Relationship between diaphragm MEP and swallowing, respiratory function and survive in ALS patients

Nazan Şimşek Erdem[1] , Ferda İlgen Uslu[2] , Selen Bozkurt[3] , Hilmi Uysal[1]

[1]Department of Neurology, Akdeniz University, School of Medicine, Antalya, Turkey
[2]Department of Neurology, Bezmialem Vakif University, School of Medicine, İstanbul, Turkey
[3]Department of Biostatistic, Akdeniz University, School of Medicine, Antalya, Turkey

Abstract

Objective: To investigate the relationship between diaphragm motor evoked potential (Dia-MEP) with swallowing, respiratory function and survive in amyotrophic lateral sclerosis (ALS) patients.

Methods: Twenty-three ALS patients and 15 healthy subjects were included in the study. Pulmonary function tests were performed using forced vital capacity and maximal sniff nasal pressure. Swallowing functions of patients were examined using the dysphagia limit. Transcranial magnetic stimulation (TMS) was applied in ALS patients and healthy subjects. Bilateral cortical and spinal motor evoked potential (MEP) of hemidiaphragm and abductor pollicis brevis (APB) muscles were recorded. Latencies and amplitudes of cortical and spinal MEPs and central motor conduction time (CMCT) were measured.

Results: In the ALS group, obtaining rates of cortical MEP from APB and diaphragm muscles were statistically significantly lower than the healthy group. Obtaining rates of cortical diaphragm MEP (Dia-Cx-MEP) were lower in patients with dysphagia and respiratory dysfunction and patients who died but the difference was statistically significant for only patients with respiratory dysfunction. There were no significant difference between amplitudes and latencies of Dia-Cx-MEPl and spinal diaphragm MEP (Dia-Sp-MEP) in patients with and without dysphagia or respiratory dysfunction and patients who died or survived.

Conclusion: There were no significant correlations between the Dia-Cx-MEP and Dia-Sp-MEP latency values and the CMCT values of Dia-MEP and the respiratory measures. In ALS patients, the disappearance of Dia-Cx-MEP in spite of the Dia-Sp-MEP can reflect the deterioration of the respiratory pathway from motor cortex.

Keywords: ALS patients, diaphragm motor evoked potential, dysphagia limit

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder of the upper and lower motor neurons (1). Median survival time of ALS patients is usually three years after onset of symptoms (2). In ALS patients, respiratory function and dysphagia are the most important life expectancy predictors (3, 4). Elderly age, female gender, bulbar involvement, and rapid decline of the ALS Functional Rating Scale-Revised (ALSFRS-R) are factors that negatively affect life expectancy in ALS patients (5-7).

Transcranial magnetic stimulation (TMS) is a noninvasive test used to diagnose ALS and to distinguish it from other similar neurological diseases. Transcranial magnetic stimulation also detects the corticomotoneuronal function abnormalities in ALS patients (8-15). For several years, TMS has been used to determine deterioration of the cortico-diaphragmatic pathway in several neurological disorders, including ALS (16-22).

Swallowing and respiratory functions are often affected in patients with ALS (23). In the current body of literature, many studies have investigated the correlation between diaphragm motor evoked potential (Dia-MEP) and pulmonary function tests in ALS patients (21, 22). However, we were unable to find any study that investigated the relationship between dysphagia and Dia-MEP. Several researchers have studied the relationship between

electrophysiological studies of the phrenic nerve and survival in patients with ALS (24-26). To the best of our knowledge, there is no systematic study that investigates the relationship between survival and Dia-MEP. Thus, our study aimed to investigate the relationship between Dia-MEP and swallowing, respiratory function, and survival in ALS patients.

METHODS

Twenty-three ALS patients, diagnosed according to the revised El Escorial criteria, were included in the study (27). Patients with percutaneous endoscopic gastrostomy (PEG) and tracheostomy were excluded. The patients included in the study were followed for 4 years (2011 to 2015). The Medical Research Council Scale and the ALSFRS-R were used to assess the ALS patients (28, 29). Fifteen healthy, age-matched subjects were included in the study as the control group. The study was conducted in accordance with the Declaration of Helsinki. All of the patients and control subjects were asked to sign a written informed consent form.

Respiratory and Swallowing Function

We recorded the percentages of the estimated values of forced vital capacities (FVC) and sniff nasal inspiratory pressure (SNIP). Values above 80% of the predicted FVC were accepted as normal. The SNIP test is easier for patients with orofacial muscle weakness (30). Normal SNIP values were accepted as ≥70 cm H_2O and ≥60 cm H_2O for men and women, respectively, as reported in a large study (31).

The swallowing functions of the ALS patients were evaluated using dysphagia limit (DL) and piecemeal deglutition. Piecemeal deglutition refers to dividing the bolus into two or three successive swallows. Piecemeal deglutition can be observed in healthy subjects when swallowing >20 mL of water (32, 33). Dysphagia limit is the volume at which the second swallow, or more swallows, become necessary for a person to swallow the whole of bolus.Increasing amounts of water (3, 10, 15, and 20 mL respectively) were placed in the patient's mouth with a syringe. The patients were asked to swallow the water bolus after receiving a swallow command, and their second swallow in the 8-second period was accepted as pathologic.

Transcranial Magnetic Stimulation (TMS)

Magnetic stimulation was performed using a Magstim 200 stimulator, producing a maximal magnetic field of 2 Tesla. A standard stimulation procedure was applied using a round coil with a 9 cm diameter. The cortical and spinal motor evoked potential (MEP) responses after magnetic stimulation were recorded from the bilateral diaphragm and bilateral abductor pollicis brevis (APB) muscles in all the participants in a seated position.

For the upper extremity, superficial recording electrodes were placed over each APB muscle using the bellytendon method. The stimulus was applied to the scalp region overlying the right and left primary motor cortex to obtain the cortical APB-MEP (APB-Cx-MEP). For the spinal APB-MEP (APB-Sp-MEP), the stimulus was applied to the spinous process of the C7 vertebra. For all the participants, APB-Cx-MEP and APB-Sp-MEP were recorded during complete muscle relaxation.

For the diaphragm muscle, an active electrode was placed on the seventh intercostal space, and a reference electrode was placed on the sternum. For the cortical Dia-MEP (Dia-Cx-MEP), the coil was applied to the scalp region overlying the vertex. This area corresponds to the Cz-International 10-20 EEG system. The stimulus was applied above the C5 vertebra for the spinal diaphragm motor evoked potential (Dia-Sp-MEP). For all the subjects, Dia-Cx-MEP and Dia-Sp-MEP were recorded during the inspiratory phase.

The stimulus intensity was increased in 1% increments of maximum stimulator output until five to ten of the largest MEP amplitudes were recorded. The MEP was accepted as being absent when no response was observed after 10 or more stimuli with 100% stimulus intensity. The latency of the MEP after magnetic stimulation was evaluated at the onset of the first negative deflection of the MEP. Central motor conduction time (CMCT) was calculated by subtracting the latency of the spinal MEP (Sp-MEP) from the cortical MEP (Cx-MEP). The MEP with the largest amplitude was accepted as the latency and MEP amplitude measurements.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, while categorical variables are given as percentages. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Statistical analysis of clinical data between two groups consisted of unpaired t-tests for parametric data and Mann Whitney U test analysis for nonparametric data, whereas one-way analysis of variance or Kruskal-Wallis tests was used to evaluate comparisons between the 3 groups. Correlations were assessed with the Pearson/Spearman correlation coefficient and the chi-square/Fisher's exact test was used for categorical variables. In addition Cox regression models were applied to identify factors correlating with the survival. Analyses were performed with PASW 22 Statistical Package for the Social Sciences (SPSS IBM Corp.; Armonk, NY, USA) software and two-tailed p value less than 0.05 was considered statistically significant.
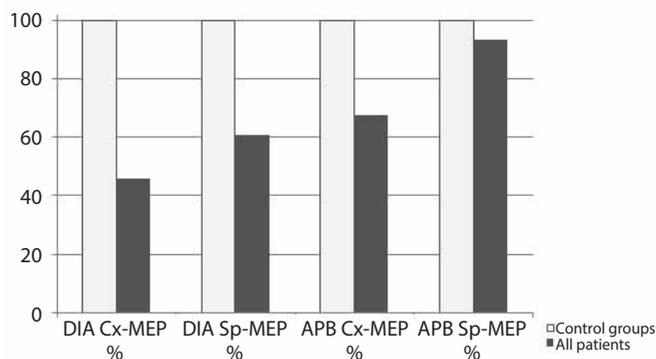
RESULTS

Twenty-three ALS patients and 15 healthy subjects (control) were included in this study. Nineteen of the 23 ALS patients were diagnosed with ALS and 4 were diagnosed as possibly having ALS based on the revised El Escorial criteria. Eighteen of 23 ALS patients were male and 5 were female. The mean age of the ALS patients was 52.6±11 years (30–75).The control group consisted of 10 men and 5 women. The mean age of the subjects in the control group was 48.4±10 years.

In the ALS patients, the mean interval from onset of symptoms to diagnosis was 10±8 (2–36) months. The mean disease duration was 24.7±28 (1–120) months from the diagnosis. The mean ALSFRS-R score was 31.9 ± 9 (15–44). The mean FVC was 63.8±21 of the predicted % (14-98%) and the mean SNIP was 54.1±20 cm H$_2$O (12–86 cm H$_2$O). Fifteen of the ALS patients (65.2%) had respiratory dysfunction based on the results of the respiratory function tests. The average DL of all the ALS patients was 14.1±7.3 cc (3–20). Twelve ALS patients (52.2%) had dysphagia based on the DL criteria. The mean values of FVC and SNIP were significantly lower in the dysphagia group (p=0.029, p=0.021, respectively) (Table1).

During the 48-month follow-up period, 12 of the 23 ALS patients died an average of 22 months after enrollment in the study. Six patients were living without PEG and tracheostomy. Two patients were living with both PEG and tracheostomy. Two patients needed only respiratory support. One patient needed only PEG. After diagnosis, the 3-year overall survival rate was 83% and the 5-year overall survival rate was 39%. After being included in the study, the 3-year overall survival rate was 74%, and 4-year overall survival rate was 48%. No significant difference in the onset age, gender, diagnostic delay, ALSFRS-R, FVC, DL, or SNIP values was observed between the ALS patients who died or survived (Table 1).

In the 15 healthy subjects, all the Sp-MEP and Cx-MEP responses were observed from the bilateral APB and diaphragm muscles. In the ALS patients, 46 APB and diaphragm muscles (total number of right and left sides) were studied, and 31 APB-Cx-MEPs (67.3%) and 21 Dia-Cx-MEPs (45.6%) were obtained. The APB-Cx-MEP and Dia-Cx-MEP response rates were significantly lower in the ALS group than the control group (p=0.0005 and p=0.001, respectively) (Figure 1).

The spinal MEP response rates for the ALS patients were 93.4% and 60.8% for the APB and diaphragm muscles, respectively. No significant difference was observed in the APB-Sp-MEP rates between the ALS group and the control group (p=0.2). However, the Dia-SP-MEP response rate was significantly lower in the ALS group than the control group (p=0.004) (Figure 1).

In the ALS patients, the APB-Sp-MEPs were significantly higher than the APB-Cx-MEPs (p=0.02). For the diaphragm muscles, 28 Sp-MEPs (60.8%) and 21 Cx-MEPs (45.6%) were recorded for this patient group; however, the difference was not statistically significant (p=0.21) (Figure 1). When the spinal responses were not recorded, the cortical responses were not recorded. The mean cortical and spinal MEP latencies for APB were 22.2±1.9 ms and 13.5±0.8 ms, respectively, in the control group and 23.2±3 ms and 15.4±2.3 ms, respectively, in the ALS patients. The mean CMCT for ABP was 8.9±1.9 and 7.9±2.8, in the healthy subjects and the ALS patients, respectively. For the diaphragm muscles, the mean Cx-MEP and Sp-MEP latencies were 13.8±2.2 ms and 4.7±1.1 ms, respectively, in the control group, and 15±2.6 ms and 6.6±2.4 ms, respectively, in the ALS patients. No significant differ-

Figure 1. For APB and Diaphragm muscles, Cx-MEP and Sp-MEP obtaining rates of all patients and healthy Group
Dia-Cx-MEP: diaphragm cortical motor evoked potential; Dia-Sp-MEP: diaphragm spinal motor evoked potential; ABP-Cx-MEP: abductor pollicis brevis cortical motor evoked potential; ABP-Sp-MEP: abductor pollicis brevis spinal motor evoked potential

Table 1. Results (mean, standard deviation) of demographic characteristics for the total ALS patients and sub-groups

Groups	All patients	Without dysphagia	With dysphagia	Without respiratory dysfunction	With respiratory dysfunction	Survive	Exitus
Demographic features	n:23	n:11	n:12	n:8	n:15	n:11	n:12
Age at onset (in years)	51±11	49±14	53±8	46±13	53±10	47±13	55±9
Sex (M:F)	18:05	09:02	09:03	07:01	11:04	09:02	09:03
Diagnostic de-lay (month)	10±8	10±6	10±10	11±6	10±9	10±9	10±7
Mean ALS-FRS-R	32±9	32±7	32±11	33±8	31±10	30±8	33±10
Mean Rof (ALS-FRS-R)	11±2	11±1	10±2	12±1	10±2	11±2	11±2
Mean SNIP (cm H$_2$O)	54±20	64±15	45±20	69±8	46±20	55±25	54±16
FVC (%)	64±21	73±15	53±23	84±12	52±16	62±24	65±19
Dysphagia limit (cc)	14±7	20±0	9±7	18±4	12±8	14±7	14±8

ALSFRS-R: revised ALS Functional Rating Scale; RofALS-FRS: the respiratory subscore of ALS-FRS-R; FVC: forced vital capacity; SNIP: sniff nasal inspiratory pressure

ence was found between the control and ALS groups for the CMCT values and the Cx-MEP and Sp-MEP latencies and amplitudes of the diaphragm and APB muscles (p>0.05 for all comparisons) (Table 2).

Eight (33.3%) and 13 (59.1%) Cx-MEPs were obtained from the diaphragm muscles of the ALS patients with and without dysphagia, respectively. Ten Cx-MEPs (33.3%) and 11 Cx-MEPs (68.7%) were recorded from the diaphragm muscles of the ALS patients with and without respiratory dysfunction, respectively. The Dia-CxMEP rates were lower in patients with dysphagia and respiratory dysfunction and the patients who died, but the difference was only statistically significant in patients with respiratory dysfunction (p=0.02). No significant difference was observed between the Sp-MEP rates in patients with and without dysphagia and respiratory dysfunction and the patients who either died or survived (Figure 2) (p>0.05 for all comparisons).

No correlation was found between the latencies, amplitudes, and CMCT values for Dia-Cx-MEP and Dia-SpMEP and FVC or SNIP (p>0.05 for all comparisons). The latencies, amplitudes, and CMCT values for Dia-CxMEP and Dia-Sp-MEP were compared in the ALS patients with and without dysphagia or re-

Figure 2. Dia-Cx-MEP and Dia-Sp-MEP obtaining rates of the patients with and without dysphagia or respiratory dysfunction and patients who died or survived


spiratory dysfunction and the patients that died or survived. No statistically significant difference was observed between the amplitudes, latencies, and CMCT values for Dia-Cx-MEP and Dia-Sp-MEP in the ALS patients with and without dysphagia or respiratory dysfunction and the patients who died or survived (p>0.05 for all comparisons).

DISCUSSION

In the present study, we investigated the difference between the Cx-MEP and Sp-MEP rates of the diaphragm and APB muscles in ALS patients and healthy subjects in the control group. The Cx-MEP rate for the APB and diaphragm muscles was significantly lower in the ALS patients than in the healthy subjects in the control group. The absence of Cx-MEP in the presence of Sp-MEP was only observed in the ALS patients. No significant differences were observed in the Cx-MEP and Sp-MEP amplitudes obtained from the diaphragm muscles of the ALS patients and the healthy subjects in the control group. Previous studies have evaluated MEP amplification in ALS patients. It has been reported that MEP amplitudes in ALS patients increase in the early stages of the disease due to cortical hyperexcitability, but they decrease in the later stages of the disease due to disease progression (8, 10, 14). In this study, we were unable to perform TMS at regular intervals for the ALS patients, so it was not possible to evaluate changes in MEP amplitude at the early and later stages of the disease. In our study, no relationship was found between Cx-MEP and Sp-MEP amplitude and duration of disease in the ALS patients. We observed that TMS amplitude cannot objectively discriminate corticospinal tract involvement in the ALS group in comparison to the control group. Although many previous studies have reported on CMCT prolongation in ALS patients, we did not find any CMCT difference between the ALS group and the control group, as indicated in the report of de Carvalho et al. (8-10, 13, 15, 34).

In this study, we showed that there were no significant correlations between the Dia-Cx-MEP and Dia-Sp-MEP latency values and the Dia-CMCT values and the respiratory measures, as indicated in Miscio et al. In the present study, no significant differences were observed in the Dia-CMCT values and the Dia-Cx-MEP and Dia-Sp-MEP latency values of the ALS patients and the healthy subjects in the control group, although Miscio et al. reported that the mean val-
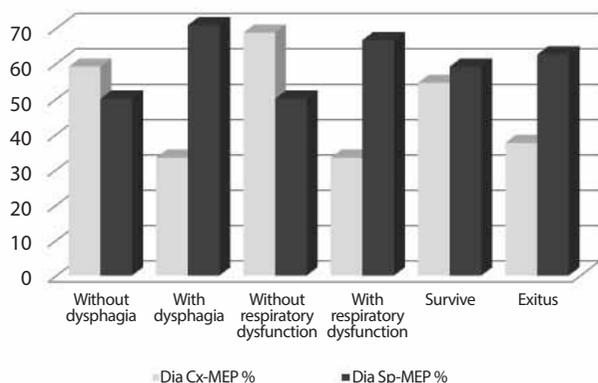
Table 2. Transcortical and transcervical magnetic stimulation results of the health and ALS groups

Groups	Muscles	Cx-MEP latency mean±SD (ms)	Cx-MEP Amplitude mean±SD (mV)	Sp-MEP latency mean±SD (ms)	Sp-MEP Amplitude mean±SD (mV)	CMCT
ALS patients n:46	APB	23.2±3	3±2.2	15.4±2.3	2.1±1.5	7.9±2.8
	Dia	15±2.6	1±0.7	6.6±2.4	1.7±1.3	7.9±2.7
Control subjects n:30	APB	22.2±1.9	3.5±2.8	13.5±0.8	5.3±4.8	8.9±1.9
	Dia	13.8±2.2	1.0±0.5	4.7±1.1	1.8±1.1	9.2±2.3

CMCT: central motor conduction time; Cx-MEP: cortical motor evoked potential; SP-MEP: spinal motor evoked potential; APB: abductor pollicis brevis; Dia: diaphragm; SD: standard deviation

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ues of the Dia-CMCT and Dia-Cx-MEP latencies were longer in the ALS patients than in the healthy subjects (21). We did not find a correlation between the Cx-MEP and Sp-MEP diaphragm amplitudes and the FVC and SNIP, although Shimuzu et al. reported that there was a weak, non-significant correlation between the inspiratory Dia-MEP amplitude and FVC (22).

This study found that the disappearance of Dia-Cx-MEP is a sign of the deterioration at the corticodiaphragmatic pathway in ALS patients, as indicated in Miscio et al. and Shimuzu et al. (21, 22). It is known that respiration and swallowing are associated in healthy people (35). It has also been shown that DL is correlated with respiration function tests in ALS patients (23). In the literature, no previous study has investigated the relationship between dysphagia and Dia-MEP. Therefore, we aimed to compare the Dia-MEP findings in ALS patients with and without dysphagia. To the best of our knowledge, our study is the first to report the association between DL and Dia-MEP. Although the data were not found to be statistically significant, the Dia-Cx-MEP rate was lower in the ALS patients with dysphagia.

In addition, we investigated the relationship between Dia-MEP and ALS survival. The Dia-Cx-MEP rate was lower in ALS patients who died than in those that survived; however, the difference was not statistically significant. It has been reported that phrenic nerve amplitude is closely correlated with mortality and the symptoms and signs of respiratory insufficiency (26). In our study, no correlation was found between survival and age of disease onset, FVC, SNIP, DL, total score, and the respiratory sub-score of the ALSFRS-R at the time the ALS patients were enrolled in the study. We think that the lower levels of FVC, SNIP, and DL in ALS patients are predictors of the need for tracheostomy and PEG, and these parameters should be frequently checked. We think that measuring the FVC, SNIP, and DL levels more frequently and at the same time would be more helpful in estimating the survival rate of ALS patients. The present study has some limitations. It had a small number of ALS patients (23 patients). We were unable to obtain the respiratory measurements, conduct the dysphagia tests, and apply TMS at regular intervals for the ALS patients.

In conclusion, our study demonstrated that the most obvious TMS finding in ALS patients is the absence of Cx-MEP in the presence of Sp-MEP; moreover, the absence of the Dia-Cx-MEP is a sign of deterioration at the corticodiaphragm patway in ALS patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Akdeniz University Hospital, Turkey.

Informed Consent: Written informed consent was obtained from all the patients and healthy subjects who participated in this study.

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