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Peripheral Nerve and Muscle Ultrasound in Amyotrophic Lateral Sclerosis

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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 (10.5mm^2 vs 12.7mm^2, p=0.0023), but no difference was seen in the sural nerve (4.5mm^2 vs 5.0mm^2, 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.

Keywords

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,[1] 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.[2] 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

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estimation (MUNE), but all of these techniques have limitations, including lack of responsiveness, operator variability, and pain.[3]

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.[4] 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.[5–8] 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.[9] There exist reports of nerve root atrophy in ALS, but the literature is sparse and does not examine nerve caliber in the limbs.[10] 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.[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.[15] 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”)[16] 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 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,[17] 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 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.

Next, the sural nerve was assessed at 10 cm above the lateral malleolus (Figure 2A). The transducer was again positioned to obtain a cross-sectional view of the nerve, and an area measurement was obtained (Figure 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]

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 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 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.

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 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).

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 3). The total median nerve area was larger in controls ($12.7mm^2$ vs $10.5mm^2$, p=0.0023), and the total muscle thickness was greater in controls (2.9cm vs 2.1cm, p=0.0007). No differences were noted when comparing the sural nerve cross-sectional area between the two groups (Table 3).

Statistically significant correlation was only seen when comparing the thickness of the biceps/brachials 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 4).

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 (12.7mm^2 in controls vs 10.5mm^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 8.9mm2 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.[17] 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 (2.9cm vs 2.1cm, 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/brachials 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[12]), muscle atrophy (as opposed to muscle edema and swelling, which have been described in acute inflammatory myopathies[19]), and the presence of fasciculations.[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.[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 echogencity 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.[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.

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Abbreviations

ALS	amyotrophic lateral sclerosis
ALSFRS	amyotrophic lateral sclerosis functional rating scale
BMI	body mass index
FVC	forced vital capacity

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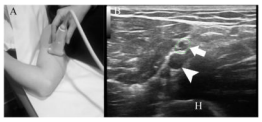

Figure 1.
Image A demonstrates the transducer position used to visualize the median nerve in the mid-arm and obtain the ultrasound image shown in panel B. The arrow points to the median nerve, and the arrowhead points to the adjacent brachial artery. The “H” is placed over the humerus.

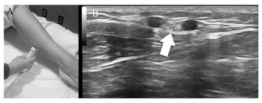

Figure 2.
Image A demonstrates the transducer position used to visualize the sural nerve and obtain the ultrasound image shown in panel B. The arrow points to the sural nerve, which is located between two superficial veins.

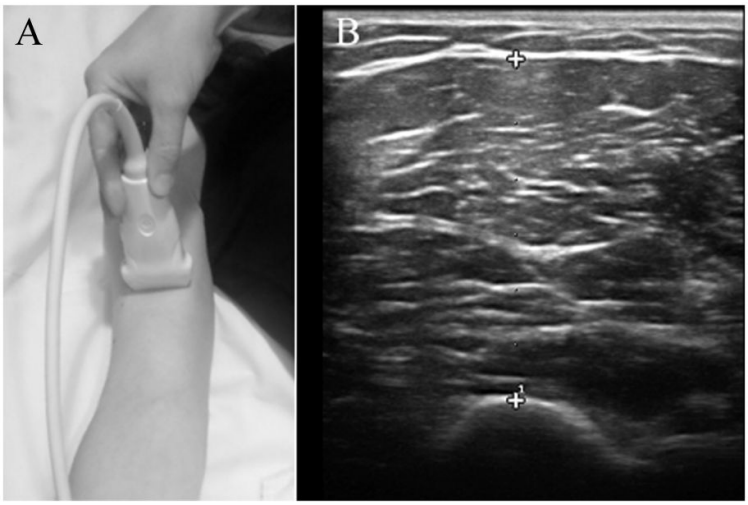

Figure 3.
Image A demonstrates the probe position used to visualize the biceps/brachialis muscle complex shown in panel B. The superficial extent of the muscle and the echogenic reflection from the humerus are marked with plus signs (+).

Table 1

Demographics

Variable	Controls n = 20	ALS Patients n = 20	p-value
Age	58.1 (42 – 76)	58.4 (40 – 71)	0.9231
Gender (male)	10 (50%)	10 (50%)	1.0000
Race (Caucasian)	20 (100%)	19 (95%)	0.3112
Height	66.7 (61 – 75)	67.1 (61 – 71)	0.7140
Weight	171.6 (135 – 235)	162.3 (117 – 212)	0.2984
BMI	27.3 (20.9 – 39.5)	25.4 (19.3 – 33.8)	0.2090

Table 2

ALS Participant Characteristics

Variable	Mean (range)
FVC (%)	62.3 (20 – 99)
ALSFRS	30.5 (12 – 48)
Months Since Onset	25.1 (6 – 60)

Table 3

Ultrasonographic Comparisons between ALS Patients and Controls.

Variable	Controls n = 20	ALS Patients n = 20	p-value
Left Median Area (mm^2)	12.6 (9.5 – 15.0)	9.9 (7.0 – 15.0)	0.0004
Average Median Area (mm^2)	12.7 (9.3 – 16.3)	10.5 (7.0 – 15.5)	0.0023
Left Sural Area (mm^2)	5.0 (3.0 – 8.0)	4.5 (2.0 – 7.0)	0.1858
Average Sural Area (mm^2)	5.0 (3.0 – 8.0)	4.5 (2.5 – 6.5)	0.1927
Left Muscle Thickness (cm)	3.0 (1.7 – 4.2)	2.0 (0.4 – 3.7)	0.0001
Average Muscle Thickness (cm)	2.9 (2.0 – 4.3)	2.1 (0.4 – 3.8)	0.0007

Table 4

Correlation Between Ultrasonographic Parameters and Other Variables

Comparison	Correlation Coefficient	p-value
Average Median Area vs FVC	−0.0075	0.9750
Average Median Area vs ALSFRS	0.1280	0.5908
Left Median Area vs Left APB strength	0.4206	0.0648
Muscle Thickness vs Biceps Strength	0.5062	0.0228
Average Muscle Thickness vs FVC	0.3721	0.1062
Average Muscle Thickness vs ALSFRS	0.3325	0.1520
Average Median Area vs Months since onset	−0.3106	0.1825
Average Muscle Thickness vs Months since onset	−0.0806	0.7356