.
Neuromuscular Ultrasound

Neuromuscular ultrasound involves the use of high-resolution ultrasound to image peripheral nerves and muscles, which can assist in the diagnosis of a variety of neuromuscular diseases. Its use was first described in the early 1980s in patients with muscular dystrophy, but since then it has been used to improve diagnostic capabilities in focal neuropathies, inherited neuropathies, inflammatory muscle diseases, and autoimmune mediated neuropathies. In general, diseased muscle has increased echogenicity and increased homogeneity of echotexture, and some diseases result in muscle atrophy with others showing edema and hypervascularity. Diseased nerves often enlarge, are hypoechoic, and may have increased vascularity. In addition to providing information about muscle and nerve anatomy and pathophysiology, neuromuscular ultrasound is also a promising technique because it is painless, does not use radiation, is relatively inexpensive, is readily available, and often can be performed rapidly. While it has been used to assess many conditions, neuromuscular ultrasound has been studied only minimally in the evaluation of ALS.

Neuromuscular Ultrasound in ALS

There are several potential methods in which neuromuscular ultrasound could be used to assess individuals with ALS, some which have been explored preliminarily and others which have not. Muscle ultrasound has been evaluated in the motor neuron disease spinal muscular atrophy (SMA) and in ALS, with typical echotexture findings listed in
Table 1.2. Muscle ultrasound has also been used to detect the presence of fasciculations, with ultrasound.

Table 1.2 Neuromuscular Ultrasound Findings in Motor Neuron Disease

| 1. Increased muscle echogenicity |
| 2. Increased muscle heterogeneity |
| 3. Increased subcutaneous tissue thickness |
| 4. Muscle atrophy |
| 5. Increased subcutaneous tissue-to-muscle thickness ratio |
| 6. Increased calf size |
| 7. Long duration fasciculations |

demonstrating higher sensitivity than both visual inspection and EMG. Three longitudinal studies have examined muscle thickness, as measured by ultrasound, in individuals with ALS, and all have demonstrated a small but statistically significant decrease in muscle thickness over several months. Conversely, neuromuscular ultrasound of peripheral nerves in those with motor neuron disease has not previously been reported, and while autopsy studies have shown nerve root atrophy, there is a surprising lack of any imaging studies confirming this finding in peripheral nerves in vivo. Since peripheral nerve imaging has not previously been reported in ALS and muscle imaging has only been preliminarily explored, this study was designed to explore these two imaging targets further using high resolution neuromuscular ultrasound.

Study Design and Specific Aims

This project was designed as a pilot study to examine the use of neuromuscular ultrasound as a potential tool for diagnosis and possibly as a surrogate marker of disease.
progression in those with ALS. Two questions were of specific interest. First, do peripheral nerves carrying motor fibers change in size (either increase or decrease), as measured with neuromuscular ultrasound, in individuals with ALS compared to controls? Second, does neuromuscular ultrasound demonstrate muscle atrophy in those with ALS compared to controls?

To address these questions, a prospective study with 20 individuals with ALS and 20 age and sex matched controls was designed. A specific effort was made to target and enroll individuals with advanced weakness and atrophy of at least one upper extremity, so this proof-of-concept pilot study would not be limited by the presence of subtle changes in those early into the disease process. In all 40 individuals neuromuscular ultrasound was performed to assess the following:

1. Cross-sectional area of the median nerve at the mid-point of the upper arm. This site was chosen because it is a nerve that is commonly studied with neuromuscular ultrasound, it carries motor fibers to many muscles in the distal arm and hand, it is a site that is easy to visualize, and it is site at which the nerve is not often compressed (as opposed to the wrist, where it is frequently entrapped and causes carpal tunnel syndrome and nerve enlargement).

2. Cross-sectional area of the sural nerve 10 cm above the lateral malleolus. This nerve was chosen because it is a pure sensory nerve that should not be affected by the neurodegeneration that occurs in motor and mixed nerves in ALS. It is also a nerve that is easily visualized with neuromuscular ultrasound and is not frequently entrapped.
3. Thickness of the biceps brachii and brachialis muscle complex at the midpoint of the upper arm.

It was hypothesized that there would be no difference in sural nerve area between the two groups and there would be significant atrophy in the biceps/brachialis muscle complex in patients with ALS. However, it was difficult to speculate whether the median nerve would show an increase or decrease in size in ALS compared to controls. One line of thought was that the nerve would increase in size because other neuropathic conditions, such as entrapment, inflammatory neuropathies, and inherited neuropathies have all demonstrated nerve enlargement as part of the disease process.\textsuperscript{44, 56, 57} This includes processes that involve progressive axon death, such as CMT Type 2 and diabetic polyneuropathy, although nerve enlargement is greater in demyelinating hereditary polyneuropathies compared to axonal hereditary polyneuropathies.\textsuperscript{58, 59} Alternatively, one might expect the median nerve to be smaller in those with ALS compared to controls, since there is significant axon loss in ALS once distal atrophy is present,\textsuperscript{60} and autopsy studies reveal thinning of nerve roots.\textsuperscript{55}

These thoughts led to the development of the following \textbf{Specific Aims}:

\textbf{Specific Aim 1.} To determine if neuromuscular ultrasound measurement of the median nerve in the upper arm can demonstrate measurable changes in nerve cross-sectional area in 20 adults with ALS compared to 20 age and gender matched controls.
Specific Aim 2. To determine if neuromuscular ultrasound measurement of the biceps brachii/brachialis muscle complex can demonstrate measurable atrophy in 20 adults with ALS compared to 20 age and gender matched controls.


32. de CM, Scotto M, Lopes A, Swash M. Quantitating progression in ALS. Neurology 2005; 64:1783-1785.


CHAPTER II

PERIPHERAL NERVE AND MUSCLE ULTRASOUND IN AMYOTROPHIC LATERAL SCLEROSIS

The following manuscript was published in the journal *Muscle & Nerve* September, 2011 and is reprinted with permission. Stylistic variations are due to requirements of the journal. MS Cartwright performed the experiments, data analysis, and prepared the manuscript. Drs. Walker and Caress acted in advisory and editorial capacities, and Ms. Griffin assisted with statistical analyses.
Peripheral Nerve and Muscle Ultrasound in Amyotrophic Lateral Sclerosis

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Running Title: Ultrasound in ALS

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Abstract

Introduction: High-resolution ultrasound has been used to evaluate several neuromuscular conditions, but it has only been used on a limited basis in ALS patients. It has not been used to assess their peripheral nerves. This study was designed to use neuromuscular ultrasound to investigate nerve cross-sectional area and muscle thickness in ALS.

Methods: Twenty individuals with ALS and 20 matched controls underwent neuromuscular ultrasound to measure the cross-sectional area of their median and sural nerves and the thickness of their biceps/brachialis muscle complex.

Results: The cross-sectional area of the median nerve in the mid-arm was smaller in the ALS group than controls (10.5mm² vs. 12.7mm², p=0.0023), but no difference was seen in the sural nerve (4.5mm² vs. 5.0mm², p=0.1927). The ALS group also had thinner biceps/brachialis than controls (2.1cm vs. 2.9cm, p=0.0007).

Discussion: Neuromuscular ultrasound demonstrates nerve and muscle atrophy in ALS and should be further explored as a disease biomarker.

Key Words: Amyotrophic lateral sclerosis, ultrasound, median nerve, sural nerve, muscle
Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease for which there is neither cure nor treatment to significantly slow the progressive weakness. Multiple obstacles hinder the ability to study and effectively treat ALS, one of which is the limited number of tests available to assist in the early diagnosis and monitoring of disease progression. Diagnosis of ALS is not typically made until 9-10 months after the onset of symptoms, and the diagnosis is based on history and clinical examination. Excluding other causes of progressive weakness through the use of blood work, central nervous system imaging, and electrodiagnostic studies helps support the diagnosis of ALS. Monitoring disease progression can be done with manual strength testing, assessment of forced vital capacity (FVC), the ALS functional rating scale (ALSFRS), and motor unit number estimation (MUNE), but all of these techniques have limitations, including lack of responsiveness, operator variability, and pain.

Over the past decade, high-frequency diagnostic ultrasound of peripheral nerve and muscle has emerged as a tool to assist in the evaluation of individuals with neuromuscular conditions, and it has become known as neuromuscular ultrasound. This technique has only been assessed on a limited basis in those with ALS, and the few studies of neuromuscular ultrasound in ALS evaluated muscle and did not assess nerve characteristics. In addition, there are surprisingly few studies of peripheral nerve caliber and muscle thickness using other imaging modalities or macroscopic analysis at autopsy in individuals with ALS. There exist reports of nerve root atrophy in ALS, but the literature is sparse and does not examine nerve caliber in the limbs. Therefore, this
study was undertaken to use neuromuscular ultrasound to compare nerve caliber and
muscle thickness in individuals with ALS and age and gender matched controls.

In other systemic conditions affecting the peripheral nerves, such as diabetes,
multifocal motor neuropathy, Charcot-Marie Tooth disease, and chronic inflammatory
demyelinating polyneuropathy, neuromuscular ultrasound has demonstrated increased
nerve cross-sectional area.\textsuperscript{11-14} It was unknown if a similar finding would be detected in
ALS, or if nerve cross-sectional area would be reduced because of progressive axon loss.
We hypothesized that muscle ultrasound would demonstrate atrophy.
Materials and Methods

Participants

Prior to the collection of data, this study was approved by the Institutional Review Board at Wake Forest University School of Medicine, and all participants provided signed informed consent. Initially, 20 patients with “probable,” “laboratory-supported probable,” or “definite” ALS based on Revised El Escorial Criteria were recruited. These participants were diagnosed with ALS by experienced ALS clinicians (MSC and JBC), and each participant had extremity strength testing (performed by the diagnosing physicians and graded on Medical Research Council scale), FVC (performed by a respiratory therapist and recorded as “percent of predicted”), and ALSFRS (recorded as the “global score”) on the same day the ultrasound was performed. The number of months since the onset of symptoms, weight, height, and race were also recorded.

Once 20 participants with ALS were recruited and assessed, 20 age and gender matched controls were recruited. The control group included friends and family of the ALS participants and medical center employees. Controls were excluded if they reported any symptoms referable to the nervous system. Controls underwent ultrasound and strength testing, and their weight, height, and race were recorded.

Ultrasound

All 40 participants (20 with ALS and 20 controls) underwent neuromuscular ultrasound, performed by the same physician (MSC). A Biosound MyLab 25 (Esaote Group, Genoa, Italy) with an 18 MHz linear array transducer was used for each study. The participants were in the supine or seated position, with the ultrasonographer facing
the patient, and all imaging was performed bilaterally. First, the mid-point of the arm was identified at the half-way mark between the medial epicondyle and the axilla, and the median nerve was imaged at this site (Figure 2.1A). This point was selected for study because the median nerve is commonly assessed with neuromuscular ultrasound, reference values are available for the median nerve at this site, and it is an uncommon site of entrapment. The transducer was placed so that a cross-sectional view of the median nerve was obtained. The cross-sectional area of the nerve was measured using the trace function on the ultrasound device and tracing along the hyperechoic rim of the nerve, erring just to the inside of the rim (Figure 2.1B). This was performed three times, and all three measurements were then averaged to obtain a final median nerve cross-sectional area measurement. The right and left median nerves were recorded separately, and the two were averaged to obtain a mean median nerve cross-sectional area for each participant.

Figure 2.1. Image A demonstrates the transducer position used to visualize the median nerve in the mid-arm and obtain the ultrasound image shown in panel B. The arrow points to the median nerve (outlined in white), and the arrowhead points to the adjacent brachial artery. The “H” is placed over the humerus.
Next, the sural nerve was assessed at 10 cm above the lateral malleolus (Figure 2.2A). The transducer was again positioned to obtain a cross-sectional view of the nerve, and an area measurement was obtained (Figure 2.2B). This was performed three times, and mean values were recorded for each side. A total sural nerve mean cross-sectional area was obtained by averaging both sides together. The sural nerve was selected because there are reference values available and it is a pure sensory nerve that should not be affected by ALS.¹⁸

![Image 2.2](image2.2.jpg)

**Figure 2.2.** Image A demonstrates the transducer position used to visualize the sural nerve and obtain the ultrasound image shown in panel B. The arrow points to the sural nerve (outlined in white), which is located between two superficial veins.

Finally, we returned to the mid-point of the arm to measure the thickness of the biceps brachii and brachialis muscle complex. The transducer was placed over the anterior portion of the mid-arm, with the elbow extended, to obtain a cross-sectional view of the arm (Figure 2.3A). Using the straight line measuring function on the ultrasound device, the thickness of the biceps/brachialis complex was measured from the most superficial portion of the muscle to the hyperechoic reflection of the humerus (Figure 2.3B). Care was taken to minimize pressure from the transducer on the muscle to avoid muscle
compression. This measurement was repeated twice to obtain a mean value for each side, and the two sides were averaged in each participant to obtain an overall mean biceps/brachialis thickness value.

Figure 2.3. Image A demonstrates the probe position used to visualize the biceps/brachialis muscle complex shown in panel B. The superficial extent of the muscle and the echogenic reflection from the humerus are marked with plus signs (+).

Statistical Analyses

Descriptive statistics include means and ranges for continuous measures and counts and percentages for categorical measures. All statistical tests were two-sided, and significance was determined at the 0.05 probability level. Comparisons between the ALS and control groups were done with two-tailed t-tests for continuous variables and chi-squared tests for categorical variables. Pearson product-moment correlation coefficients were calculated to determine correlation between ultrasonographic parameters and strength testing, FVC, ALSFRS, and months since disease onset.
Results

Twenty participants with ALS and 20 controls were included in this study. No significant differences in age, gender, race, height, weight, or body mass index (BMI) were noted between the two groups (Table 2.1). The 20 individuals with ALS had symptoms for an average of 25.1 months prior to enrollment in this study, and their mean FVC was 62.3% and the ALSFRS was 30.5 (Table 2.2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls n = 20</th>
<th>ALS Patients n = 20</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mean Age (range)</td>
<td>58.1 (42 – 76)</td>
<td>58.4 (40 – 71)</td>
<td>0.9231</td>
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<tr>
<td>Gender (male)</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
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</tr>
<tr>
<td>Race (Caucasian)</td>
<td>20 (100%)</td>
<td>19 (95%)</td>
<td>0.3112</td>
</tr>
<tr>
<td>Mean Height (range)</td>
<td>66.7 (61 – 75)</td>
<td>67.1 (61 – 71)</td>
<td>0.7140</td>
</tr>
<tr>
<td>Mean Weight (range)</td>
<td>171.6 (135 – 235)</td>
<td>162.3 (117 – 212)</td>
<td>0.2984</td>
</tr>
<tr>
<td>Mean BMI (range)</td>
<td>27.3 (20.9 – 39.5)</td>
<td>25.4 (19.3 – 33.8)</td>
<td>0.2090</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (%)</td>
<td>62.3 (20 – 99)</td>
</tr>
<tr>
<td>ALSFRS</td>
<td>30.5 (12 – 48)</td>
</tr>
<tr>
<td>Months Since Onset</td>
<td>25.1 (6 – 60)</td>
</tr>
</tbody>
</table>

Significant differences were found when comparing median nerve cross-sectional area and biceps/brachialis thickness between the two groups, and these differences were found when using just the left arm and the total values for each individual (Table 2.3). The total median nerve area was larger in controls (12.7 mm$^2$ vs. 10.5 mm$^2$, $p = 0.0023$), and the total muscle thickness was greater in controls (2.9 cm vs. 2.1 cm, $p = 0.0007$). No
differences were noted when comparing the sural nerve cross-sectional area between the two groups (Table 2.3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls n = 20 Mean (range)</th>
<th>ALS Patients n = 20 Mean (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Median Area (mm²)</td>
<td>12.6 (9.5 – 15.0)</td>
<td>9.9 (7.0 – 15.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Average Median Area (mm²)</td>
<td>12.7 (9.3 – 16.3)</td>
<td>10.5 (7.0 – 15.5)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Left Sural Area (mm²)</td>
<td>5.0 (3.0 – 8.0)</td>
<td>4.5 (2.0 – 7.0)</td>
<td>0.1858</td>
</tr>
<tr>
<td>Average Sural Area (mm²)</td>
<td>5.0 (3.0 – 8.0)</td>
<td>4.5 (2.5 – 6.5)</td>
<td>0.1927</td>
</tr>
<tr>
<td>Left Muscle Thickness (cm)</td>
<td>3.0 (1.7 – 4.2)</td>
<td>2.0 (0.4 – 3.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average Muscle Thickness (cm)</td>
<td>2.9 (2.0 – 4.3)</td>
<td>2.1 (0.4 – 3.8)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Statistically significant correlation was only seen when comparing the thickness of the biceps/brachialis muscle complex to the MRC-graded strength testing of the biceps muscle (r=0.5062, p=0.0228), although the correlation between the cross-sectional area of the left median nerve and the strength of the abductor pollicis brevis (APB) muscle approached statistical significance (r=0.4206, p=0.0648). No significant correlation was seen when comparing the total median nerve cross-sectional area to the FVC, ALSFRS or months since onset, or when comparing the total biceps/brachialis thickness to the FVC, ALSFRS or months since onset (Table 2.4).
Table 2.4  Correlation Between Ultrasonographic Parameters and Other Variables

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Correlation Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Median Area vs. FVC</td>
<td>-0.0075</td>
<td>0.9750</td>
</tr>
<tr>
<td>Average Median Area vs. ALSFRS</td>
<td>0.1280</td>
<td>0.5908</td>
</tr>
<tr>
<td>Left Median Area vs. Left APB strength</td>
<td>0.4206</td>
<td>0.0648</td>
</tr>
<tr>
<td>Muscle Thickness vs. Biceps Strength</td>
<td>0.5062</td>
<td>0.0228</td>
</tr>
<tr>
<td>Average Muscle Thickness vs. FVC</td>
<td>0.3721</td>
<td>0.1062</td>
</tr>
<tr>
<td>Average Muscle Thickness vs. ALSFRS</td>
<td>0.3325</td>
<td>0.1520</td>
</tr>
<tr>
<td>Average Median Area vs. Months since onset</td>
<td>-0.3106</td>
<td>0.1825</td>
</tr>
<tr>
<td>Average Muscle Thickness vs Months since onset</td>
<td>-0.0806</td>
<td>0.7356</td>
</tr>
</tbody>
</table>

Discussion

This study compared nerve cross-sectional area measurements in individuals with ALS to age and gender matched controls. The 20 individuals in the control group matched well with the ALS group, with no significant differences in the groups with respect to age, gender, race, height, weight, or BMI. When the ultrasonographic cross-sectional area of the median nerve was compared between the two groups, those with ALS had significantly smaller median nerves than controls (12.7 mm$^2$ in controls vs. 10.5 mm$^2$ in ALS, $p=0.0023$), but no difference was noted in sural nerve cross-sectional area between the groups. The cause of the median nerve difference is not definitely known, but the most likely explanation is that progressive motor axon loss, which occurs in ALS, results in mild atrophy of the nerve. Interestingly, a previous study to establish reference values for median nerve cross-sectional area found an average area of 8.9 mm$^2$ at the mid-arm, which is much smaller than the median nerve area of controls in this study and smaller than the area in those with ALS.$^{17}$ At least some of this discrepancy may be explained by age differences between the studies. The mean age in this study was 13
years older than in the study to establish reference values (mean age of 58 years in the current study and 45 in the reference values study), and it has been shown that median nerve area positively correlates with age. It is also possible that differences in ultrasound devices, transducer frequency, or examiner technique could have contributed to the differences in median nerve cross-sectional area between the two studies.

The other significant difference between the two groups occurred when the thickness of the biceps/brachialis muscle complex was compared; the control group had thicker muscles (2.9 cm vs. 2.1 cm, p=0.0007). A difference in muscle thickness between the two groups was expected, because those with ALS demonstrate visible muscle atrophy. It was unknown how large a difference would be detected by assessing just one muscle group, because there is variability in the body region affected in individuals with ALS. The difference noted in this study was statistically significant, and those with ALS had biceps/brachialis thickness less than 75% that of controls. This difference would likely be even more striking if muscle volume, rather than thickness, was measured.

One objective of this study was to determine if neuromuscular ultrasound revealed peripheral nerve or muscle abnormalities obvious enough to assist in the diagnosis of ALS. While statistically significant differences were seen in median nerve cross-sectional area and biceps/brachialis muscle thickness between the ALS and control groups, the absolute differences were either not unique to ALS or difficult to apply as universal diagnostic criteria. For example, decreased muscle thickness can be seen in other neuropathic and chronic myopathic conditions, and the affect of age, body habitus, and other factors on nerve area prohibits the establishment of a single cut-off level for the detection of median nerve atrophy in ALS. Despite these limitations and the inability to
establish universal diagnostic criteria, neuromuscular ultrasound can assist in the diagnosis of ALS now that the typical findings are known. Neuromuscular ultrasound findings consistent with ALS include normal to decreased nerve cross-sectional area (as opposed to nerve enlargement described in demyelinating polyneuropathies\textsuperscript{12}), muscle atrophy (as opposed to muscle edema and swelling, which have been described in acute inflammatory myopathies\textsuperscript{19}), and the presence of fasciculations\textsuperscript{5}.

The second objective was to initiate exploration of neuromuscular ultrasound as a surrogate marker of disease progression in ALS. While this study did not have a longitudinal component to directly address this issue, we showed that both median nerve cross-sectional area and muscle thickness are decreased in those with ALS, indicating they could be further explored as surrogate markers of disease progression. In addition, thickness of the biceps/brachialis complex correlated with strength testing, which has been used as a marker of disease progression. There is one recent study in which muscle ultrasound was examined over 6 months as a potential marker of disease progression in 22 individuals with ALS, and the authors concluded there was too much variability in their measures for it to serve as an effective marker of disease progression.\textsuperscript{8} However, their study had limitations, including the use of two different ultrasound devices, not all participants being assessed at all time points, repeated measures statistical analyses not being performed, use of a composite ultrasound score from multiple different muscle groups (not including a distal intrinsic hand or foot muscle), and a focus on the presence of fasciculations. Conversely, another recent study of muscle ultrasound in spinal muscular atrophy showed that calculating a ratio of echogenicity in subcutaneous tissue compared to muscle could discriminate between degrees of disease severity, and the
authors concluded that muscle ultrasound could potentially serve as a marker of progression in this motor neuron disease.\textsuperscript{20} Given the results in our study, as well as the limitations in other studies, muscle ultrasound as a surrogate marker of disease progression deserves further investigation, and nerve cross-sectional area could also be studied in a longitudinal manner. The likely small changes in nerve cross-sectional area over time would make it necessary to closely standardize the ultrasonographic examination, and it may be helpful to study a larger nerve, such as the sciatic.

While some limitations occurred in our study, including small sample size, the ultrasonographer not being blinded to participant group, no measures of muscle or nerve echotexture, and a lack of longitudinal data collection, it did permit an initial investigation into neuromuscular ultrasound measurements in ALS and demonstrated nerve and muscle atrophy in ALS compared to controls. Future investigations using neuromuscular ultrasound to evaluate individuals with ALS are warranted. These could include longitudinal data, study of other muscles such as the diaphragm and distal extremity muscles, muscle volume measurements, and quantitative assessments of nerve and muscle echotexture.
Reference List


CHAPTER III

DISCUSSION

This is the seventh published study in which neuromuscular ultrasound was used specifically to evaluate individuals with ALS (Table).\textsuperscript{1-7} Of the previous studies, five used high-resolution ultrasound to evaluate peripheral muscle size, echotexture, and/or fasciculations, one studied bulbar musculature and function, and one assessed diaphragm characteristics. None of the previous studies assessed ultrasonographic characteristics of peripheral nerves.

Muscle Ultrasound in ALS

In this study, the thickness of the biceps brachii and brachialis muscle complex was measured by placing the ultrasound transducer at the anterior portion of the mid-arm to obtain a cross-sectional view of the biceps/brachialis muscle complex. The thickness of this complex was obtained using the measuring tool function on the ultrasound device, and care was taken to avoid compressing the tissue as the image was obtained. Those with ALS had a mean muscle thickness of 2.0 cm in the left arm and 2.1 cm when the left and right arms were averaged, whereas the controls had a left arm thickness of 3.0 cm and a left/right average thickness of 2.9 cm. In addition to being statistically significant (p = 0.0007), the difference seen in muscle thickness between those with ALS and controls was large enough to visualize without relying on overly sensitive measurement techniques, as the muscle thickness in ALS patients was less than 75\% the thickness seen
in controls. This was expected, as ALS causes visible atrophy, and four previous studies have used ultrasound to demonstrate some degree of muscle atrophy in ALS.\textsuperscript{2, 4-6} The current study showed a significant correlation between biceps/brachialis thickness and biceps strength (0.5062, \( p = 0.0228 \)), but no correlation between muscle thickness and ALSFRS-R or FVC.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Was Extremity Muscle Atrophy Present?</th>
<th>Were Fasciculations Assessed?</th>
<th>Other Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Misawa S et al.\textsuperscript{7}</td>
<td>Not studied</td>
<td>Yes; US was more sensitive than exam and EMG</td>
<td>None</td>
</tr>
<tr>
<td>2011</td>
<td>Arts IM et al.\textsuperscript{5}</td>
<td>Yes; muscle size declined over time</td>
<td>Yes</td>
<td>Muscle EI increased over time</td>
</tr>
<tr>
<td>2011</td>
<td>Arts IM et al.\textsuperscript{6}</td>
<td>Yes; muscle size declined over time</td>
<td>Yes</td>
<td>Muscle EI increased over time</td>
</tr>
<tr>
<td>2010</td>
<td>Lee CD et al.\textsuperscript{4}</td>
<td>Yes; muscle size declined over time</td>
<td>Yes</td>
<td>Muscle EI without change</td>
</tr>
<tr>
<td>2010</td>
<td>Tamburrini et al.\textsuperscript{3}</td>
<td>Not studied</td>
<td>No</td>
<td>Swallowing evaluated</td>
</tr>
<tr>
<td>2008</td>
<td>Arts IM et al.\textsuperscript{2}</td>
<td>Yes</td>
<td>Yes</td>
<td>Muscle EI increased at baseline</td>
</tr>
<tr>
<td>2007</td>
<td>Yoshioka Y et al.\textsuperscript{1}</td>
<td>Not studied</td>
<td>No</td>
<td>Diaphragm paralysis noted</td>
</tr>
</tbody>
</table>
None of the previous studies of muscle thickness used matched controls, but two did assess the progression of atrophy over time. Both studies with longitudinal components showed that muscle thickness decreased significantly in those with ALS over several months. For example, Lee et al. showed the biceps/brachialis complex decreased in thickness by 0.66 mm per month in those with ALS ($p = 0.0014$), and this correlated with a summed strength score, but not the ALSFRS. In the study by Arts et al. the progressive atrophy did not correlate with a summed strength score nor the ALSFRS. In addition to assessing the biceps/brachialis complex, these previous studies also assessed the thickness of the sternocleidomastoid, wrist flexor, wrist extensor, quadriceps, and tibialis anterior muscles.

After completing our study, we were encouraged by the ability to detect muscle atrophy with neuromuscular ultrasound, but it was clear that several methodological changes could be made to improve the sensitivity of ultrasonographic measures of muscle thickness. First, inclusion of distal muscles in the hands and feet, which are often affected early in ALS, would be beneficial. Second, extreme precision needs to be exercised in marking and measuring the exact same site each time, and this could be accomplished with a small, permanent skin marking to guide transducer placement in subsequent visits. Third, ultrasound settings, including gain, time gain compensation, depth, and focus need to be standardized and applied in the same manner for each muscle studied. Finally, it may be more sensitive, and less prone to error based on transducer position, if muscle area or even volume was calculated, instead of depth, as the depth can be changed with subtle pressured applied to the transducer.
In this study the decision was made to not assess echotexture, but the four previous studies did evaluate muscle echointensity using gray-scale analyses. In those studies, the ultrasound images were downloaded and then assessed using software such as Adobe Photoshop to obtain mean gray-scale numbers (termed echointensity), with a range of 0 (black) to 255 (white). Two studies, both by the same group, generated results that suggested echointensity could be used to prognosticate and accurately follow ALS patients over time, but one study showed no trend in echointensity over 6 months. Our experience with echotexture analysis of muscle ultrasound images is that it is variable, and it changes based upon factors such as transducer type, angle of insonation, gain, and depth, and therefore it is a difficult technique for analyzing subtle changes over time. Recent studies have confirmed this, and demonstrated that transducer selection can significantly affect echotexture analyses. However, gray-scale analysis is a field that is evolving, and future developments in image processing and analysis could improve the reliability of muscle echotexture measurements.

The final use of muscle ultrasound in the assessment of those with ALS has been to detect fasciculations. The first report of ultrasound for the detection of fasciculations was in 1988, and it was demonstrated to be a sensitive technique as it allowed for scanning of multiple muscles, painlessly and efficiently. Since then other studies have confirmed the sensitivity of ultrasound for the detection fasciculations, and very recent data from Misawa et al. have demonstrated that the addition of ultrasound for the detection of fasciculations greatly increases the sensitivity of the Awaji criteria for the diagnosis of ALS (Figure 3.1). Taken together, these studies suggest that muscle ultrasound is
sensitive for the detection of fasciculations and that it greatly increases the diagnostic sensitivity of the currently used diagnostic criteria.

Figure 3.1. This shows that the proportion of people in the “probable” and “definite” category by El Escorial (EE) criteria was 48% and this increased to 79% when the Awaji criteria, along with the use of EMG and ultrasound, was applied.7

Nerve Ultrasound in ALS

Unlike muscle ultrasound, nerve ultrasound has not been previously examined as a diagnostic technique in individuals with ALS. In this current study, ultrasound was used to examine the cross-sectional area of the median nerve in the mid-portion of the upper
In 20 individuals with ALS, the mean cross-sectional area of the median nerve was 10.5 mm$^2$, which was significantly smaller ($p = 0.0023$) than the 12.7 mm$^2$ mean seen in 20 age and sex matched controls. In addition, no difference in cross-sectional area was seen when the sural nerve was compared between these two groups ($p = 0.1927$). While the median nerve in the upper arm was statistically significantly smaller in those with ALS, the absolute difference in size between the two groups was not large and there was overlap in the range of nerve sizes seen between the two groups. This indicates that neuromuscular ultrasound as a tool to detect nerve atrophy is unlikely to be sensitive enough to assist in the diagnosis of ALS. However, this finding is quite helpful because other conditions that mimic ALS, such as multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy, are associated with increased cross-sectional area of peripheral nerves.$^{11, 12}$ It should also be noted that median nerve area did not correlate with ALSFRS or FVC, but it did approach statistical significance in correlating with strength of the abductor pollicis brevis muscle ($0.4206, p = 0.0648$).

**Neuromuscular Ultrasound in the Diagnosis of ALS**

Given the findings of the current study, as well as the results of the previous studies listed in Table 3.1, neuromuscular ultrasound is a technique that can be considered to improve diagnostic accuracy in the evaluation of individuals suspected to have ALS. If used, based on the current state of knowledge, the highest yield parameters would be to assess nerve cross-sectional area and muscle to detect fasciculations. Specifically, neuromuscular ultrasound should first be used to assess the extremity in which weakness
initially occurred or is most pronounced. In this extremity, the major nerve branches (median, ulnar, and radial in the arm and sciatic, tibial, and fibular in the leg) should be scanned with the transducer positioned to obtain cross-sectional images. Several measurements should be obtained along the length of each nerve, and if the upper extremity is assessed the brachial plexus should be imaged as well, as it is often enlarged in multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy.\textsuperscript{11, 13} Next, at least one distal and one proximal muscle should be assessed in the extremity of interest for the presence of fasciculations. The transducer should be oriented to obtain a cross-sectional view of a large segment of the muscle and imaging of each region should last for at least 10 seconds. Finally, the other extremities, as well as the genioglossus and thoracic paraspinal muscles, should be assessed in the same manner, looking for the presence of fasciculations. It may be appropriate to perform the ultrasonographic evaluation first, as it can then be used to guide the electrodiagnostic study and perhaps limit the number of electrical stimulations from nerve conduction studies and EMG needle sticks needed.

**Future Directions**

Further exploration of neuromuscular ultrasound for the diagnosis, prognosis, and tracking of disease progression in ALS is needed, and a single large, prospective, multi-site study could address several questions. One potential design would be to invite all individuals referred to select ALS Center for possible ALS to undergo a neuromuscular ultrasound evaluation (Figure 3.2). Close to 10\% of those referred to ALS Centers are
ultimately diagnosed with an ALS mimic, so this design would enroll individuals with ALS and those with conditions that mimic ALS. After the typical evaluation was performed, including a thorough history, physical examination, and electrodiagnostic evaluation, the participant would undergo a neuromuscular ultrasound examination by a sonographer blinded to all clinical and electrodiagnostic information. The neuromuscular ultrasound examination would be standardized and include peripheral nerve cross-sectional areas at several sites in the weakest extremity; precise muscle size measurements at distal and proximal sites in the arms and legs (area instead of depth, when feasible); evaluation for fasciculations in the genioglossus, paraspinals, arms and legs; and diaphragm thickness and excursion. Those with confirmed ALS would then be followed every 3 months for the next 2 years with serial muscle size measurements of the distal and proximal upper and lower extremity muscles. This design would allow for comparison of all parameters between those with ALS and those with ALS mimics, which is a design that would prevent the introduction of spectrum bias. Prospective data collection and blinding of the ultrasonographer would also fulfill STARD criteria for the complete and accurate reporting of tests of diagnostic accuracy. It would also allow creation of statistical models to determine which neuromuscular ultrasound parameters best predict prognosis. Finally, serial measurements of muscle size would permit calculation of typical atrophy rates, which could then be used as surrogate markers of disease progression. If this type of study was performed at approximately 10 ALS Centers it could likely recruit at least 100 participants in a year, and a multi-site design would allow for comparison of neuromuscular ultrasound techniques across sites, since components of ultrasonographic examinations are operator dependent.
Figure 3.2. Study design to assess the diagnostic accuracy, prognostic ability, and usefulness as a surrogate marker of disease progression of neuromuscular ultrasound in individuals with ALS.
REFERENCES


CURRICULUM VITAE

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EDUCATION:

1994-1998 Wake Forest University
Bachelor of Science in Biology
Summa Cum Laude
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1998-2002 Wake Forest School of Medicine
Doctor of Medicine
Alpha Omega Alpha

2006-Present Wake Forest School of Medicine
Master of Science in Health Science Research

POSTDOCTORAL TRAINING:

2002-2003 Internship in Internal Medicine
Wake Forest University Baptist Medical Center

2003-2005 Residency in Neurology
Wake Forest University Baptist Medical Center

2005-2006 Chief Residency in Neurology
Wake Forest University Baptist Medical Center

2006-2008 MDA Clinical Research Training Fellowship
Focus in Neuromuscular Disease
Wake Forest University Baptist Medical Center

PROFESSIONAL LICENSURE:

2006-Present State of North Carolina
BOARD CERTIFICATION:

2007-Present  Diplomat, American Board of Psychiatry and Neurology

2009-Present  Diplomat, American Board of Electrodiagnostic Medicine (with recognition for scoring in top 10% on certification examination)

ACADEMIC APPOINTMENTS:

2006-2008  Instructor in Neurology
            Wake Forest School of Medicine

2008-Present  Assistant Professor in Neurology
               Wake Forest School of Medicine

2010-Present  Cross-appointment in Center for Worker Health
               Wake Forest School of Medicine

2011-Present  Cross-appointment in Family Medicine, Sports Medicine Section
               Wake Forest School of Medicine

EMPLOYMENT:

1993-2000  Tennis Instructor
            Rochester, MN Indoor and Outdoor Clubs

1996-1997  Teaching Assistant Aide
            Wake Forest University

1996-1998  Academic Tutor
            Wake Forest University

PROFESSIONAL APPOINTMENTS AND ACTIVITIES:

Ad hoc reviewer for:
• Prinses Beatrix Fonds, Funding Agency in the Netherlands
• *American Journal of Critical Care*
• *Archives of Neurology*
• *Archives of PMR*
• *Atherosclerosis*
• *BMC Medical Imaging*
• *Clinical Neurology and Neurosurgery*
• *Clinical Neurophysiology*
• *Journal of Child Neurology*
• *Journal of Neurology*
• *Journal of the Peripheral Nervous System*
- *Journal of Postgraduate Medicine*
- *PLoS One*
- *Muscle and Nerve*

INSTITUTIONAL SERVICE:

1999-2002 Academic tutor for first and second year medical students
2000-2002 Student Identification and Recruitment Committee
2001-2008 AOA Executive Committee
2004-2005 Graduate Medical Education Committee
2005-2006 Chief Resident Committee
2008-2009 Dean’s Advisory Committee
2005-Present Neurology Residency Advisory Committee
2006-Present Medical School Admissions Interviewer
2006-Present Standardized Patient Assessment evaluator for medical students
2007-Present Core Mentoring Faculty Member for medical students
2007-Present WFUHS Translational Science Institute member
2009-Present WFUHS Center for Worker Health member
2009-Present WFUHS Intramural Research Support Committee ad hoc member
2009-Present WFU Neuroscience Faculty Member
2010-Present Translation Science Institute Scholar
2010-Present WFU Admissions and Premedical Relations Committee Member
2011-Present WFU Faculty Development Advisory Committee
2011-Present P&T Subcommittee – Standardized Order Sets

PROFESSIONAL MEMBERSHIP AND SERVICE:

2004-Present American Academy of Neurology (AAN), Member
2004-Present  American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), Member

2006-Present  Huntington Study Group (HSG), Junior Investigator

2009-Present  The Neuropathy Association, Member

2009-Present  Western North Carolina Society for Neuroscience (WNCSN), Executive Committee Clinical Councilor

2009-Present  AANEM Neuromuscular Ultrasound Task Force

2010-Present  AANEM Marketing Committee

HONORS AND AWARDS:

Research
• 2009 AANEM President’s Research Initiative Award
• 2002 G. Milton Shy AAN Clinical Research Award
• 2002 Outstanding Scholarly Project Poster

Teaching
• Wake Forest Class of 2004 Resident Teaching Award

Scholarship
• 2011 Best Doctors
• 2011 Leading Physicians of the World
• 2009 ABEM Top 10% Score on Certification Examination
• 2007 ANA Junior Faculty Development Course Scholarship
• 2002 WFSM Medical Alumni Association Excellence Award
• 2002 WFSM Excellence in Neurology Student Award
• 2002 AAN Annual Meeting Scholarship Recipient
• 2001 Alpha Omega Alpha
• 2000 WFSM Dewitt Cromer Cordell Scholarship
• 1998 Phi Beta Kappa
• 1996 WFU Carswell Scholarship
• Dean’s List 1994-1998

PROFESSIONAL INTERESTS:

• Neuromuscular ultrasound
• Polyneuropathy
• Amyotrophic lateral sclerosis
• Myasthenia gravis
Current Research


2. Milligan CE, Cartwright MS, Oppenheim R, Delbono O, Caress JB. Early changes in the spinal cord and neuromuscular junction with ALS.

3. Strowd R, Cartwright MS, Kapoor S, Siddiqui M. Intracranial hemorrhage following DBS.


GRANTS:

Active

2006-present NIH/NINDS
RO1 NS049640-01 (Cudkowicz)
A Clinical Trial of Ceftriaxone in Subjects with Amyotrophic Lateral Sclerosis
Role: Co-investigator (enroll patients)
PI: Cudkowicz

2007-present ALS Association
Electrical Impedance Myography in ALS
Role: Co-investigator (perform studies)
PI: Rutkove

2008-present NIOSH
R01OH009251
Work-relate Injuries in Migrant Poultry Workers
Role: Co-investigator (5% effort, perform diagnostic studies)
PI: S Quandt

2008-present ALS Association
ALS Biomarker Study
Role: Co-investigator (enroll patients)
PI: Cudkowicz
2008-present   NIH  
R21NS061084-01  
CSF Indicators for Diagnosis and Disease Progression in ALS  
Role: Co-investigator (enroll patients)  
PI: Milligan  
$275,000

2008-Present   NINDS/NIH  
1K23NS062892  
*Diagnostic Ultrasound for Focal Neuropathies*  
Role: Principal Investigator (75% effort)  
$690,287

*Completed*

2006-2008   William E. Winter Clinical Research Training Fellowship  
Muscular Dystrophy Association  
Role: Principal Investigator (100% effort)  
$180,000

2007-2009   Translational Team Science Grant  
WFSM Translational Science Institute  
*Amniotic Fluid Derived Stem Cell Therapy in a Canine Model of Duchenne Muscular Dystrophy*  
Role: Co-investigator (performed studies)  
PI: MK Childers  
$125,000

2008-2010   Translational Team Science Grant  
WFSM Translational Science Institute  
*Detection of Early Nervous System Changes in ALS*  
Role: Co-investigator (enrolled patients, performed studies)  
PI: CE Milligan  
$125,000

2008-2010   NIH/NINDS  
A clinical trial of lithium and riluzole in ALS  
Role: Co-investigator (enrolled patients)  
PI: Aggarwal
BIBLIOGRAPHY:

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Non-peer Reviewed Manuscripts


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Podcasts

1. Neuromuscular ultrasound: part I. *Neurology* 2010

2. Neuromuscular ultrasound: part II. *Neurology* 2010
Abstracts


11. Yoon JS, Walker FO, Cartwright MS. Ultrasonography in four cases of ulnar neuropathy with negative conduction studies. AANEM 2008 pg 128.


**PRESENTATIONS:**

*International, National, and State-wide Presentations (* indicates symposium coordinator)*


2. Diagnostic ultrasound for nerve transection. Grand rounds lecture at Vanderbilt University School of Medicine, October 2007, Nashville, TN.


10. Amyotrophic lateral sclerosis. Presentation at the 29th Annual Mountain Medical Meeting, October 2009, Asheville, NC.


International, National, and State-wide Hands-on Workshops


**International, National, and State-wide Poster Presentations**

1. High-resolution ultrasound in the evaluation of carpal tunnel syndrome. Poster at the American Academy of Neurology Annual Meeting, April 2002, Denver, CO.

2. Experiences with high-resolution ultrasound in the evaluation of carpal tunnel syndrome. G. Milton Shy Essay Award poster at the American Academy of Neurology Annual Meeting, April 2002, Denver, CO.


4. Ultrasonographic characteristics of the normal median nerve. Poster at the American Academy of Neurology Annual Meeting, April 2006, San Diego, CA.


9. Median nerve changes following steroid injection for carpal tunnel syndrome. Poster presentation at the American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting, October 2009, San Diego, CA.

**Institutional (Wake Forest School of Medicine)**


5. How to be a good rotating intern – Class of 2005 Phase 5 Lecture, May 2005.


13. Meningitis and Encephalitis – Neurology Update for Primary Care Providers, May 2008


17. Introduction to Neurology – First Year Medical Students, August 2010, August 2011
18. The Brachial Plexus – First Year Medical Students, October 2010, October 2011

19. Ultrasonographic Assessment of Carpal Tunnel Syndrome – Neuroscience lecture series, April 2011

20. The Neurologic Examination – Organized and taught Phase 5 course, March 2011

21. Carpal Tunnel Syndrome in Poultry Workers – Workers Health Seminar, April 2011

22. Neuromuscular Ultrasound – Medical Imaging Graduate Course, VT-Wake Forest School of Biomedical Engineering, May 2011

23. HIV Neuropathies – HIV section meeting, May 2011

24. Guillain-Barre Syndrome – Hospitalists section meeting, May 2011


Departmental (Wake Forest School of Medicine, Department of Neurology)


17. Steroid injection for carpal tunnel syndrome – Rehab Fellows Conference, May 2010

18. Carpal Tunnel Syndrome in Poultry Workers – Neurology Grand Rounds, February 2011

FELLOWS TRAINED

1. 2008-2009: Kara Eickman, MD; Joseph Chipman, MD

2. 2009-2010: B. Lee Kennedy, MD; Kashyap Patel, MD

3. 2010-2011: Chaman Preet Chahal, MD; Waqas Sohail, MD