Received: 31 May 2022 | **Accepted:** 12 Aug 2022
DOI: 10.54005/geneltip.1124013

ORIGINAL ARTICLE

The Relationship Between Structural Measurements of the Corpus Callosum and Disability in Patients with Multiple Sclerosis

Multiple Skleroz Hastalarında Korpus Kallosumun Yapısal Ölçümlerinin Disabilite ile İlişkisi

[1]Ayşegül Demir, [2]Fettah Eren, [2]Süeda Ecem Yılmaz, [3]Necat İslamoğlu

[1]Sağlık Bilimleri Üniversitesi, Konya Şehir Hastanesi, Nöroloji Kliniği, Konya.
[2]Selçuk Üniversitesi Tıp Fakültesi, Nöroloji Kliniği, Konya.
[3]Sağlık Bilimleri Üniversitesi, Konya Şehir Hastanesi, Radyoloji Kliniği, Konya.

Correspondence

Ayşegül Demir, Sağlık Bilimleri Üniversitesi, Konya Şehir Hastanesi, Nöroloji Kliniği, Konya.

E-Mail: D_Raysegul@hotmail.com

How to cite ?

Demir A, Eren F, Yılmaz SE, İslamoğlu N. The Relationship Between Structural Measurements of the Corpus callosum and disability in patients with multiple sclerosis. Genel Tıp Derg.2022; 32(4):433-438

ABSTRACT

Purpose: The corpus callosum (CC) is the largest commissural pathway connecting both cerebral cortices.
Materials and Methods: Forty MS patients and 40 healthy controls were included in this research, which was planned as a case-control study. Disability was evaluated with the expanded disability rating scale. The number of attacks, disease duration, and MS disease subtype were determined. CC genu, truncus, splenium, and anterior-posterior diameters were measured in brain magnetic resonance imaging TSE/T1 sagittal sequence, and the corpus callosum index (CCI) was calculated using these measurements. The relationship of all these parameters with each other was examined.
Results: There were 40 patients (29 females, 11 males) with a mean age of 36.47±11.14 years in the study. In the CC morphometric measurements of the patients, the genu (mean±SD) was 11.46±1.60, truncus (median, min-max) 5.29 (4.6-6.52), splenium 11.09±1.82, anterior-posterior diameter 65.20 (63.64-67.22) and CCI was determined as 0.43±0.05 millimeters. The anterior-posterior diameter was smaller in MS patients (p=0.022). A negative correlation was determined between CCI and disease duration, the number of attacks, and EDSS scores in MS patients (p<0.05; r=-0.319; r=-0.316; r=-0.349; respectively). In the severe disability group, CC splenium, AP diameter, and CCI were lower (p=0.007; p=0.020; p=0.046; respectively).
Conclusion: In MS disease, the CC structure is affected, as in many central nervous system regions. The study results revealed that changes in the corpus callosum could be examined as a parameter in evaluating the disease process in MS patients.

Keywords: Multiple sclerosis; corpus callosum; morphometry; disability.

ÖZ

Amaç: Korpus kallosum (KK) her iki serebral korteksi birbirine bağlayan en büyük komissural yoldur. Multiple sklerozda (MS) santral sinir sisteminde birçok bölgede değişik derecelerde değişiklikler görülmektedir. Bu nedenle MS hastalarında KK yapısı ve bunun disabilite ile ilişkisi değerlendirilmiştir.
Gereç ve Yöntem: Vaka-kontrol çalışması olarak planlanan bu araştırmaya 40 MS hastası ve 40 sağlıklı kontrol dahil edildi. Disabilite genişletilmiş disabilite değerlendirme ölçeği ile değerlendirildi. Atak sayısı, hastalık süresi ve MS hastalık subtipi belirlendi. Beyin manyetik rezonans görüntüleme TSE/T1 sagittal sekansında KK genu, trunkus, splenium ve anterior-posterior çapı ölçüldü. Korpus kallosum indeksi (KKI) hesaplandı. Tüm bu parametrelerin birbiri ile ilişkisi incelendi.
Bulgular: Çalışmada yaş ortalamaları 36,47±11,14 yıl olan 40 (29 kadın, 11 erkek) hasta vardı. Hastaların KK morfometrik ölçümlerinde genu (ortalama±SD) 11,46±1,60; trunkus (ortanca, min-maks) 5,29 (4,6-6,52), splenium 11,09±1,82, anterior-posterior çapı 65,20 (63,64-67,22) ve KKI 0,43±0,05 milimetre (mm) olarak belirlendi. MS hastalarında anterior-posterior çapı daha küçüktü (p=0,022). MS hastalarında KKI ile hastalık süresi, atak sayısı ve EDSS skoru arasında negatif korelasyon saptandı (p<0,05; r=-0,319; r=-0,316; r=-0,349; sırasıyla). Ağır disabilitede KK splenium, AP çapı ve KKI daha düşüktü (p=0,007; p=0,020; p=0,046; sırasıyla).
Sonuç: MS hastalığında santral sinir sisteminde birçok bölgede olduğu gibi KK yapısı da etkilenmektedir. Çalışmamız sonucunda MS hastalarında hastalık sürecinin değerlendirilmesinde korpus kallosumda ki değişikliklerinde bir parametre olarak incelenebileceği gösterilmiştir.

Anahtar kelimeler: Multiple skleroz; korpus kallosum; morfometri; disabilite

Introduction

The corpus callosum (CC) is the largest commissural pathway that connects the cerebral hemispheres. Recent studies have indicated structural and functional changes in the CC in many neurological diseases (1). These changes may be related to the neurologic disease subtype as well as to the individual structural characteristics of the patients (2). Furthermore, these structural changes might be caused by environmental factors and the neuropathological process of the disease (1-3). Imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) provide the opportunity to examine the structural features of the brain in diseases such as epilepsy, dementia, and multiple sclerosis (MS) (1,2). In particular, MRI is a more sensitive imaging method for detecting brain structural changes and evaluating changes in the process. For this, planimetric measurement methods are used, and thus the anatomical structures and dimensions of tissues and organs can be determined more easily (4,5).

MRI is the imaging modality that plays a key role in the diagnosis, evaluation of treatment response, and follow-up of patients with MS. With conventional

MRI parameters, the volume of brain lesions can be evaluated as well as the volume of white and gray matter (6). However, evaluating them often requires three-dimensional and complex processing techniques that are time-consuming and have limited clinical applicability. Therefore, two-dimensional measurements of CC have been proposed as alternative markers of brain atrophy (7), and unlike volumetric measurements, these can be determined in seconds with conventional methods without the need for special software MRI techniques. Thus, this method has greater potential for clinical applicability. However, growing evidence demonstrates the value of CC structural features as a biomarker in MS. It was revealed that this might indicate cortical-spinal atrophy and lesion burden. Correlation has also been shown between the structural measurements of the CC and the volumetric properties of the brain (8,9). It has also been determined that CC injury is associated with cognitive impairment in MS patients and may be a clinically significant marker of cognitive impairment (10-12). Nonetheless, few studies have evaluated the structural features of CC, clinical status, and disability of MS patients. Hence, the present study aimed to examine the relationship of CC structural measurements with disease duration, disease subtype, disability, and attack frequency in MS patients.

Material and Method

Field of study and ethical approval

MS patients who were followed up regularly in the neurology outpatient clinic for the last year were included in this study. Study principles were approved by Karatay University Local Ethics Committee (Mt. No: 10 Decree no: 2021/013).

Patients included in the study

G*Power program was used to reach medium effect size with sample size calculation. The two-way analysis of variance determined that 40 patients and 40 control groups were needed, and the patient and control groups were formed accordingly.

Pregnant patients, patients those with mass brain lesions, cancer, and autoimmune diseases other than MS, under the age of 18, and over the age of 65 were excluded from the study. Patients of similar age and gender, who had MRI examinations in the last six months for different indications, were determined as the control group.

The purpose and methods of the study were explained to all participants. Patients with informed consent were included in the study. The frequency of the number of attacks on the patients was questioned, and their hospitalization and treatment were confirmed through the hospital system. According to the frequency of attacks, the patients were divided into two groups as "over 5" and "5 and below." According to the MS disease subtype, the patients were evaluated in three groups as "relapsing-remitting MS," "secondary progressive MS," and "primary progressive MS."

MS disease duration of the patients was questioned. Accordingly, the patients were divided into two groups as "below 10 years" and "10 years and above."

Evaluation forms

An extended disability status scale (EDSS) was used to evaluate disability status. This scale, frequently used in the numerical determination of disability, has scores ranging from 0 to 10. Normality is expressed as "0," while "10" represents disease-related deaths. Increasing score points from 0 to 10 indicates an increase in disability (13,14). As a result, according to the scores obtained, the patients were divided into three groups as 0-3.5=mild, 3.5-5.5=moderate, 5.5 and above severe disability.

Structural measurement of the corpus callosum

Measurements were made using only MRI of the patients obtained within the last six months. CC measurements were performed on the TSE/T1 sagittal sequence included in the routine brain MRI protocol. Also, the highest length of the CC (anterior-posterior diameter) was measured. The height of the CC was measured on a perpendicular line drawn on its long axis by dividing the CC into three parts. Genu, splenium, and the widest anterior-posterior diameters were measured by manual drawing on the line passing through the intercommissural line. Finally, genu, truncus, splenium, and anterior-posterior diameters were determined. The corpus callosum index (CCI) was calculated using the formula [(genu + truncus + splenium) / (anterior-posterior diameter)] (1,4) (Figure 1). All measurements were made by the same blind investigator, unaware of the patient and control groups.

Statistical analysis

The data obtained as a result of the research were analyzed in a computer environment with the SPSS (Statistical Package for Social Sciences) 18.0 package program. In descriptive analyses, frequency data were presented as numbers (n) and percentage (%), and numerical data as mean±standard deviation and median (1st-3rd quartile) values. The corpus callosum has no normal values. The difference between groups was analyzed comparatively. Compliance of numerical data with normal distribution was examined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The distribution of numerical data in two normally distributed independent groups was evaluated with the Independent Samples T-test and the distribution of numerical data in more than two groups with the One-Way ANOVA test. The distribution of numerical data in two independent groups that were not normally distributed was determined with the Mann Whitney U test and the distribution of numerical data in more than two groups with the Kruskal Wallis test.

The relationship between two numerical variables was analyzed by Pearson Correlation analysis. The relationship between categorical and numerical data was evaluated by Spearman Correlation analysis. In the correlation relationships, r=0.05-0.30 was considered as weak or insignificant correlation, r=0.30-0.40 as weak-moderate correlation, r=0.40-0.60 as moderate correlation, r=0.60 -0.70 as strong correlation, r=0.70-0.75 as very strong correlation, r=0.75-1.00 as excellent correlation. The corpus callosum measurement levels were evaluated by a two-way ANOVA test according to smoking status in age groups. The effects of variables on corpus callosum measurements were analyzed by Linear Regression analysis. The results were evaluated at the 95% confidence interval, and the statistical significance level was $p<0.05$.

Results

A total of 40 patients, 29 (72.5%) females and 11 (27.5%) males, with a mean age of 36.47±11.14 years, were included in the study. Data were compared with 40 healthy control patients of similar age and gender ($p>0.05$). The mean disease duration was 8.87±6.43 years. The number of attacks was 3.67±2.92, and the EDSS score was 2.41±2.01. The sociodemographic and clinical characteristics of the patients are presented in Table 1.

CC measurements in MS patients were determined as genu 11.46±1.60, truncus 5.66±1.44, splenium 11.09±1.82, anterior-posterior diameter 65.11±2.44, and CCI 0.43±0.05 millimeters (mm). When all these measurement parameters were compared with the control group, the anterior-posterior diameters of the CC were statistically significantly smaller (p=0.022). Other parameters were similar to the control group (p=0.568; p=0.324; p=0.237; P=0.583; respectively). The CC measurement parameters of the patient and control groups are summarized in Table 2.

Eight (20.0%) of the MS patients smoked, and 3 (7.5%) used alcohol. There was no statistically significant difference between cigarette and alcohol use between MS patients and the control group (p=0.430; p=0.241; respectively). There was no statistical difference between corpus callosum measurements according to smoking status in MS patients ($p>0.05$). 21 (52.5%) of the patients were 35 years of age or younger, and 19 (47.5%) were over 35 years old. When the measurements were compared in age groups, no statistically significant difference was determined between CC genu, truncus, splenium, AP diameters, and BMI (p=0.205; p=0.592; p=0.555; p=0.592; p=0.405; respectively). 25 (62.5%) of the patients had a disease duration of 10 years or less, and 15 (37.5%) had more than 10 years. Similarly, there was no statistically significant difference between CC genu, truncus, splenium, AP diameters and CCI according to disease duration (p=0.119; p=0.699; p=0.083; p=0.699; p=0.082; respectively).

When the groups were formed according to the frequency of attacks of the patients, the frequency of attacks was below 5 in 29 (72.50%) patients and 5 or more in 11 (27.5%) patients. Corpus callosum measurements were compared according to attack frequency, and no statistically significant difference was observed between genu, truncus, splenium, AP diameters, and CCI (p=0.096; p=0.858; p=0.064; p=0.654; p=0.124; respectively).

Of the patients included in the study, 31 (77.50%) had relapsing-remitting MS, 6 (15%) had secondary progressive MS, and 3 (7.50%) had primary progressive MS subtype. When the corpus callosum measurements were compared regarding the disease subtype, a statistically significant difference was determined between the CC splenium and AP diameters (p=0.007; p=0.012; respectively). This difference was due to the lower CC measurements in primary and secondary progressive MS patients compared to relapsing-remitting MS. No difference was detected between other parameters (p=0.138; p=0.191; p=0.094; respectively).

When the patients were divided into groups according to their EDSS scores, mild disability was found in 30 (75.0%) patients (EDSS=0-3.5), moderate disability (EDSS=3.5-5.5) in 6 (15.0%), and severe disability (EDSS≥5.5) in 4 (10%) patients. The corpus callosum measurements were compared according to the EDSS groups, and a statistically significant difference was observed between the CC splenium and AP diameters and CCI (p=0.007, p=0.020, p=0.046, respectively). This difference was due to the decrease in splenium, AP diameter, and CCI in mildly severe disabilities and also from the decrease in splenium diameter in moderately severe disabilities. No difference was found between genu and truncus diameters (p=0.104; p=0.251).

When the correlations between the patients' age, disease duration, number of attacks, EDSS scores, and CC measurements were evaluated, the following results were obtained. There was a weak-moderate correlation between increase in age and genu (p=0.026; r=-0.353), moderate correlation between disease duration and splenium (p=0.002, r=-0.467), weak-to-moderate correlation between disease duration and CCI (p=0.002, r=-0.467), weak-to-moderate correlation between attack number and splenium and CCI (p=0.024; p=0.047; r=-0.355; r=-0.316), moderate correlation between splenium and AP diameter with EDSS (p=0.001; p=0.010; r=-0.500; r=-0.405) and between EDSS and genu and CCI (p=0,023; p=0,027; r=-0,360; r=-0,349). No statistically significant difference was determined between other parameters. The correlation parameters of the patients' age, disease duration, number of attacks, EDSS scores, and CC measurements are presented in Table 3.

CC measurements in PPMS and SPMS patients were determined as genu 10.47±1.26, truncus 4.80 (4.15-5.35), splenium 9.48±2.00, anterior-posterior diameter 61.20 (60.82-64.35), and CCI 0.40±0.032 millimeters

(mm). When all these measurement parameters were compared with the RRMS group, the anterior-posterior diameters of the splenium, AP diameter and CCI were statistically significantly smaller (p=0.002; p=0.002; p=0.031; respectively). Other parameters were similar in the groups (p=0.055; p=0.106). The CC measurement parameters of the patient and control groups are summarized in Table 4.

To predict CC measurements, linear regression analysis was performed in the model established by patients' age, disease duration, number of attacks, and EDSS score. According to the results of this analysis, an increase of 1 unit in the EDSS score decreased the genu diameter by 0.360, the splenium diameter by 0.500, the AP diameter by 0.405, and the CC index by 0.433 times. There was no correlation between other parameters and CC measurements (p>0.05).

Table 1. Distribution of patients' sociodemographic and clinical characteristics

	n	%
Gender		
Female	29	72.50
Male	11	27.50
Age		
≤35 age	21	52.50
>35 age	19	47.50
Smoking		
Yes	8	20.00
No	32	80.00
Alcohol Use		
Yes	3	7.50
No	37	92.50
Disease duration		
≤10 year	25	62.50
>10 year	15	37.50
Number of attacks		
<5	29	72.50
≥5	11	27.50
MS type		
RRMS	31	77.50
SPMS	6	15.00
PPMS	3	7.50
EDSS		
0-3.5	30	75.00
3.5-5.5	6	15.00
≥5.5	4	10.00

Table 2. Corpus callosum measurements in patient and control groups

	Patient (n=40) Mean ± SD / Median (1-3. quartile)	Control (n=40) Mean ± SD / Median (1-3. quartile)	t/z	p
Corpus callosum Genu	11.46±1.60	11.27±1.33	0.574	0.568
Corpus callosum Trunkus	5.29 (4.60-6.52)	5.83 (5.34-6.25)	-0.987	0.324
Corpus callosum Splenium	11.09±1.82	11.54±1.56	-1.191	0.237
Corpus callosum AP	65.20 (63.64-67.22)	66.80 (64.80-69.24)	-2.290	0.022*
Corpus callosum index	0.43±0.05	0.42±0.041	-0.548	0.583

* Statistically significant value, AP=Anterior-posterior

Table 3. Correlation scores of patients according to age, duration of disease, number of attacks and disability scores

Age		r	p
	Corpus Callosum Genu	-0.353	0.026*
	Corpus Callosum Trunkus	-0.047	0.774
	Corpus Callosum Splenium	-0.141	0.387
	Corpus Callosum AP	-0.204	0.208
	Corpus Callosum İndex	-0.159	0.328
Disease Duration		r	p
	Corpus Callosum Genu	-0.224	0.165
	Corpus Callosum Trunkus	-0.200	0.217
	Corpus Callosum Splenium	-0.467	0.002*
	Corpus Callosum AP	-0.171	0.292
	Corpus Callosum İndex	-0.319	0.045*
Number of Attacks		r	p
	Corpus Callosum Genu	-0.220	0.173
	Corpus Callosum Trunkus	-0.227	0.159
	Corpus Callosum Splenium	-0.355	0.024*
	Corpus Callosum AP	-0.205	0.204
	Corpus Callosum İndex	-0.316	0.047*
EDSS Score		r	p
	Corpus Callosum Genu	-0.360	0.023*
	Corpus Callosum Trunkus	-0.245	0.127
	Corpus Callosum Splenium	-0.500	0.001*
	Corpus Callosum AP	-0.405	0.010*
	Corpus Callosum İndex	-0.349	0.027*

* Statistically significant value, AP=Anterior-posterior

Table 4. Corpus callosum measurements according to multiple sclerosis subgroups

	RRMS (n=31) Mean ± SD / Median (1-3. quartile)	PPMS and SPMS (n=9) Mean ± SD / Median (1-3. quartile)	p
Corpus callosum Genu	11.62±1.61	10.47±1.26	0.055
Corpus callosum Trunkus	5.50 (4.60-6.70)	4.80 (4.15-5.35)	0.106
Corpus callosum Splenium	11.56±1.50	9.48±2.00	0.002*
Corpus callosum AP	65.74 (63.80-67.30)	61.20 (60.82-64.35)	0.002*
Corpus callosum index	0.44±0.051	0.40±0.032	0.031*

* Statistically significant value, RRMS=Relapsing remitting multiple sclerosis, PPMS=Primary progressive multiple sclerosis, SMPS=Secondary progressive multiple sclerosis, AP=Anterior-posterior

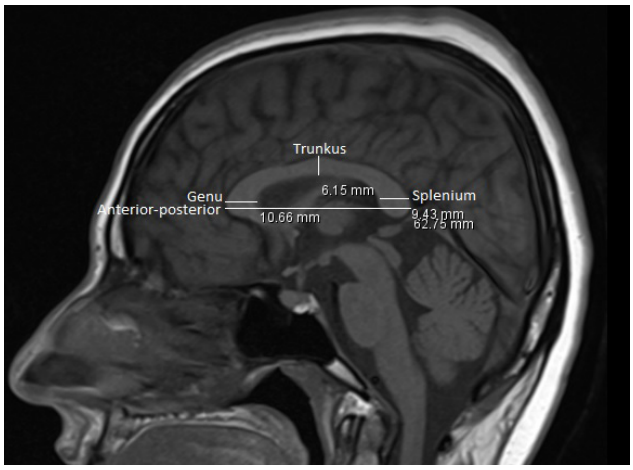

Figure 1. Corpus callosum structural measurement technique

Discussion

In MS, CC, which connects the cerebral hemispheres, can be affected at different levels secondary to focal demyelinating lesions and axonal degeneration. This situation represents a process related to Wallerian degeneration, especially neuropathologically (10). Therefore, evaluation and follow-up of the structural changes of the CC by MRI can provide important information about the pathogenesis and progression of the disease. Several imaging-based assessment methods have been introduced for the structural examination of the CC. In particular, two-dimensional QC measurements with manual drawing techniques or evaluations with some volumetric software methods are used (7,10). The most common and easiest technique is the two-dimensional manual measurement, which we also used in our study. Many studies have revealed that this method is reliable among evaluators and can be applied easily (7,10,15-17). A previous study concluded a strong correlation between CC structural measurements and CC volumetric measurements and that they could be used as alternatives to each other (18). At the same time, structural measurements of the corpus callosum are thought to be a predictable marker of brain atrophy. A recent study has determined a strong correlation between CC measurements and brain volume as a marker of brain atrophy in MS (18). However, their volumetric measurements are much more difficult than their two-dimensional counterparts. Therefore, we preferred to focus on manual two-dimensional morphometric measurements in our study.

As the disease duration and disability increase in MS patients, cerebral cortical volume is known to decrease and atrophy deepens. It has been indicated that this situation is also associated with T2 lesion volume (19). In a study by Yaldızlı et al., the relationship between corpus callosum index and EDSS and cortical volume was revealed, and the CCI value decreased by 9% in 7 years (16). CCI reduction has been reported to be more than doubled in SPMS patients compared to RRMS patients. Different studies have also confirmed the decrease in CCI in SPMS patients (7). Some studies have reported that whole brain volume is more markedly reduced in progressive patients when comparing SPMS and RRMS patients (20–23). The study by Tedeschi et al., performed on 597 MS patients using a fully automated multi-parametric segmentation method, determined that SPMS patients had more atrophy of both white and gray matter (24). Another study by Vrenken et al. reported that normalized brain volume was lower in 18 patients with SPMS (1,406 ml) than in 36 RRMS patients (1,473 ml) (23). Ge et al. found higher rates of brain parenchymal loss in 9 SPMS patients compared to 27 RRMS patients (-1.5% per year for RRMS and -2.0% per year for SPMS) (21). This result showed that parenchymal atrophy was more common, especially in SPMS patients, and the periventricular region was sensitive to brain atrophy. In our study, the anterior-posterior diameter of the CC was smaller in MS patients. CC splenium and AP diameters were lower, especially in primary and secondary progressive MS patients. In severe disability, corpus CC splenium, AP diameters, and CCI were lower. Moreover, a statistically negative correlation was determined between disease duration, the number of attacks, EDSS score, and CCI. Our current study results have revealed findings in favor of the progression of the disease in MS patients and the atrophic process at different levels in the CC structure, especially in CCI.

In conclusion, lesions at different levels are detected in the cortex and spinal cord structures in MS disease during the disease diagnosis and the follow-up period. Besides, it is expected that there will be a decrease in cortical volume in the process. Hence, CC measurements have an important place in better understanding the process of the disease and are closely related to the increase in disability. However, the number of patients in the study was relatively small, and it was thought that these emission data should be validated with a larger sample size.

The limitations of the study were that it was a single center, and a relatively small number of patients could be reached. The number of patients and control groups in the study is low. The number of subgroup patients is

low. The relationship between the treatments used in the treatment of MS and CC measurements has not been evaluated. Brain or corpus callosum volume was not measured in this study. Minimal differences can be observed in CC measurements depending on the cross-section angle. So that this situation would not affect the results, the measurements were made by a researcher who was unaware of the patient and control groups.

Financial support: None

Conflict of interest: None of the authors of the paper has any conflict of interest to declare.

Author Contributions Study concept/design: AD, FE; Data acquisition: AD, FE, SEY; Data analysis and interpretation: AD, FE, Nİ; Article draft: AD, FE, Nİ, SEY; Critical review of the content: AD, FE, Nİ, SEY; Final approval and responsibility: AD, FE, Nİ, SEY; Technical and material support: -; Supervision: AD, FE, Nİ, SEY; Funding (if applicable): none.

Ethical Approval: Ethical approval was obtained for this study from the Ethics Committee of KTO Karatay University Faculty of Medicine, Non-Pharmaceutical and Medical Device Researches, with the decree dated 27.12.2021 and numbered 2021/013.

References

1.Firat A, Tascioglu AB, Demiryurek MD et al. Evaluation of corpus callosum morphometry in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Surg Radiol Anat 2014;36:47-54.

2.Giedd JN, Rumsey JM, Castellanos FX et al. A quantitative MRI study of the corpus callosum in children and adolescents. Brain Res Dev Brain Res 1996;91:274-80.

3.Kurkcuoglu A, Zagyapan R, Pelin C. Stereological evaluation of temporal lobe/telencephalon volume in temporal lobe epilepsy using the Cavalieri principle. Turk Neurosurg 2010;20:358-63.

4.Sahin B, Ergur H. Assessment of the optimum section thickness for the estimation of liver volume using magnetic resonance images. Eur J Radiol 2006;57:96-101.

5.Barboriak DP, Padua AO, York GE, Macfall JR. Creation of DICOM--aware applications using ImageJ. J Digit Imaging 2005;18:91-9.

6.Matthews PM, Roncaroli F, Waldman A et al. A practical review of the neuropathology and neuroimaging of multiple sclerosis. Pract Neurol 2016;16:279-87.

7.Figueira FF, Santos VS, Figueira GM, Silva AC. Corpus callosum index: a practical method for long-term follow-up in multiple sclerosis. Arq Neuropsiquiatr 2007;65:931-5.

8.Sugijono SE, Mulyadi R, Firdausia S, Prihartono J, Estiasari R. Corpus callosum index correlates with brain volumetry and disability in multiple sclerosis patients. Neurosciences (Riyadh) 2020;25:193-9.

9.Gonçalves LI, Dos Passos GR, Conzatti LP et al. Correlation between the corpus callosum index and brain atrophy, lesion load, and cognitive dysfunction in multiple sclerosis. Mult Scler Relat Disord 2018;20:154-8.

10.Granberg T, Martola J, Bergendal G et al. Corpus callosum atrophy is strongly associated with cognitive impairment in multiple sclerosis: Results of a 17-year longitudinal study. Mult Scler 2015;21:1151-8.

11.Papathanasiou A, Messinis L, Zampakis P, Papathanasopoulos P. Corpus callosum atrophy as a marker of clinically meaningful cognitive decline in secondary progressive multiple sclerosis. J Clin Neurosci 2017;43:170-5.

12.Llufriu S, Blanco Y, Martinez-Heras E et al. Influence of corpus callosum damage on cognition and physical disability in multiple sclerosis: a multimodal study. PLoS One 2012;7:e37167.

13.Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-52.

14.Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions. Mult Scler Relat Disord. 2017;16:31-39.

15.Yaldizli Ö, Penner IK, Frontzek K et al. The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients. Mult Scler. 2014;20:356-64.

16.Yaldizli O, Atefy R, Gass A et al. Corpus callosum index and long-term disability in multiple sclerosis patients. J Neurol. 2010;257:1256-64.

17.Van Schependom J, Jain S, Cambron M et al. Reliability of measuring regional callosal atrophy in neurodegenerative diseases. Neuroimage Clin. 2016;12:825-31.

18.Gonçalves LI, Dos Passos GR, Conzatti LP et al. Correlation between the corpus callosum index and brain atrophy, lesion load, and cognitive dysfunction in multiple sclerosis. Mult Scler Relat Disord. 2018;20:154-58.

19.Hardmeier M, Wagenpfeil S, Freitag P et al. Atrophy is detectable within a 3-month period in untreated patients with active relapsing remitting multiple sclerosis. Arch Neurol. 2003;60:1736-9.

20.Bermel RA, Sharma J, Tjoa CW, Puli SR, Bakshi R. A semiautomated measure of whole-brain atrophy in multiple sclerosis. J Neurol Sci. 2003;208:57-65.

21.Ge Y, Grossman RI, Udupa JK et al. Brain atrophy in relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis: longitudinal quantitative analysis. Radiology. 2000;214:665-70.

22.Sharma J, Sanfilipo MP, Benedict RH et al. Whole-brain atrophy in multiple sclerosis measured by automated versus semiautomated MR imaging segmentation. Am J Neuroradiol. 2004;25:985-96.

23.Vrenken H, Geurts JJ, Knol DL et al. Whole-brain T1 mapping in multiple sclerosis: global changes of normal-appearing gray and white matter. Radiology. 2006;240:811-20.

24.Tedeschi G, Lavorgna L, Russo P et al. Brain atrophy and lesion load in a large population of patients with multiple sclerosis. Neurology. 2005;65:280-5.