

Correlations Between Median Nerve Sonography and Conduction Study Results and Functional Scales in Amyotrophic Lateral Sclerosis

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Received: 03 Jul. 2019; Accepted: 24 Nov. 2019

Abstract- We aimed to compare the sonographic measurement of median nerve cross-section area (CSA) in patients with Amyotrophic Lateral Sclerosis (ALS) and healthy individuals. The effect of duration of the disease on correlations between paraclinical findings and ALS functional rating scale (ALSFRS) were secondarily aimed to be evaluated. The cross-sectional study was approved by the Ethical Committee of Iran University of Medical Sciences and conducted between January 2017 and December 2018. We evaluated the median nerve surface area by means of sonography in 35 ALS patients and 35 healthy controls. Compound muscle action potential (CMAP) amplitudes during nerve conduction study and ALSFRS were recorded by the same trained specialist. Data were analyzed using SPSS software version 18. We did not find a significant difference between CSA in ALS patients and the normal population ($P>0.05$). Comparing to normal individuals, the mean CMAP decreased significantly in ALS patients (6.6 ± 3.07 mV versus 10.25 ± 2.2 mV, $P<0.001$). ALSFRS correlated with both CSA of the median nerve at the wrist ($P<0.001$, $r:0.78$) and the CMAP ($P<0.001$, $r:0.74$) that were confirmed by regression models designed to consider the effect of disease duration on these correlations. CSA was not different between ALS patients and the normal population, but CMAP decreased in ALS patients. ALSFRS correlated with both CSA and CMAP of the median nerve.

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Acta Med Iran 2019;57(11):658-662.

Keywords: Amyotrophic lateral sclerosis (ALS); Median nerve; Cross-sectional area; Compound muscle action potential (CMAP); ALS functional rating scale (ALSFRS)

Introduction

Amyotrophic lateral sclerosis (ALS), as a devastating neurodegenerative disease, is associated with atrophy of peripheral nerves (1).

Diagnosis and treatment are both under ambiguity, and the progression of the disease cannot be controlled at this time. Although current diagnostic criteria have been useful in diagnosis, the definite diagnosis usually cannot be achieved until 9 to 10 months of symptom onset (3).

Electrodiagnostic (EDX) is not always helpful in diagnosis at the early stages of the disease due to the compensatory reinnervation that occurred for neuronal

loss in ALS. This compensatory reinnervation may cause compound muscle action potential (CMAP) to remain unchanged, at least in the early phase of the disease. Therefore, studies have raised to help early detection of axon loss (3).

Ultrasonography, as a cost-effective and non-invasive technique, allows clinicians to evaluate the anatomy of suspected peripheral nerve lesions in superficial areas. Swelling and atrophy of peripheral nerves can be assessed by measuring cross-sectional areas in sonography (2,4). However, there are limited controversial results regarding sonographic findings in ALS. In ALS, the median nerve is one of the firstly involved neurons that may lead to split hand syndrome.

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Although there are lots of studies about the changes in the median nerve in ALS, the correlation between the degree of devastation in clinical function and paraclinical findings has not to be considered enough.

The aim of our study was to evaluate the effect of the duration of the disease on possible correlations between paraclinical findings and the ALS functional rating scale (ALSFRS). Comparing the median nerve cross-section area (CSA) (using ultrasonography) and CMAP in ALS patients with the healthy group was another objective.

Materials and Methods

Ethics

All patients and controls were explained about the study, and informed consent was signed by individuals before entering to the investigation. The study was approved by the Ethical Committee of Iran University of Medical Sciences (IUMS) (Code 1396.9311158004). Helsinki's declaration was respected in all steps.

Subjects

This was a cross-sectional study conducted between January 2017 and December 2018. Applying a convenient sampling method, patients were selected from those referred to ALS clinics at tertiary hospitals of IUMS, Tehran, Iran.

ALS patients were entered regarding the revised El Escorial and Awaji diagnostic criteria (1). Healthy age and sex-matched controls were selected from the normal population who underwent EMG for any suspected neurological issues with a normal result and did not have any other medical diseases. The included patients and controls had normal sensory nerve conduction study. All patients and healthy controls underwent neurological examination, and values of ALSFRS were recorded.

Coincidental carpal tunnel syndrome (CTS) was diagnosed when patients had sensory symptoms or signs in median nerve territory or slowed median sensory nerve conduction velocity with normal ulnar sensory nerve conduction study results. Those participants who had any abnormalities in the sensory nerve conduction study (NCS) with or without the diagnosis of CTS were excluded.

Ultrasonography (USG)

Ultrasound was carried out by a trained specialist using SonoSite M-Turbo with an 8-18 Hz linear probe. CSA of the median nerve at the wrist was measured bilaterally. The ultrasound was performed when the patient was in a seated position with straight and

supinated arms. The median nerve was evaluated by a linear transducer between the flexor digitorum superficialis and flexor digitorum profundus muscles in the ventral aspect of the wrists. In order to maintain a specific angle, the ultrasound probe was retained in a perpendicular position. CSA was measured by tracing the areas inside the hyperechoic rims. Three separate CSAs with the repositioned probe for each time were measured, and the average measurement was reported (2). Sonography was performed by the same blinded specialist to reduce observational bias.

Nerve conduction study

Complete electromyography was performed via Nicolet EDX Synergy System for patients and controls. In NCS, CMAP amplitude for both right and left median nerves in patients, and healthy controls were recorded. The wrist stimulation site was 3 cm proximal to the distal wrist crease. CMAP amplitude was measured from baseline to negative peak. The room temperature was 23-25 °C and the skin temperature at forearm and hand were maintained >32 °C by covering a blanket.

Statistics

Data were analyzed using SPSS software version 18. We compared differences in CSAs between patients and healthy groups. Correlations between CSAs and demographic features, as well as CMAP amplitude and ALSFRS, were analyzed. The significance level was determined at $P < 0.05$. Independent sample *t*-test and *Chi*-square were performed to compare the results between groups. Regression models were designed to assess the possible effect of confoundings on any significant correlations between ultrasonographic parameters and CMAP amplitude and ALSFRS.

Results

Representation of basic data

Thirty-five ALS patients and 35 healthy controls were included. In ALS and the control group, 54.3% and 62.9% of persons were male, respectively ($P:0.4$). Persons were categorized regarding their age; ≤ 35 , >35 , and >50 years old, that the prevalence was not significantly different (Table 1). The mean duration of the disease was 4.43 ± 1.1 years. Medical history was positive for hypertension in 6 patients, hyperlipidemia in 2 patients, and ischemic heart disease in one patient. No medical history was recorded in healthy individuals. Two patients (5.7%) declared a positive family history for ALS. FRS was equal to or less than 30 in 4 (11.4%)

patients.

Table 1. Description of data

	ALS patients	Controls	P
Age	39.2±14 Range: 19-71	38±11 Range: 23-61	0.6
Age ranges (years)	≤35 >35 >50	15(43%) 14(40%) 6(17%)	0.4
RMCSA (cm²)	0.053±0.01	0.055±0.01	0.4
LMCSA(cm²)	0.052±0.01	0.056±0.01	0.08
MMCSA(cm²)	0.05±0.009	0.05±0.009	0.1
RCMAP (mV)	6.7±3.2	10.5±2.4	<0.001
LCMAP(mV)	6.5±3.1	10.06±2.5	<0.001
MCMAP(mV)	6.6±3.07	10.25±2.2	<0.001
R.DL (msec)	3.7±0.5	3.5±0.4	0.08
L.DL (msec)	3.7±0.3	3.4±0.3	<0.001

LCMAP: compound muscle action potential of the left median nerve, MCMAP: mean compound muscle action potential of the left and right median nerves, RMCSA: right median nerve cross-sectional area, LMCSA: left median nerve cross-sectional area, MMCSA: mean cross-sectional area of right and left median nerves, RDL: right distal latency, LDL: left distal latency, cm: centimeter, msec: millisecond, mV: millivolt

All patients and controls had normal sensory nerve action potential (SNAP). Compound muscle action potential of the right median nerve (RCMAP) was ≤4 mV in 7 ALS patients and >4 mV in other persons, even healthy or patient. In addition, the compound muscle action potential of the left median nerve (LCMAP) was ≤4 mV in 11 (31.4%) of patients. Right distal latency (RDL) was >4.4 msec in 4 (11.4%) ALS patients, and left distal latency (LDL) was ≤4.4 msec in all 70 individuals. The mean FRS was 36.5±5.3. Quantitative data are described in (Table 1).

Correlations

EDX data had no correlation with demographics (age, sex) in both groups (P>0.05). In our study, ALSFRS did not correlate with the duration of the disease (P=0.1), although the correlation was significant by the mean age of our patients (P=0.005, Pearson Correlation: -0.46).

Correlation between continuous variables, including disease duration in ALS patients, are illustrated in (Table 2).

Table 2. Correlation between continues variables in 35 ALS patients

	ALSFRS	RCMAP	LCMAP	RMCSA	LMCSA	MMCSA	MCMAP
Disease duration	P:0.1	P:0.1	P:0.01 PC:0.4	P:0.3	P:0.5	P:0.3	P:0.04 PC:0.34
ALSFRS		P:<0.001 PC:0.7	P:<0.001 PC:0.7	P:<0.001 PC:0.6	P:<0.001 PC:0.7	P:<0.001 PC:0.78	P:<0.001 PC:0.74
RCMP				P:0.04 PC:0.3			
LCMAP					P:<0.001 PC:0.6		
MCMAP						P:<0.001 PC:0.56	
Age	P:0.005 PC:-0.46	P:0.058 PC:-0.32	P:0.02 PC:-0.4	P:0.1	P:0.1	P:0.06	P:0.03 PC:-0.36

PC: Pearson Correlation, P: P-value, ALSFRS: Amyotrophic lateral sclerosis functional rating scale, RCMAP: compound muscle action potential of the right median nerve, LCMAP: compound muscle action potential of the left median nerve, MCMAP: mean compound muscle action potential of the left and right median nerves, RMCSA: right median nerve cross-sectional area, LMCSA: left median nerve cross-sectional area, MMCSA: mean cross-sectional area of right and left median nerves right median nerves, RMCSA: right median nerve cross-sectional area, LMCSA: left median nerve cross-sectional area, MMCSA: mean cross-sectional area of right and left median nerves

Multivariate analysis

Regarding the low number of cases (35), each model

could not include more than 3 variables. Because disease duration was clinically the most important confounding,

the model was designed considering the effect of this factor on the correlations between amplitude, CSA, and ALSFRS. The disease duration significantly correlated with LCMAP and mean compound muscle action potential of the left and right median nerves (MCMAP) (Table 2). The linear regression models are presented in

Table 3.

Receiver operating characteristic (ROC) curve analysis was provided to assess the diagnostic value of CMAP in ALS, but the results did not provide an appropriate cutoff point.

Table 3. Multivariate analysis for considering the effect of disease duration on significant correlations between clinical and EDX findings

Dependent	P for model	adjusted R square for model	Disease duration	ALSFRS
LCMAP	<0.001	0.5	P: 0.05, B: includes 1	P<0.001, B: 0.4, 95% CI: 0.25-0.53
MCMAP	<0,001	0.5	P:0.1	P<0.001, B: 0.4, 95% CI: 0.26-0.54

LCMAP: compound muscle action potential of the left median nerve, MCMAP: mean compound muscle action potential of the left and right median nerves, ALSFRS: Amyotrophic lateral sclerosis functional rating scale

Discussion

In the current study, we did not find a significant difference between CSA in ALS patients and the normal population (Table 1). It was not the first time that the median CSA at the wrist was found as a similar size as the normal population (5). The size of the median nerve at the wrist was found unchanged in ALS patients in some previous studies (6), although further results were controversial, particularly about the size of the nerve in the arm. Some publications in 2018 and 2011 revealed a significant reduction in the size of the median nerve CSA among ALS patients (1,3,7).

Regarding the insignificant difference between the CSA of the median nerve in ALS patients and healthy patients in our study, checking the values (sensitivity and specificity) of median nerve size in ALS diagnosing was not possible. Following some studies insisted on the diagnostic values of CMAP in ALS (9), we performed ROC curve analysis, but it did not present an acceptable reportable cut off point.

Comparing to normal individuals, CMAP decreased significantly in our ALS patients (Table 1), which was in accordance with most of the previous studies (8,9).

Surprisingly, the functional scale did not correlate with the duration of the disease. It showed unpredictable changes in the function of ALS patients, which was not related to the time that they were involved with ALS. The functional scale indirectly correlated with age (Pearson correlation: -0.46) that showed the older patients suffered from more devastation, but it did not mean that they had more duration of the disease, as if there was no correlation between ALSFRS and disease duration in our study. It might be hypothesized that

elders present in more anguish and devastation than the younger population. However, our sample size was not much enough to confirm this theory.

ALSFRS correlated directly with both CSA of the median nerve at the wrist and the CMAP in EDX (Table 2). Correlation between CMAP and functional scale could be affected by the duration of the disease since both left CMAP and the average CMAP of the left and right sides correlated with disease duration. By applying multivariate analysis (Table 3), disease duration could not affect the correlation between EDX findings and clinical function scale. In other words, the functional score was in accordance with CMAP regardless of the period that the patient had been suffering from the disease. Some previous studies (3,10) did not find CMAP correlated with disease duration that was in conflict with our findings. However, ALSFRS was positively associated with CMAP in the median nerve, regarding the same study. These controversies show that more investigations are still needed about the role of paraclinical methods in predicting functional impairments of ALS patients.

ALSFRS also correlated with CSA of the median nerve that signifies the concept that the more CSA in the median nerve, the more function. Although having more function following more neurons at the section is somehow obvious per se, some studies did not find significant results between the CSA of the median nerve and ALSFRS (1).

CSA has been reported in different sizes among ALS patients. We reported means (mean of right and left sides) of 0.05 ± 0.009 cm² in the ALS group and 0.05 ± 0.009 cm² in the healthy group. In another study, Cartwright MS *et al.*, found an average area of 8.9 mm²

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at the mid-arm (5), and in another study, they found the mean area of 10.5 (7.0-15.5) mm² in ALS patients and 12.7 (9.3-16.3) mm² in controls. Nodera, H. *et al.*, found median nerve area 6.72±1.2 mm² in healthy controls and 5.74±1.5 mm² in ALS patients (3).

The relatively small number of subjects is considered as the main limitation of our study.

Furthermore, other nerves evaluation, such as ulnar nerve, might add some diagnostic strategies. Although we considered the duration of the disease in this survey, it lacked long term follow up. It is recommended to investigate long term follow up whether any relationships between these findings and the disease progression over time are presented.

A high degree in the diversity of results is representative of the absolute need for more investigations about the role of sonography of peripheral nerves in ALS diagnosis or progression. Also, these huge sources of data have to be organized by a meta-analysis that provides more comprehensive announcements.

CSA was not different between ALS patients and the normal population, but CMAP decreased in ALS patients. ALSFRS correlated with both CSA and CMAP of the median nerve. Our results may help to provide a revolution in the diagnosis of ALS following further meta-analyses of our data plus previous articles.

Acknowledgments

We would like to thank Dr. Amir Rouhi for his effective contribution to this work.

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