Original Article

Upper Extremity Peripheral Nerve Ultrasonography, as a Diagnostic Aid in Amyotrophic Lateral Sclerosis

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a life-threatening progressive motor neuron disease whose diagnosis is challenging because of lacking specific diagnostic means. The current study aims to assess the value of upper extremity peripheral nerves ultrasonography in ALS detection.

Materials and Methods: In this case-control study, 30 ALS subjects were assessed regarding the cross-sectional area (CSA) of the proximal (at distal part of arm or the proximal of elbow) and distal (at wrist level) median and ulnar nerves, assessed via ultrasonography. Similarly, 30 age- and gender-matched healthy controls were evaluated. The receiver operating curve (ROC) was depicted to determine a cut-point for ALS-associated peripheral nerve involvement.

Results: Proximal CSA and the proximal-to-distal ratio of the median nerve was remarkably lower in both upper extremities of the ALS subjects compared to the controls (P value < 0.05), while the distal median nerve CSAs did not differ between the groups (P value > 0.05). Distal ulnar nerve CSA in the right hand (P value = 0.007) and the proximal ulnar nerve CSA in the left hand (P value = 0.001) were remarkably lower in the cases than the controls, but the other measurements did not differ (P value > 0.05). There was no significant cut-points to differentiate ALS-affected peripheral nerves from the healthy controls (P value > 0.05).

Conclusion: Based on this study, CSA of the proximal median nerve in the cubital fossa seems a rational and valuable means to diagnose ALS; but the distal parts of the median nerve and the ulnar nerve in its all length remained a matter of debate.

Keywords: Amyotrophic lateral sclerosis, electromyography, motor neuron disease, ultrasonography, upper extremity

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Introduction

Amyotrophic lateral sclerosis (ALS) is a relatively rare but a devastating progressive neurodegenerative disorder involving both upper and lower motor neurons (LMN). The exact pathophysiology of ALS that leads to muscle weakness and atrophy is not well-recognized; however, an increasing body of evidence supports the neuroinflammatory process in its incidence.[1] Given that, it has been proposed that in the absence of a positive family history of ALS, neuroinflammation, oxidative stress, and mitochondrial dysfunction are responsible for the incidence of ALS.[2] Nevertheless, the current investigations have noted some genetic factors in the pathophysiology of this disorder, as well.[3] Although ALS has a rapidly progressive manner that potentially causes a short survival period, studies in the literature have estimated a year of delay in its diagnosis, mainly because of lacking any specific diagnostic means. Other than diagnosis, the estimation of ALS progressive trend and prognosis are the matters of debate that requires urgent trials.[4]

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Electromyography (EMG) has been considered a sensitive instrument to assess motor neuron diseases in both acute and chronic courses of denervation and applied as a diagnostic tool in Awaji criteria and Gold Coast Criteria.[5,6] Nevertheless, invasive bothersome painful features of EMG caused to search for further methods. Besides, despite its ability to assess LMN loss quantitatively, EMG has considerable limitations hindering its widespread use. Scientists have utilized neurofilaments as another diagnostic and prognostic biomarker in ALS; however, it is an unspecific marker of motor neuron death.[7,8]

Ultrasonographic assessment of muscles is widely available by which muscles fasciculation can be easily explored. Moreover, numerous other muscular parameters can be applied to differentiate ALS patients from healthy subjects or prognosticate the disease progression.[9] The point that questions muscle ultrasonography is the nature of ALS that affects motor neurons, while muscular alterations require a longer time to appear. The other point refers to the limited body of evidence in favor of muscle-associated biomarkers for ALS diagnosis and prognosis determination.[10]

Neuropathological studies of patients with ALS revealed a remarkable reduction of large, myelinated fibers in ventral roots and peripheral nerves that are directly associated with the intensity of muscle loss and weakness in the corresponding myotomes. Accordingly, the neuropathic nature of ALS can support the theories regarding neural changes in ultrasonography assessments in advance to muscular manifestations.[11] Limited studies in the literature have shown smaller cross-sectional area (CSA) of median or ulnar nerve in ALS patients compared to healthy subjects in ultrasonographic investigations; however, the knowledge in this issue is inadequate. The current study aims to assess the value of ultrasonography of upper extremity in ALS detection.

Materials and Methods

Study population

The current case-control study has been conducted on 30 patients with documented ALS diagnosis referring to outpatient neuromuscular clinics affiliated with Isfahan University of Medical Sciences from March 2021 to March 22. Apparently, 30 cases from the normal population were evaluated.

The study protocol was primarily designed based on the Helsinki Declaration and approved by the Ethics Committee of Isfahan University of Medical Sciences via code number IR.MUI.MED.REC.1401.029. The study was entirely explained to the study participants including the patients, their legal guardians, and the controls; they were reassured regarding their personal information confidentiality and signed written consent.

The documented ALS diagnosis made based on the clinical manifestations, using EMG and nerve conduction velocity and considering the Gold Coast criteria[6] by an expert neuromuscular subspecialist and willingness to participate in the study were the inclusion criteria. The patients with other diagnoses than ALS such as neuropathies (e.g., carpal tunnel syndrome or cubital tunnel syndrome), the previous history of any neuromuscular disorders, traumatic injury, deformity or amputation in one of the upper extremities, and inappropriate cooperation during the study conduction and those who received medical or surgical treatments affecting the nerves were considered as exclusion criteria.

Due to the limited number of ALS patients, the cases entered into the study through convenience sampling among all the subjects who met the study criteria, whereas the controls were age- and gender-matched individuals from the healthy first-degree family of the cases who did not have any exclusion criteria of the study.

Study design

An ultrasonography study was performed for the patients to determine median and ulnar nerve cross-section diameter and circumference. The assessments were done using a 12-MHz linear array probe (GE High-End LOGIQ®7 System, the United States) and done via a broadband probe (frequency band, 17-5 MHz). The ultrasonographies were performed twice by two expert neuromuscular specialists and the mean measured values were reported.

Accordingly, the patients were sitting positioned, while their upper extremity was extended. The proximal diameters of ulnar and median nerves were evaluated at the distal part of the arm or in the proximal elbow, and distal assessments were done in the wrists.

The nerve cross-sectional circumference was measured in axial plane. Therefore, for the assessment of the median nerve, the wrist was 10–30 degrees, the elbow 80–90 degrees, and the shoulder 60 degrees flexed. The probe was placed at the distal fold of the wrist, exactly at the level of the pisiform bone. The median nerve was located between the flexor retinaculum and the tendons of the flexor muscles. The proximal part of the nerve was explored with a full-extended elbow between the tendons of flexor digitorum profundus and flexor digitrum superficialis.

Ulnar assessments were done with 90–135 degrees elbow and 60 degrees shoulder flexion, while the forearm was supine positioned. The proximal part cross-sectional diameter was measured in the cubital tunnel at the site of the ulnar artery and nerve separation. The ulnar nerve distal part was evaluated using the ultrasonography probe perpendicular to the ulnar nerve at the level of the pisiform bone.

All the assessments were done for both cases and controls and recorded in the study checklist. The recruited data included age, gender, proximal, and distal cross-section of ulnar and median nerves, and the proportion of proximal to distal parts of the nerves.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) (version 18 SPSS Inc., Chicago, IL).

Continuous data were reported as mean ± standard deviation and the categorical data as frequency and percentages. Shapiro-Wilk test was applied to determine the normality of data distribution. Chi-square test was used to compare the categorical variables. Independent *t*-test was applied for the comparison of the continuous ones. Besides, the receiver operation curve (ROC) was depicted in order to determine a cut-point to differentiate ALS subjects from healthy individuals as well as measure the sensitivity, specificity, and area under the curve (AUC) of the parameters to diagnose ALS. *P* value of less than 0.05 was considered the level of significance.

Results

The studied population had a mean age of 50.63 ± 11.95 years old and predominantly consisted of men (58.33%). The studied groups were statistically similar in terms of age (*P* value = 0.192) and gender distribution (*P* value = 0.793) [Table 1].

Table 2 demonstrates ulnar and median nerves ultrasonographic characteristics. Accordingly, proximal CSA of the median nerve was remarkably lower in both the right (*P* value = 0.044) and left hands (*P* value = 0.022), and the proximal-to-distal ratio was statistically lower in both the right (*P* value = 0.042) and left hands (*P* value = 0.003) among the cases. The distal parts did not differ between the groups (*P* value > 0.05). Considering the ulnar nerve, distal CSA of the nerve in the right upper extremity of the patients with ALS was significantly lower (*P* value = 0.007), whereas in the left hand did not differ (*P* value = 0.060). Lower CSA was notified in the assessment of the proximal part of the left ulnar nerve in ALS patients (*P* value = 0.001), but the right hand did not have statistically significant differences (*P* value = 0.131). Besides, the proximal-to-distal ratio of the ulnar nerve revealed no statistically significant difference (*P* value > 0.05).

ROC curve was depicted in order to determine an appropriate cut-point for the CSAs of the statistically significant different indices in Table 2, including median nerve proximal CSA and proximal-to-distal ratio and ulnar nerve proximal and distal CSA to be applied for ALS diagnosis. Despite the high sensitivities measured for all the assessed region of the nerves, none of the assessments were statistically significant (*P* value > 0.05). Detailed information is shown in Table 3 and Figure 1.

Table 1: Demographic characteristics of the studied population

Variable	Case group (*n*=30)	Control group (*n*=30)	*P*
Age (year), mean±standard deviation	48.35±12.65	53.14±11.20	0.192*
Gender, *n* (%)			
Male	17 (56.7)	18 (60)	0.793**
Female	13 (43.3)	9 (40)	

*Chi-square test. **Independent *t*-test

Discussion

Considering the recent attention on the efficacy and utility of ultrasonography study of peripheral nerves in ALS, the current study mainly aimed to evaluate two major peripheral nerves of the upper extremity, ulnar and median nerves, through a case-control study. Accordingly, our findings in the study of median nerve revealed significant reduction in the CSA of the proximal part as well as the proximal-to-distal CSA ratio among the ALS patients; however, the distal parts have not been remarkably affected. Ulnar nerve ultrasonographic assessment revealed no statistically significant differences between the cases and healthy individuals. The latter assessment of our study indicates the necessity of determining a cut-point to distinguish ALS in patients referring with neuropathy; however, none of the indices revealed a statistically significant threshold.

These findings support the previous studies regarding the general reduction of CSA in peripheral nerves' of ALS patients due to distal axonal degeneration.[12-14] The exact mechanism by which axonal degeneration occurs remains a question; it may reflect local axonal damage, failure to trophic support from a diseased cell body or both.[13,15] However, the increasing body of evidence supports the idea that axons are not passive extensions of a parent cell body and might die due to mechanisms that are independent of cell death. Furthermore, oxidative stress which is notified in SOD1 knockout mice,

Table 2: Neural ultrasonographic characteristics

Variable		Case group (*n*=30)	Control group (*n*=30)	*P**	Case group (*n*=30)	Control group (*n*=30)	*P**
		Right upper extremity (cm²)			Left upper extremity (cm²)		
		Mean (standard deviation)					
Median nerve	Distal CSA	0.094 (.027)	.078 (.030)	0.060	0.078 (.026)	.098 (.040)	0.052
	Proximal CSA	.065 (.021)	.083 (.035)	0.044	.091 (.044)	.066 (.021)	0.022
	Proximal-to-distal ratio	.763 (.427)	1.396 (1.380)	0.042	.734 (.289)	1.291 (.719)	0.003
Ulnar nerve	Distal CSA	.031 (.012)	.042 (.012)	0.007	.031 (.011)	.038 (.012)	0.060
	Proximal CSA	.042 (.016)	.050 (.018)	0.131	.040 (.011)	.055 (.016)	0.001
	Proximal-to-distal ratio	1.461 (.593)	1.209 (.421)	0.110	1.661 (1.217)	1.497 (.835)	0.609

*Independent *t*-test. CSA: cross-sectional area

Table 3: The receiver operation curve of peripheral nerves cross-sectional areas

The assessed peripheral nerve	Side	Sensitivity	95% CI	Specificity	95% CI	Cut of point	AUC	95% CI	*P**
Median nerve proximal cross-sectional area	Left	100	85.2–100	38.10	18.1–61.6	≤0.09	0.673	0.515–0.807	0.899
	Right	86.96	66.4–97.2	47.62	25.7–70.2	≤0.08	0.659	0.501–0.795	
Median nerve proximal-to-distal ratio	Left	65.22	42.7–83.6	85.71	63.7–97	≤0.82	0.807	0.661–0.911	0.566
	Right	82.61	61.2–95	71.43	47.8–88.7	≤0.83	0.753	0.599–0.870	
Ulnar nerve distal cross-sectional area	Left	95.65	78.1–99/9	33.33	14.6–57	>0.02	0.663	0.504–0.798	0.550
	Right	69.57	47.1–86.8	66.67	43–85.4	>0.03	0.728	0.573–0.851	
Ulnar nerve proximal cross-sectional area	Left	73.91	51.6–89.8	76.19	52.8–91.8	>0.04	0.812	0.665–0.913	0.115
	Right	82.61	61.2–95	52.38	29.8–74.3	>0.03	0.653	0.495–0.790	

*Pairwise comparison of ROC curves

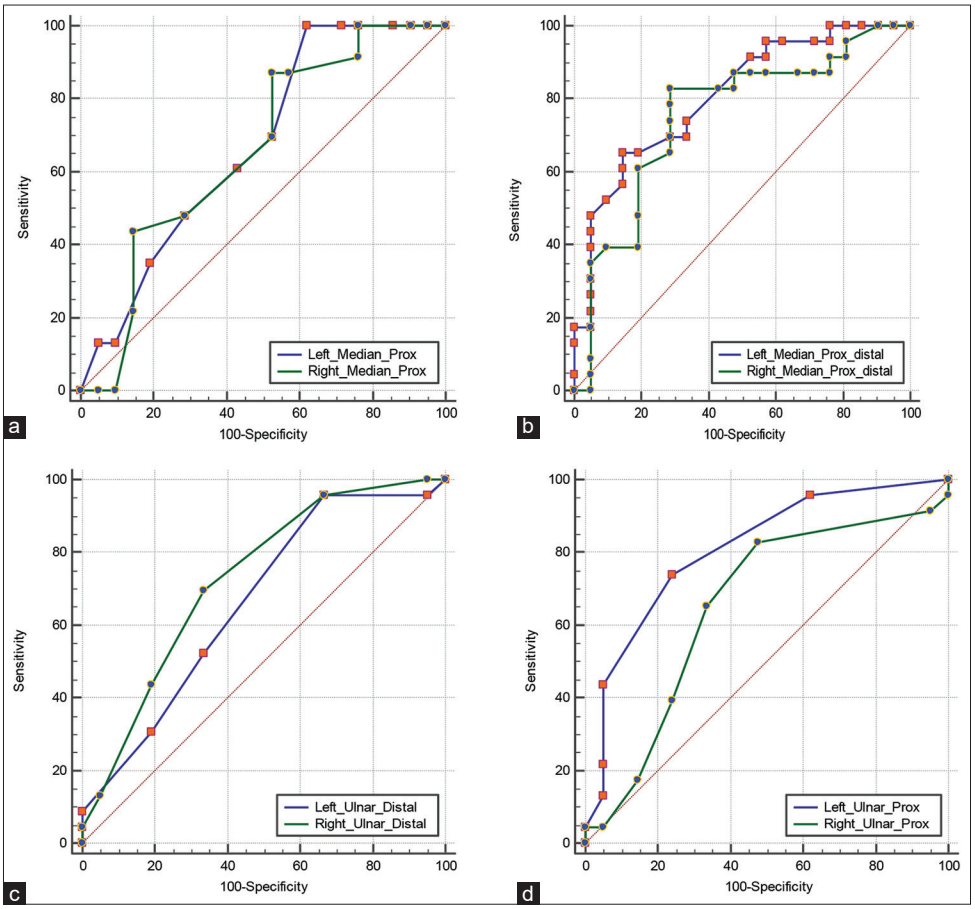

Figure 1: ROC curve of the peripheral nerves cross-sectional areas to determine a cut-point for ALS diagnosis. Based on these figures, none of the indices revealed a statistically significant cut-point. (a) Bisided median nerve proximal cross-sectional area, (b) bisided median nerve proximal-to-distal cross-sectional area, (c) bisided ulnar nerve distal cross-sectional area, and (d) bisided ulnar nerve proximal cross-sectional area

SOD1 mutant mice, and in humans with ALS plays a critical role in distal axonal degeneration.[16-18]

The assessments of the current study for the median nerve are consistent with the previous investigations representing proximal patterns of atrophy involving the median nerve in ultrasonography study of ALS individuals.[11,15,19] The hypothesis regarding more severe involvement of the proximal than distal parts refers to the nature of ALS as a motor neuron disease. Given that, reduced CSA of the median nerve in the cubital area is likely to be associated with the pattern of motor axonal loss. In this regard, the proximal part of the median nerve has predominantly a motor-innervating function in the forearm and hand than the wrist region. We can justify the insignificant difference of CSA in distal median nerve between cases and controls by the theory that the major part of the median nerve after the cubital fossa are sensory axons, while the nature of ALS is to involve motor neurons; therefore, the distal parts of the median nerve have not been lost.[13,20] Further evaluations of the proportion of motor and sensory axons on nerve CSA separately at each part of the nerve can better clarify this theory.

The split hand phenomenon, a condition explaining median nerve atrophy at the proximal part, confirms the above hypothesis. Muscle wasting process mostly affects the lateral parts of the hand, known as the thenar area, where the abductor pollicis brevis (APB), a median innervated muscle, is affected with a relative sparing of the hypothenar muscles (the abductor digiti minimi (ADM)). However, the mechanism of this condition is complex and not well-recognized; recent investigations show that both cortical and spinal/peripheral sites should be involved for split hand to appear in ALS.[21] In confirmation, the measured compound muscle action potential ratio of APB/ADM revealed less than 1 in ALS, while the normal range in healthy subjects is above 1.[22-24]

Consistent with our study, in Ahmed and Vucic's studies, the pattern of proximal part atrophy in the ulnar nerve is not as supportive for ALS diagnosis as the median nerve[25,26]; however, in contrast to us, Schreiber and colleagues represented that the ulnar nerve CSA was remarkably less in the proximal parts compared with the healthy subjects, but the other areas did not differ.[19] Nevertheless, as the major body of the ulnar nerve is sensory and considering the motor neuropathic nature of ALS, most of the studies in the literature are in favor of more median nerve susceptibility to be affected than the ulnar nerve in ALS patients.[27]

Considering the pattern of involvement in the median versus ulnar nerves, the proximal-to-distal ratio seems to be a more valuable index for the median nerve to assess motor neuropathies, such as ALS. This proportion has been evaluated in the previous studies as well and not only does appear as a means of ALS diagnosis but also can be applied to differentiate the type of neuropathies.[11,14] Nevertheless, further evaluations to discover cut-off points are required.

One of the surprising findings in the current study is a lack of similarity between the measures done for right versus left hands; however, we have not evaluated the statistical measures of the differences, and they were not in relatively close ranges. Although we have no ratio for this incident, we assume that the hand predominance might play a role in this area. Nevertheless, to the best of our knowledge, this issue has not been considered in previous studies. Further studies are strongly recommended.

The last step in the current study was to determine a threshold for the assessed parameters as an aid in ALS diagnosis; however, unfortunately, we found no statistically significant index. Noto and colleagues reported that at the threshold of 0.9 cm^2, the proximal CSA of the median nerve had the sensitivity and specificity of 92.4 and 55.6% to differentiate ALS from the other neuropathies.[14] This cut-point is similar to ours for this region of median nerve, while ours was not statistically significant. The other study in this area measured both median and ulnar nerve CSA from the most proximal to the most distal parts and represented the highest sensitivity and specificity for the proximal median nerve regions accounting for 85 and 82%, respectively. Nevertheless, the measurements for the ulnar nerves were not notable.[15] To the best of our knowledge, limited studies in the literature have focused on this issue to determine a cut-point for ALS diagnosis through ultrasonography study of peripheral nerves CSA. Further studies are strongly recommended.

Limitations

Despite all the strong points of the current study, its small sample population limits its generalizability. Other significant limitations include failure to consider the duration of the disease as a confounding variable or to include newly diagnosed cases only. Furthermore, the patients have not been evaluated regarding their symptoms, the duration, or the severity of their nerve involvement which might have affected the outcomes. Moreover, the included healthy subjects have entered into the study based on lacking any symptoms, while they might have had nerve involvement due to other pathologies such as carpal tunnel syndrome or to less probability; they could have undiagnosed ALS. Further evaluations with better quality of data collection can lead to more comprehensive and conclusive outcomes.

Conclusion

Based on the findings of this study, CSA of proximal median nerve in the cubital fossa was remarkably lower in ALS subjects than the healthy controls which seems a rational and valuable means to diagnose ALS, but the distal parts of the median nerve and the ulnar nerve in its all length are still matter of debate. Besides, considering the motor nature of median nerve, it is generally superior to ulnar nerve as a peripheral nerve with major sensory function. Nevertheless, the suggested method is not an alternative for current EDX method and it is an adjunctive method. Further investigations are recommended.

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Conflicts of interest

There are no conflicts of interest.

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