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Ultrasonographic evaluation of the diaphragm thickness in patients with multiple sclerosis

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ABSTRACT

Background: Diaphragm weakness or dysfunction have been previously reported in multiple sclerosis (MS) patients. The aim of this study was to evaluate diaphragm thickness and thickenning ratio (TR) using ultrasound in MS patients.

Methods: This prospective study comprised MS patients and a control group. Ultrasound examination was performed using a linear transducer (6–15 MHz). The diaphragm was seen as a hypoechoic structre between the peritoneum and pleura. End-expirium and end-inspirium measurements were obtained. Change levels and TR (%) were calculated. All participants were assessed using the Expanded Distability Status Scale (EDSS) and Fatigue Severity Scale (FSS).

Results: Evaluation was made of 45 MS patients (11 males, 34 females) with a mean age of 37.36 ± 9.0 years and 36 healthy subjects (3 males, 33 females) with a mean age of 35.19 ± 9.3 years. The diaphragm thicknesses were similar at end-expirium (1.86 ± 0.3 vs. 1.83 ± 0.3 mm) and end-inspirium (3.14 ± 0.6 vs. 3.46 ± 0.6 mm). The change level with inspirium (0.90 ± 0.6 vs. 1.31 ± 0.7 mm) and TR (49.77 ± 37.7 vs. 72.30 ± 40.1%) were significantly higher in the control group compared to the values of MS patients. A weak and negative correlation was determined between EDSS and TR values (r = -0.293, p = 0.008), and no significant correlation was observed between the FSS values and diaphragm thickness ($p > 0.05$ for all).

Conclusion: Although the diaphragm thickness of MS patients seems to be similar to those of healthy subjects, the change level and TR of MS patients seem to be lower. Furthermore, the change level and TR were found to be associated with EDSS.

1. Introduction

Multiple sclerosis (MS) is an autoimmune, chronic neurological disease characterized by inflammation, demyelination and axon damage in the central nervous system (Goldenberg, 2012). Variable distribution of MS lesions across the central nervous system can result in impaired muscle strength and endurance, including the pulmonary system muscles. It has been well established that pulmonary system dysfunction is an important cause of morbidity (e.g. cough, aspiration pneumonia, acute respiratory failure) and mortality in MS (Rietberg., 2017; Tzelepis and McCool, 2015; Sumelahti et al., 2010). In addition, respiratory dysfunctions can be seen even in MS patients with no pulmonary complaints (Altintas et al., 2007). Moreover, the impairment of respiratory muscles and pulmonary functions worsens with disease progression (Rietberg., 2017).

The diaphgragm is the main inspiratory muscle formed by skeletal muscle fibers. It is dome-shaped and separates the thorax from the abdomen. During inspiration, the diaphragm contracts, flattens, and moves distally, decreasing the thoracic pressure and increasing the intraabdominal pressure (McCool et al., 2018). Diaphragm weakness or dysfunction have been previously reported in MS patients. However, the evaluations were based on clinical findings, electrophysiological evaluation, pulmonary function tests or other methods (Tzelepis and McCool, 2015). To the best of our knowledge, there has been no study evaluating the diaphragm using ultrasound (US) in MS patients. Therefore, the aim of this study was to evaluate diaphragm thickness and thickening ratio (TR) using US in MS patients.

Abbreviations: EDSS, Expanded Distability Status Scale; FSS, Fatigue Severity Scale; MS, multiple sclerosis; TR, thickening ratio; US, ultrasound

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2. Methods

2.1. Study design and participants

This prospective study was designed as a case-control study. MS patients who were followed up in the Neurology Department of a university hospital were enrolled. The study was conducted between November 2018 and June 2019. Patients with any history of respiratory system disorder (e.g. asthma, chronic obstructive pulmonary disease, etc.) or respiratory symptoms, any neurological disease other than MS (spinal cord injury, stroke, neuropathy, etc.), drug usage for the respiratory system, or any other conditions that may affect the pulmonary system were excluded. Patients who had experienced an MS attack within the last 3 months were also excluded. A control group was formed of healthy subjects. The data of the MS group and control group were compared.

This study protocol was approved by the Local Ethics Committee (2019/04 - 07) and informed consent was obtained from all the participants.

2.2. Ultrasound evaluation

Ultrasonographic evaluations were admistered by the same physician using a LOGIQ E9 XDclear 2.0 ultrasound machine (GE Healthcare, 2017, USA) and a linear transducer (6–15 MHz xd, Matrix clear). The examiner was blinded to the study groups. The probe was placed over the chest wall in the anteriory axillary line. As the probe was moved caudally, the diaphragm was seen as a hypoechoic structre between two hyperechoic lines. The measurements were obtained from the most caudal part of the diaphragm. While the upper line corresponded to the pleura, the lower line corresponded to the peritoneum (Fig. 1). The thickness of the diaphragm was measured with electronic calipers. End-expirium and end-inspirium measurements were obtained from the right side. This measurement technique is valid, simple, and reliable (Khurana et al., 2018; Goligher et al., 2015). Change level was accepted as the thickness at end-expirium subtracted from the thickness at end-inspirium. The thickening ratio% (TR) was calculated as percentage (%); change level/thickness end-exspirium × 100

2.3. Assessment tools

The assessment tools used were the Expanded Distability Status Scale (EDSS) and the Fatigue Severity Scale (FSS). EDSS is a measure of the disability status of MS patients, comprising eight functional areas of the pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, mental and other functions. While zero corresponds to the normal health status, increased values show more disability and 10 refers to death (Kurtzke, 1983). The FSS is a 9-item questionnaire to evaluate the severity of fatigue symptoms. Each item is scored 1 to 7, and the average of the scores is calculated. Higher values of FSS denote more severe level of fatigue (Krupp et al., 1989).

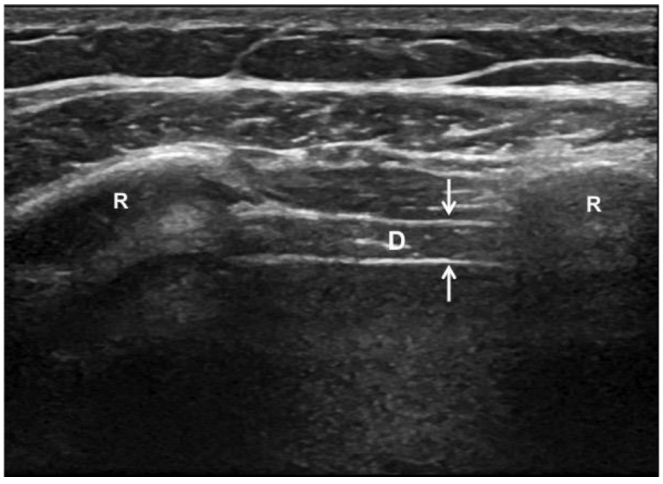

Fig. 1. Ultrasound imaging of the diaphragm
The diaphragm (D) is seen as a hypoechoic structre between two hyperechoic lines (*thin arrows*). The upper and lower lines correspond to the pleura and peritoneum, respectively (r: rib).

2.4. Statistical analysis

Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Normal distribution was confirmed with the Shapiro Wilk test and histograms. Descriptive data were stated as mean ± standard deviation, median (25–75%), number or percentage. Categorical variables were compared using the Chi-square Test. The Student's t-test was used for comparisons between the groups. Pearson correlation analyses were performed to measure the strength of association between two variables. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

Evaluation was made of 45 MS patients (11 males, 34 females) with a mean age of 37.36 ± 9.0 years (ranges 21 to 56) and 36 healthy subjects (3 males, 33 females) with a mean age of 35.19 ± 9.3 years (ranges 18 to 55). No significant difference was observed between the groups in terms of age and gender ($p > 0.05$ for both). The clinical and demographical features of the MS patients are summarized in Table 1.

The comparison of the diaphragm thickness and TR between the groups is shown in Table 2. The diaphragm thicknesses were similar at end-expirium and end-inspirium. The change level with inspirium and the TR were significantly higher in the control group compared to values of the MS patients.

The correlation analyses are shown in Table 3. A weak and negative correlation was determined between the EDSS and TR values. In addition a weak and negative correlation was found between the disease duration, number of attacks and TR values. No significant correlation was observed between the FSS values and diaphragm thickness.

Table 1
Clinical and demographical features of the multiple sclerosis patients.

Variables	MS Group (n = 45)
Age (years)	37.36 ± 9.0
Gender	
- Male	11 (24.4)
- Female	34 (75.6)
Height (cm)	165.02 ± 7.2
Multiple sclerosis type	
- Relapse-remitting	42 (93.3)
- Secondary progressive	2 (4.4)
- Primary progressive	1 (2.2)
Number of attacks	
- 0	7 (15.6)
- 1	20 (44.4)
- 2	9 (20.0)
- 3	3 (6.7)
- 4	4 (8.9)
- 5	1 (2.2)
- > 5	1 (2.2)
Involvement	
- Cerebral	45 (100)
- Spinal	0 (0)
Disease duration (months)	72.46 ± 10.8
Expanded Disability Status Scale	1 (0–2)
Fatigue Severity Scale	4.88 (2.99–5.66)

*The data are shown as mean ± standard deviation, median (25–75%) or n, (%).

Table 2
Diaphragm thickness values of the groups.

Variables	MS Group (n = 45)	Control Group (n = 36)	P value
End-expirium (mm)	1.86 ± 0.3	1.83 ± 0.3	0.718
End-inspirium (mm)	3.14 ± 0.6	3.46 ± 0.6	0.059
Change level (mm)	0.90 ± 0.6	1.31 ± 0.7	0.014
Thickening ratio (%)	49.77 ± 37.7	72.30 ± 40.1	0.011

*The data are given as mean ± standard deviation.

4. Discussion

In this study, we sought to investigate the diaphragm thickness and TR in MS patients using US. Three main findings emerged from the study. First, the diaphragm thickness of MS patients was similar to that of healthy subjects. Second, the change level and TR were lower in MS patients compared to the healthy control group, and third, the change level and TR were associated with EDSS values.

Ultrasonography is a valid and reliable imaging method in the evaluation of diaphragm thickness. In addition, US provides an insight to the diaphragm morphology (Khurana et al., 2018; Goligher et al., 2015; Özçakar et al., 2015; Fayssoil et al., 2018). US has many advantages over other imaging methods, primarily the ease of application, low cost, widely availability, the provision of dynamic imaging and bedside evaluation, high spatial resolution, lack of ionizing radiation and it is non-invasive (Özçakar et al., 2015; Fayssoil et al., 2018). In this context, the diaphragm of MS patients was evaluated with US in this study, which, to the best of our knowledge, this is the first study on this topic. This fact is the main strength of the study.

Diaphragm thickness has been measured in different patient populations (Fayssoil et al., 2018; Gottesman and McCool,1997; Noda et al., 2016; De Bruin et al., 1997; Jung and Kim,2017). The thickness has been shown to be less in patients with neurological disorders such as diaphragm paralysis, amyotrophic lateral sclerosis, neuropathies, and stroke (Gottesman and McCool,1997; Noda et al., 2016). In contrast, diaphragm thickness has been found to be higher in myopathies due to possible pseudohypertrophy (De Bruin et al., 1997). Diaphragm thickness is quite important because there is a relationship between the pulmonary functions and the thickness as well as the excursion (De Bruin et al., 1997; Jung and Kim, 2017). In the current study, the diaphragm thickness was measured in MS patients and was not found to be any different from that of the control group. This might be attributed to two facts. First, overall the clinical status of the MS patients was not very advanced according to the EDSS scores. If the patients in the study had worse levels of EDSS, the thickness values might have been different. Likewise, previous reports have highlighted diaphragmatic weakness in MS usually in patients with advanced disease, tetraplegia, and bulbar dysfunction (Sumelahti et al., 2010). Second, all the patients in the current study sample had cortical lesions. If the patients had spinal lesions particularly cervical lesions, the diaphragm and respiratory muscles might be more affected.

As the diaphragm contracts during inspiration, its thickness increases. The TR is an indicator of diaphragm function and the excursion or TR are associated with respiratory functions (De Bruin et al., 1997; Jung and Kim, 2017). Demyelinating plaques involving different areas of the central nervous system particularly the brainstem and spinal cord can cause respiratory muscle weakness and diaphragm dysfunction in MS (Tzelepis and McCool, 2015). The results of the current study showed that the TR and change levels in diaphragm thickness were significantly lower in MS patients, and the TR was significantly correlated with EDSS values. As the EDSS increased, so the change level and TR decreased. This fact may indicate diaphragm weakness or impaired respiratory functions in relevant patients. It has been reported that respiratory muscle weakness is more prominent in bedridden or wheelchair bound patients, which correspond to the higher levels of EDSS (Tzelepis and McCool, 2015) and this fact is compatible with the current study results.

There are some important drawbacks to this study. The lack of pulmonary function tests is the main limitation. Furthermore, the sample size could have been larger, but all MS patients who met the inclusion criteria were included. Since diaphragmatic involvement is a rather late occurrence in MS, the study would have been more informative if patients with moderate to severe disability were included. Nonetheless, these results can be considered noteworthy and provide both functional and morphological insights to the diaphragm in MS patients.

5. Conclusion

In conclusion, although the diaphragm thickness of MS patients seems to be similar to that of healthy subjects, the change level and TR of MS patients seem to be lower. In addition, change level and TR are associated with EDSS. Decreased excursion of diaphragm during in-

Table 3
Correlation analyses.

Variables		End-expirium	End-inspirium	Change level	Thickening ratio	EDSS	FSS	Disease duration	Number of attacks
End-expirium	r	1.000	0.683**	0.193	−0.335**	0.043	0.124	0.050	0.036
	p		< 0.001	0.136	0.008	0.740	0.340	0.701	0.782
End-inspirium	r	0.683**	1.000	0.801**	0.376**	−0.280*	0.081	−0.204	−0.165
	p	< 0.001		< 0.001	0.003	0.029	0.533	0.115	0.203
Change level	r	0.193	0.801**	1.000	0.925**	−0.290	0.161	−0.258	−0.272
	p	0.136	< 0.001		< 0.001	0.009**	0.150	0.020*	0.014*
Thickening ratio	r	−0.335**	0.376**	0.925	1.000	−0.293**	0.128	−0.273	−0.287
	p	0.008	0.003	< 0.001		0.008	0.256	0.014*	0.009**
EDSS	r	0.043	−0.280*	−0.290**	−0.293**	1.000	0.201	0.769	0.700
	p	0.740	0.029	0.009	0.008		0.072	< 0.001**	< 0.001**
FSS	r	0.124	0.081	0.161	0.128	0.201	1.000	0.230	0.177
	p	0.340	0.533	0.150	0.256	0.072		0.039*	0.114
Disease duration	r	0.050	−0.204	−0.258	−0.273	0.769	0.230	1.000	0.878
	p	0.701	0.115	0.020*	0.014*	< 0.001**	0.039*		< 0.001*
Number of attacks	r	0.036	−0.165	−0.272	−0.287	0.700	0.177	0.878	1.000
	p	0.782	0.203	0.014*	0.009**	< 0.001**	0.114	< 0.001*	

EDSS: Expanded disability severity scale **FSS**: Fatigue severity scale.
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

spiration may indicate decreased inspiratory function in MS patients and US can play a role in the evaluation of relevant patients. Further studies exploring the association with pulmonary function tests, diaphragmatic pressure and US findings in MS patients are awaited.

Declaration of Competing Interest

H.Ş. reports no conflict of interest.
A.D. reports no conflict of interest.
T.E. reports no conflict of interest.

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