doi: 10.53446/actamednicomedia. 1514240

Acta Medica Nicomedia

Cilt: 7 Sayı: 3 Ekim 2024 / Vol: 7 Issue: 3 October 2024
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article / Araştırma Makalesi

MORPHOLOGICAL EVALUTION OF CORPUS CALLOSUM ATROPHY OVER TIME IN RELAPSING REMITTING MULTIPLE SCLEROSIS

RELAPSING REMITTING MULTIPLE SKLEROZDA KORPUS KALLOZUM ATROFİSİNİN ZAMAN İÇİNDE MORFOLOJİK DEĞERLENDİRMESİ

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ABSTRACT

Objective: Multiple sclerosis (MS) is a chronic central nervous system (CNS) disease that generally affects young adults and is marked by inflammation, demyelination, and neurodegeneration. Magnetic resonance imaging (MRI) is widely used diagnosis tool for relapsing remitting MS (RRMS). Corpus callosum (CC), the largest commissural tract in brain which is associated with both cognitive and physical impairment by atrophy in MS. Our study aimed to evaluate CC in RRMS patients using MR images and compare it to measurements from healthy controls within the same age

Methods: We manually measured changes in CC thickness in T1 brain MR images of RRMS patients in 2017, 2019, and 2022.

Results: Our results showed that control group had greater thickness, length, and index values in all CC sections compared to patient group. Additionally, a significant difference was observed in thickness of genu and splenium sections and CC index between patient and control groups. However, no significant difference was detected in truncus part of CC or overall CC length. CC measurements in patient group decreased over time, with 1st MRI showing greater values than 2nd and 3rd MRI scans. Furthermore, there was a statistically significant difference in thickness of truncus part of CC and volume values of subcortical areas between 2nd-3rd and 1st-3rd MRI measurements.

Conclusion: As a result of these findings, our study provides important information about changes in CC measurements for MS patients.

Keywords: Atrophy, Corpus Callosum, Magnetic Resonance Imaging, Relapsing Remitting Multiple Sclerosis

ÖZ

Amaç: Multiple skleroz (MS), genellikle genç yetişkinleri etkileyen ve inflamasyon, demiyelinizasyon ve nörodejenerasyon ile kendini gösteren kronik bir merkezi sinir sistemi (MSS) hastalığıdır. Manyetik rezonans görüntüleme (MRG), relapsing remitting MS (RRMS) için yaygın olarak kullanılan bir tanı aracıdır. Beyindeki en büyük komissural kanal olan korpus kallozum (KK) MS'te atrofiye uğrayarak hem bilişsel hem de fiziksel bozulma ile ilişkilendirilmektedir. Çalışmamızın amacı, MR görüntüleri kullanarak RRMS hastalarında KK'yi değerlendirmek ve aynı yaştaki sağlıklı kontrollerden elde edilen ölçümlerle karşılaştırmaktır.

Yöntem: RRMS hastalarının 2017, 2019 ve 2022 yıllarındaki T1 beyin MR görüntülerinde KK kalınlığındaki değişiklikleri manuel olarak ölçtük.

Bulgular: Sonuçlarımız, kontrol grubunun hasta grubuna kıyasla tüm KK bölümlerinde daha fazla kalınlık, uzunluk ve indeks değerlerine sahip olduğunu gösterdi. Ayrıca, genu ve splenium bölümlerinin kalınlığında ve KK indeksinde hasta ve kontrol grupları arasında anlamlı bir fark gözlendi. Ancak, KK'nin trunkus kısmında veya toplam KK uzunluğunda anlamlı bir fark saptanmadı. Hasta grubundaki CC ölçümleri zaman içinde azaldı ve 1. MRG, 2. ve 3. MRG taramalarından daha yüksek değerler gösterdi. Ayrıca, KK'nin trunkus kısmının kalınlığında ve subkortikal alanların hacim değerlerinde 2.-3. ve 1.-3. MRG ölçümleri arasında istatistiksel olarak anlamlı bir fark vardı.

Sonuç: Elde ettiğimiz bulgular neticesinde araştırmamız MS hastaları için KK ölçümlerindeki değişiklikler hakkında önemli bilgiler sunmaktadır.

Anahtar Kelimeler: Atrofi, Korpus Kallozum, Manyetik Rezonans Görüntüleme, Relapsing Remitting Multiple Skleroz

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Submitted/Başvuru: 10.07.2024 • **Accepted/Kabul:** 03.10.2024 • **Published Online/Online Yayın:** 27.10.2024

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory and demyelinating disease of the central nervous system (CNS) that usually affects young adults.[1] In MS, demyelination occurs in the cortex particularly in the white matter of the CNS, leading to symptoms caused by chronic inflammation.[2,3] The evaluation of multiple sclerosis (MS) involves the use of four primary spectrums, including relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS).[4] RRMS is the most pre-valent subtype of MS, accounting for 85% of cases.[5] RRMS is a subtype of MS that is characterized by complete or sequential recovery after relapses (attacks) associated with transient neurological dysfunctions.[6]

Magnetic resonance imaging (MRI) is a vital tool for diagnosing MS with identifying lesion location and morphology, as well as assessing disease progression and response to treatment. In order to diagnose, monitor, and treat MS, MRI protocols typically include T2, FLAIR, and T1-weighted imaging with contrast. Axial and sagittal slices need be obtained, and it is recommended to use a 1.5 Tesla or 3 Tesla MRI system.[7] The 2017 McDonald diagnostic criteria have increased the importance of para-clinical evaluations, particularly imaging, in the diagnosis and management of MS.[8]

The corpus callosum (CC), which is the largest commissural tract comprised of thick myelinated fibers, connects the corresponding centers in the right and left cerebral hemispheres. The CC has been found to be the brain region that undergoes the most atrophy in multiple sclerosis (MS), and this atrophy has been linked to both cognitive and physical impairment.[9] Furthermore, the atrophy of the CC has been shown to predict cognitive outcomes in MS, making it a valuable biomarker for monitoring the disease.[10]

Our primary objective is to evaluate the CC from magnetic resonance (MR) images of individuals diagnosed with RRMS and compare it to the measurement values obtained from MR images of healthy control subjects within the same age range. Additionally, our study aims to uncover the changes in corpus callosum thickness measurements over time in MR images of RRMS patients in three different years between 2017 and 2022, and to determine the proportionate effect on affected parameters. Moreover, we aim to establish a volumetric data set for monitoring MS patients and provide a preliminary basis for future studies. The primary target of our investigation is to underscore the changes that occur in the corpus callosum over time, in order to monitor the prognosis of MS disease and identify the causes of clinical symptoms.

Methods

Experimental design

Our research was approved by the Kocaeli University Non-Interventional Clinical Research Ethics Committee, which granted approval number GOKAEK-2022/19.13 and project number 2022/321. The research was executed at Kocaeli University Training and Research Hospital, Department of Radiology and Department of Neurology. Our retrospective investigation was carried out using data from patients who were treated in the Department of Neurology, diagnosed with RRMS, and undergone follow-up. The study included patients with RRMS aged between 20-40 years and healthy control subjects in the same age range who presented to the Department of Neurology with headache complaints. T1 brain MR images taken at Kocaeli University Training and Research Hospital, Department of Radiology, were used to measure corpus callosum thickness and indices of patients diagnosed with RRMS and healthy control subjects. A total of 1317 individuals with T1 brain MRI images who were diagnosed with MS or admitted to the hospital with headache complaints between 2017 and 2022 were retrospectively evaluated. Based on the exclusion criteria, 1217 patients were excluded from the study. We included 50 patients diagnosed with RRMS and 50 healthy control subjects, according to the predetermined inclusion and exclusion criteria.

Participants

The 50 individuals diagnosed with RRMS and the 50 healthy control subjects underwent assessments of CC thicknesses and indices derived from T1 brain MR images. Measurements of volume and thickness were conducted on the T1 brain MR images of the RRMS patient group from 2017, 2019, and 2022. In contrast, the healthy control group's measurements were taken from a single T1 brain MR image. The CC thickness measurements were performed manually. The alterations in thickness observed over time in the MR images from different years were proportional and expressed as percentages. Moreover, immunomodulatory agents were incorporated as a standard component of the drug therapy regimen and routine treatment for all individuals within the RRMS patient group.

Inclusion and exclusion criteria

The criteria for inclusion in our study were as follows: patients who were diagnosed with RRMS at Kocaeli University Training and Research Hospital, Department of Neurology, and underwent T1 brain magnetic resonance imaging (MRI) at three different times between 2017 and 2022 were included in our study. Additionally, patients between ages of 20 and 40 who were diagnosed with RRMS and followed up at XXX University Training and Research Hospital, Department of Neurology, as well as healthy individuals in the same age range who were admitted to Kocaeli University Training and Research Hospital, Department of Neurology with complaint of headache but had no cranial pathology, were included in control group. The criteria for exclusion in our study were as follows: the presence of neoplastic, degenerative, or vascular pathologies that could be mistaken for MS, as well as presence of any cranial pathology in control group,

and individuals who did not have an MRI performed at least three times. These were determined to be necessary conditions for exclusion from our study.

MRI protocol

Measurements of anatomical structures were conducted with utilization of a 3-Tesla MRI scanner (Gyroscan Intera, Philips Medical) in accordance with the imaging protocol, which included sagittal and axial T1-weighted images with a TR/TE of 500/minimum and axial T2-weighted images at 4000/102, with a resolution of 256 x 256 and a slice thickness of 5 mm and a field of view of 220 mm.

Measurement parameters of CC

The thickness of the genu, truncus, splenium, length and index of the CC were measured manually on brain MR images. Genu thickness was measured by transverse width of the genu on line connecting anterior and posterior points of CC in planum midsagittale. Truncus thickness was measured by measuring the maximum thickness of the truncus portion of the CC in the planum midsagittale (Figure 1). Splenium thickness was measured by transverse width of splenium on line connecting anterior and posterior points of CC in planum midsagittale (Figure 1). The length of CC was measured by distance between anterior and posterior most prominent points of CC on planum midsagittale (Figure 1). The index of CC was obtained by summing thickness of genu, corpus, splenium in planum midsagittale and dividing by anteroposterior length of the CC (Figure 2).

Statistical analysis

The analysis of statistical data was carried out using the IBM SPSS 20.0 program (IBM Corp., Armonk, NY, USA). To assess compatibility of obtained data with a normal distribution, Kolmogorov-Smirnov and Shapiro-Wilk tests were employed. Since assumption of normal distribution was not met, numerical variables are presented as median (25th-75th percentile). The categorical variables are presented as frequency (percentage). To determine difference between groups, the Mann-Whitney U test was used, and the Friedman two-way analysis of variance was applied for dependent group comparisons. Multiple comparisons were made using Dunn's test. To examine relationships between categorical variables, chi-square analysis was employed. In hypothesis testing, a $p<0.05$ was considered to indicate statistical significance.

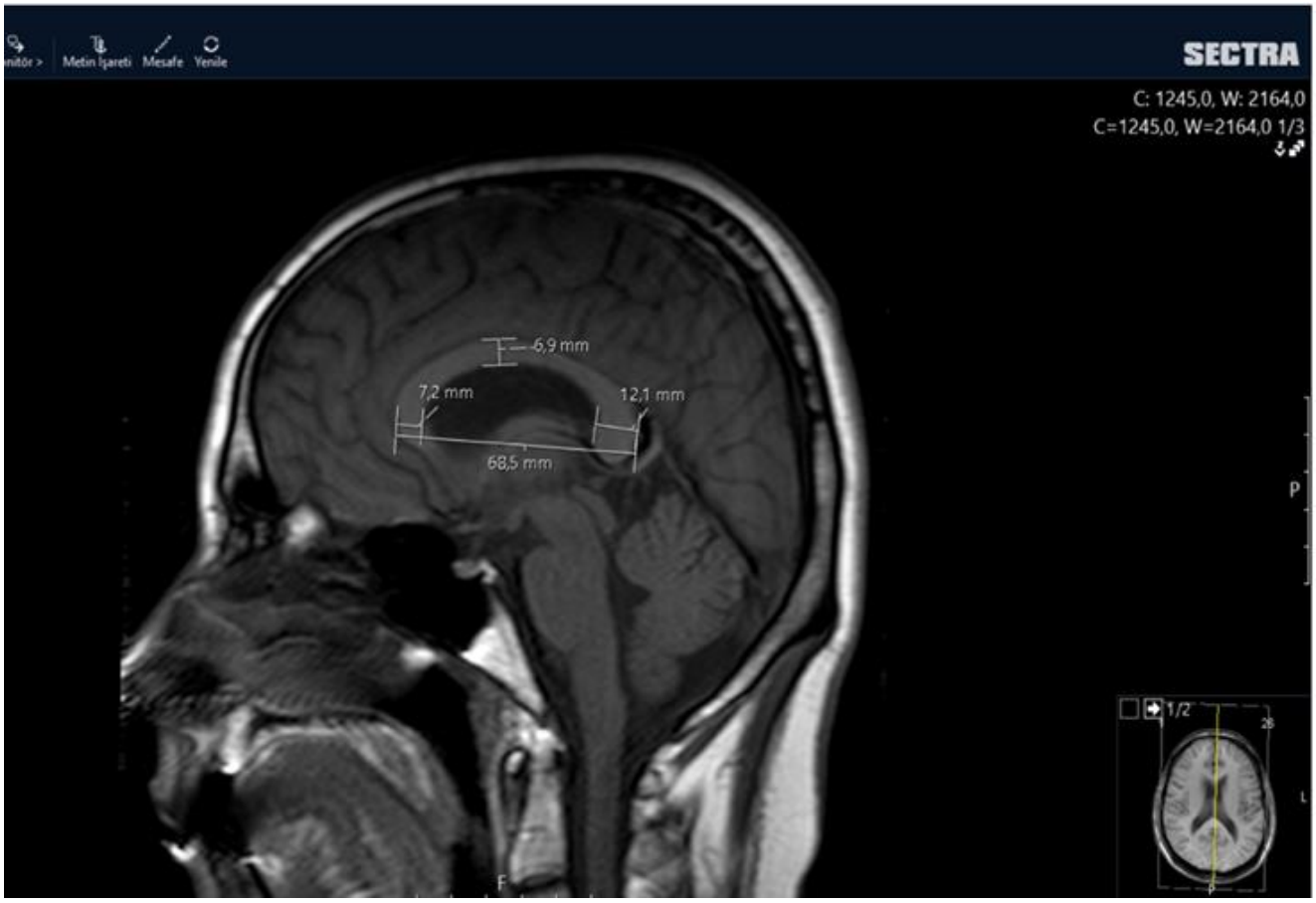

Figure 1. Corpus callosum measurements on midsagittal T1-weighted MRI.

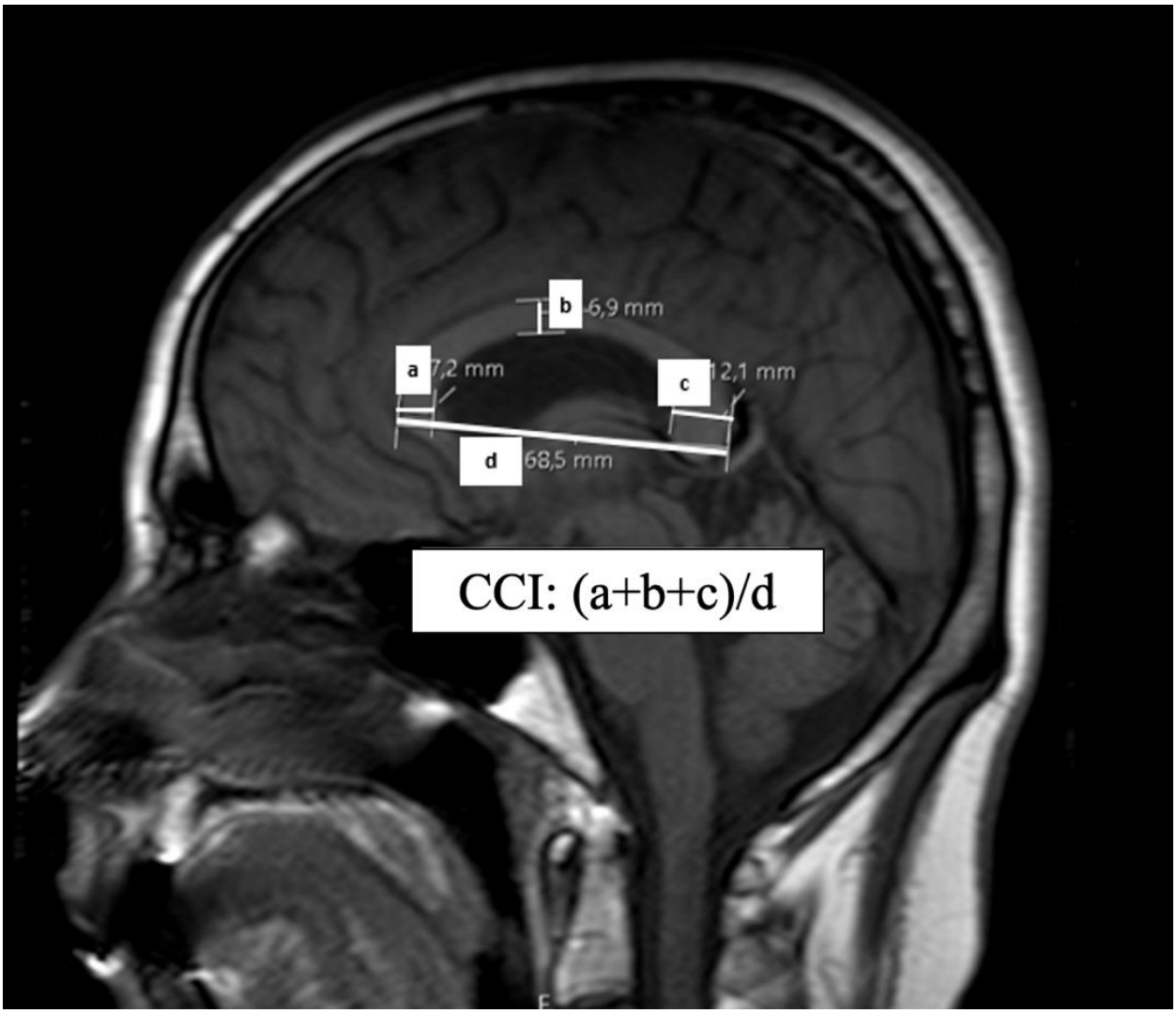

Figure 2. Corpus Callosum Index Measurement (CCI): Corpus Callosum Index, **a.** Genu thickness; **b.** Truncus thickness; **c.** Splenium thickness; **d.** Total anteroposterior length of the corpus callosum.

Results

The study population comprised of 16 male participants (32%) and 34 female participants, while the healthy control group consisted of 18 male participants (36%) and 32 female participants. The median age of the patient group was 33.50 years (25.75-38.00), whereas the median age of the healthy control group was 38.00 years (29.75-40.00).
We revealed that the genu, truncus, and splenium sections of the control group exhibited greater thickness, while the corpus callosum was longer and displayed higher indexes compared to the patient group. Additionally, there was a statistically significant difference was observed in the genu and splenium sections and corpus callosum index, when comparing the thickness measurements of the corpus callosum sections between the individuals in the patient and control groups ($p<0.05$). However, no significant difference was detected in the truncus section of the corpus callosum or the corpus callosum length ($p>0.05$) (Table 1).

Table 1. Comparison of Thickness Measurements of Corpus Callosum Sections

	Control Median (25^{th}-75^{th})	Patient Median (25^{th}-75^{th})	P value
Corpus Callosum			
Genu (mm)	9.15 (8.02-10.04)	8.45 (7.77-9.30)	**0.043**
Truncus (mm)	5.90 (5.35-6.72)	5.65 (4.97-6.45)	0.173
Splenium (mm)	10.02 (9.27-10.82)	8.55 (7.47-9.62)	**<0.001**
Length (mm)	67.00 (63.70-70.40)	66.75 (63.47-69.92)	0.677
Indexes	0.38 (0.32-0.42)	0.34 (0.30-0.37)	**0.004**

*The corpus callosum thickness measurement unit in the table was mm.

The corpus callosum measurements of the patient group were evaluated in terms of time-dependent changes. The thickness measurements, length, and index values of the genu, truncus, and splenium sections of the corpus callosum were measured in the 1st-2nd MRI, 2nd-3rd MRI, and 1st-3rd MRI pairwise comparisons, and these comparisons showed a decrease in percentage values (Table 2).

In the assessment of corpus callosum thickness measurements in the patient group across the 1st, 2nd, and 3rd MRI images, it was determined that the genu, truncus, splenium, length, and index values in the 1st MRI were greater than those in the 2nd and 3rd MRI. Furthermore, the values for the truncus, splenium, length, and index in the 2nd MRI were also greater than those in the 3rd MRI. When comparing the values between the 1st MRI and 3rd MRI, all values, except for the genu section, were higher in the 1st MRI. In the evaluation of the MRIs of individuals in the patient group at three different time points, a statistically significant difference was observed in the volume values of the subcortical areas in the 2nd-3rd and 1st-3rd MRI measurements. Additionally, a statistically significant difference was observed in the thickness measurement of the truncus section of the corpus callosum ($p<0.05$) (Table 3).

Table 2. Percentage Changes in Corpus Callosum Measurements of the Patient Group

	1st-2nd MRI Percentage Alteration Median (25th-75th)	2nd-3rd MRI Percentage Alteration Median (25th-75th)	1st-3rd MRI Percentage Alteration Median (25th-75th)
Corpus Callosum			
Genu (mm)	-0.47 (-9.84-7.76)	-2.25 (-10.85-11.85)	0.00 (-12.90-16.57)
Truncus (mm)	-4.81 (-14.77-4.97)	-2.51 (-12.11-14.83)	-4.17 (-15.20-8.02)
Splenium (mm)	-4.58 (-13.21-9.24)	-1.55 (-10.26-12.69)	-4.83 (-16.72-17.97)
Length	-0.41 (-3.46-2.51)	-0.80 (-3.42-3.14)	-0.87 (-5.00-4.57)
Indexes	-2.85 (-8.89-2.70)	0.00 (-8.70-6.61)	-3.33 (-14.73-9.61)

* The corpus callosum thickness measurement unit in the table was mm.

Table 3. Multiple Comparison of Measurement Parameters of the Patient Group

	Measurement Parameters			
	1st MRI	**2nd MRI**	**3rd MRI**	**P value**
CC Genu (mm)	8.45 (7.77-9.30)	8.40 (7.40-9.22)	8.55 (7.00- 9.92)	0.618
CC Truncus (mm)	5.65 (4.97-6.45)[a]	5.25 (4.65- 6.02)[a]	5.15 (4.60- 6.02)[b]	**0.016**
CC Splenium (mm)	8.55 (7.47-9.62)	8.40 (7.10-9.72)	8.20 (6.82- 9.52)	0.288
CC Length (mm)	66.75 (63.47-69.92)	66.50 (63.35-69.57)	65.95 (62.25-69.25)	0.379
CC Index	0.34 (0.30-0.37)	0.33 (0.30-0.36)	0.32 (0.29-0.38)	0.112

*The unit for multiple comparison of measurement of the RRMS patients in the tables was mm.
**Different letters (a or b) represent statistical significance between measurements ($p<0.05$).

Discussion

Multiple Sclerosis (MS) is a severe, autoimmune, and demyelinating disease that affects the CNS, primarily occurring in adults aged 20-40 years.[11] Our study focused on patients with RRMS, the most prevalent clinical form of MS, and investigated atrophic changes in CC parts over time. Investigating brain structures in MS patients provides essential information about disease progression and treatment, as well as insights into changes in the disease process. Several studies have explored these alterations.[12] Brain atrophy, a common consequence of MS, has been linked to myelin sheath damage, progressive axonal degeneration, and functional disorders of the nervous system.[13] Notably, brain atrophy in MS is five times more prevalent than that associated with normal aging.[14] In MS, gray matter damage could occur early on and result in irreversible disability and cognitive impair-ment.[15]

CC is a crucial pathway made up of largely myelinated fibers that connect the left and right brain hemispheres, enabling the sharing of information between them.[16] MS patients typically exhibit CC atrophy, which is one of the disease's most widely recognized symptoms. In MS, the CC is adversely affected by both focal lesions and Wallerian degeneration.[17] It is worth noting that CC atrophy increases with the progression of MS, leading to approximately 2% volume loss per year, a rate that is ten times higher than that observed in healthy individuals.[18] It has been reported that CC atrophy mainly affects the genu, posterior part of the truncus, and splenium, and develops in a postero-anterior gradient as the disease progresses.[19] Additionally, it has been noted that approximately 20% of patients with RRMS experience CC atrophy.[19]

Our study revealed a significant difference in the thick-nesses and lengths of the genu, truncus, and splenium, as well as the index values of the CC between individuals in

the patient group and those in the control group (Table 1). Specifically, the genu, splenium, and CC index values showed a statistically significant difference ($p<0.05$) (Table 1). The low CC index values indicated atrophy of the CC, and our results demonstrated that this atrophy was more pronounced in the genu and splenium regions. Previous studies have established that atrophy in these regions is associated with cognitive dysfunction.20 Additionally, CC atrophy in MS is known to cause decreased cognitive function, attention deficits, decreased information processing speed, dysfunction in visual memory, and speech fluency. In our study, we found a significant decrease in the time-dependent percentage decrease in CC as %-median in the truncus section, with values of -2.51 (-12.11-14.83) in the 2nd-3rd MRI and -4.17 (-15.20-8.02) in the 1st-3rd MRI (Table 2). We thought that the fact that time-dependent atrophy was more pronounced in the truncus section of the CC compared to other sections may be due to the fact that the truncus section was more sensitive to atrophy and affected more. We analyzed the MRI values of corpus callosum measurements obtained at 3 different times and found that atrophy occurred in all values over time except the 3rd MRI of the genu section (Table 3). It is considered that the increase in the genu section could be due to the triggering of the remyelinization mechanism by symptomatic treatments as reported in the literature.21 In our analysis of the multiple comparisons of CC measurements in MRI obtained at three different times in the patient group, we found a statistically significant difference in the truncus section of the 2nd-3rd MRI and 1st-3rd MRI CC ($p<0.05$) (Table III). Although there was a decrease in other CC measurement values over time, this decrease was not statistically significant ($p>0.05$) (Table 3).

Our study had notable limitations. First, small sample size resulted from exclusion of patients with cranial pathology or demyelinating symptoms, as well as those with neoplastic, degenerative, or vascular conditions that could be mistaken for MS. Consequently, the factors that could be compared were limited. Second, the participants' information was obtained from the hospital registration system, which has a retrospective nature and prevented us from conducting a cognitive assessment. Lastly, the study included patients with RRMS in the patient group and individuals without any cranial pathology in control group. The consequences of excluding any diseases that are not part of the hospital records could impact the outcomes.

Our investigation has contributed to the understanding of the impact of RRMS on CC. The novel aspect of our research was the calculation of the percentage values of atrophy in these structures over time, achieved by proportioning the MRI values to each other. We believe this approach adds to the existing literature on this subject, and the measurement of affected parameters expressed as percentage values could serve as a data set for monitoring MS patients and preparing for future studies.

Acknowledgements
We acknowledge no individual and/or entity to whom we owe gratitude.

Conflict of Interest
The authors declared no potential conflict of interest.

Author contributions
Study idea/Hypothesis: B.K., A.T.O.; Data preparation: B.K., A.T.O., S.D.B., Ö.Ç.; Analysis: B.K., A.T.O., S.D.B., H.E., Ö.Ç, S.B.; Literature review: B.K., A.T.O., H.E., T.Ç.; Manuscript writing: B.K., A.T.O.; Critical Review: B.K., A.T.O., T.Ç.

Financial Disclosure
The authors declared that no financial support was received for this paper.

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