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Original Article / Özgün Araştırma

Evaluation of Diffusion Tensor Imaging Findings in Clinically Isolated Syndrome and Relapsing-Remitting Multiple Sclerosis Patients

Klinik İzole Sendrom ve Relapsing-Remmitting Multipl Skleroz Hastalarında Difüzyon Tensör Görüntüleme Bulgularının Değerlendirilmesi

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Abstract

Objective: To compare diffusion tensor imaging (DTI) findings of the normal-appearing white matter (NAWM) and corpus callosum (CC) in patients with clinically isolated syndrome (CIS) and relapsing-remitting multiple sclerosis (RRMS) and a healthy control (HC) group.

Materials and Methods: The CIS (n = 10), RRMS (n = 29), and HC (n = 13) groups were evaluated by DTI in this retrospective study. Mean diffusion (MD) and fractional anisotropy (FA) maps as well as MD and FA measurements were made from the corpus callosum genu (CCG), corpus callosum splenium (CCS), and NAWM areas from the frontal, parietal, occipital and temporal lobes.

Results: The mean FA values of the NAWM in the temporal lobes were bilaterally lower in both the CIS and RRMS groups than in the HC group. However, no difference was found between the CIS and RRMS groups. In addition, the CIS group had lower FA values in the CCG, whereas the RRMS group had lower FA values in the CCS compared with the HC group. The MD values were significantly different in the CCG between the RRMS and HC groups.

Conclusion: DTI contributes to detecting early changes in the NAWM and CC in patients diagnosed with CIS and RRMS. Additionally, DTI can aid in the follow-up care and management of these patients.

Keywords: Clinically isolated syndrome, relapse-remitting multiple sclerosis, diffusion tensor imaging

Öz

Amaç: Klinik izole sendrom (KİS) ve relapsing-remmiting multipl skleroz (RRMS) tanısı almış olan hastalar ile sağlıklı kontrollerde normal görünen beyaz cevher (NGBC) ve korpus kallozumda difüzyon tensör görüntüleme (DTG) bulgularını araştırmaktır.

Gereç ve Yöntem: Retrospektif çalışmada KİS (n = 10), RRMS (n = 29) ve sağlıklı kontrol (n = 13) grupları DTG ile değerlendirildi.Ortalama difüzyon (OD) ve fraksiyonel anizotropi (FA) haritalarında korpus kallozum genu (KKG) ve spleniumdan (KKS), frontal, parietal, occipital ve temporal loblar NGBC alanlarından OD ve FA ölçümleri yapıldı.

Bulgular: Temporal loblardaki NBGC'nin ortalama FA değerleri hem KİS hem de RRMS'de bilateral olarak kontrol grubundan daha düşüktü. Ancak, KİS ve RRMS grupları arasında fark bulunmadı. KİS grubu KKG'de kontrol grubuna göre daha düşük FA değerlerine sahipken, RRMS grubu KKS'de kontrollere kıyasla daha düşük FA değerlerine sahipti. RRMS ve kontroller arasında KKG'de OD değerleri istatistiksel olarak farklıydı.

Sonuç: DTG, KİS ve RRMS hastalarında NGBC ve korpus kallozumdaki erken değişikliklerin saptanmasına katkıda bulunur. DTG, KİS ve RRMS hastalarının takibi ve yönetimine yardımcı olabilir.

Anahtar Kelimeler: Klinik izole sendrom, relapsing-remmitting multipl skleroz, difüzyon tensör görüntüleme

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Introduction

Multiple sclerosis (MS) is often diagnosed in young patients (20–40 years old) and is a chronic autoimmune and neurodegenerative disease that affects the central nervous system (CNS) in multiple localizations (1). Women are affected two to three times more frequently than men. It is one of the most common causes of neurological disabilities in young adults, and its incidence and prevalence are increasing worldwide. Although the exact mechanism of the disease has not yet been clarified, inflammation, demyelination, and axonal loss occur even in its early stages (2). The autoimmune response is against CNS antigens (myelin proteins) and results in inflammation. The inflammatory plaques are located in the white matter in the brain and spinal cord. They also cause attacks in which illness and convalescence occur sequentially. A diagnosis of MS can only be made with a clinical and radiological demonstration of lesions that are disseminated in space and time (3).

The first attacks of MS can appear as idiopathic demyelinating syndromes that last at least 24 h and affect one or more regions of the CNS; these are called clinically isolated syndromes (CIS). Typical examples of CISs are optic neuritis, transverse myelitis, and brainstem syndromes. This group of cases can be a precursor of MS or can be monophasic. The risk of development of MS is low if magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings are normal (4). Relapsing-remitting MS (RRMS) starts with a severe attack and ends with total or partial remission. Approximately 70% of patients diagnosed with MS have this disease course. The disability of the patient can be gradually increased after each relapse (5).

An MRI is a superior technique to observe plaques compared with other diagnostics. MS lesions exist in the periventricular white matter, internal capsule, corpus callosum (CC), and pons localization; however, they can also be seen in the subcortical white matter and gray matter (6,7). When white matter alterations cannot be monitored by conventional MRI sequences, and when they are evaluated using advanced MR applications such as magnetization transfer rates, diffusion measurements, and MR spectroscopy, differences are found between the healthy group and the patient group (8). Recent studies show that diffusion tensor imaging (DTI) is useful for evaluating changes and tissue damage. Quantification of white matter damage in MS is important in the reparative and protective management of the disease. In addition, DTI can quantitatively demonstrate microstructural damage as demyelination and axonal loss in the white matter with the parameters of fractional anisotropy (FA) and mean diffusion (MD) (9). This study evaluates the alterations in the normal-appearing white matter (NAWM) and CC in patients with CIS and RRMS by analyzing the FA and MD parameters (10).

Materials and Methods

Subjects

Between 2010 and 2011, 39 patients (26 females and 13 males), including patients with RRMS (n = 29) and CIS (n = 10), along with 13 people in the healthy control (HC) group, were retrospectively scanned and included in this study. The diagnoses of RRMS and CIS were based on the 2017 revised McDonald criteria. Patients underwent neurological and MRI examinations. There was an optic nerve or medial longitudinal fasciculus involvement in the CIS patients. All HC subjects also underwent neurological and clinical examinations. In addition, no patients were included if they experienced a relapse or received a course of corticosteroids or immunomodulatory treatments. The demographic information of the participants is given in Table 1. Approval for the study was received from the Dokuz Eylul University Ethical Committee (approval no: 2013/21-02, date: 06.06.2013). Written informed consent was obtained from all participants.

MRI Acquisition

An MRI was acquired using a 1.5 T MR scanner (Philips Medical Systems, Best, The Netherlands). All of the subjects were examined using the same MRI protocol, which consisted of axial T1-weighted turbo spin-echo imaging [repetition time (TR): 550 ms, echo time (TE): 15 ms, slice thickness: 5 mm, matrix: 256 x 256, field of view (FOV): 240], axial proton density and T2-weighted spin-echo imaging (TR: 4.030 ms, TE: 20/80 ms, slice thickness: 5 mm, averages: 2, matrix: 440 x 512, FOV: 240, rectangular FOV: 85), sagittal fluid attenuation inversion recovery imaging (TR: 6.000 ms, TE: 120 ms, slice thickness: 5 mm, average: 1, matrix: 256 x 256, FOV: 230, rectangular FOV: 85), axial T1-weighted imaging with magnetization transfer (TR: 517 ms, TE: 11 ms, slice thickness: 5 mm, averages: 2, matrix: 208 x 256, FOV: 240, rectangular FOV: 85), and axial T2-weighted gradient echo imaging (TR: 794 ms, TE: 26 ms, slice thickness: 5 mm, FA: 20, average: 1, matrix: 166 x 256, FOV: 230).

DTI data were collected by axial echo-planar diffusion-weighted imaging sequence with the following parameters: TR: 1.000 ms, TE: 80 ms, slice thickness: 5 mm, FOV: 230, rectangular FOV: 85, matrix: 112 x 128, *b* values 0 and 1.000 s/mm^2, and with six diffusion gradient orientations.

DTI Assessment

DTI data were analyzed using NordicICE (Diffusion/DTI Module version 2.3, Nordic Imaging Lab, Bergen, Norway). The DTI data were imported into the DTI module for computing the FA and MD maps on a voxel-by-voxel basis. The MD and FA values in each voxel were calculated for each subject. The MD and FA analyses were performed by the same person. The regions of interest (ROIs) were placed manually by a radiologist at the normal-appearing corpus callosum genu (CCG) and corpus callosum splenium (CCS) as well as the bilateral NAWM of the frontal, parietal, occipital, and temporal lobes. Each ROI (0.2 cm^2) was placed on the MD and FA maps by comparing the anatomical

Table 1. Demographic data of the subjects included in the analysis

	CIS	RRMS	Healthy control
Number	10	29	13
Sex M:F	3:7	10:19	6:7
Age: mean (SD)	33.5 (8.7)	32.8 (9.6)	29.8 (1.7)
EDSS score	2.35 ± 1.29	2.63 ± 1.57	-

CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, M: Male, F: Female, SD: Standard deviation, EDSS: Expanded Disability Status Scale

scan in the most homogenous area, avoiding the presence of the lesion for NAWM. To determine inter-rater reliability, all regions were measured again for each subject by a second observer.

Statistical Analysis

Statistical analysis was performed by SPSS software (version 15.0; IBM; Armonk, NY, USA). Inter-observer agreements were determined via the Pearson correlation coefficient. Since the distribution of the data was not a normal distribution, the difference between groups was analyzed using the Kruskal–Wallis test, followed by the posthoc Mann–Whitney U test. Afterward, the Bonferroni correction was applied to the alpha level of significance. *P* values <0.050 were considered statistically significant.

Results

The FA and MD measurements were well correlated (positively) between observer 1 and observer 2. The correlation results of the FA and MD values for all 52 subjects (10 CIS, 29 RRMS, and 13 HC) performed by observers 1 and 2 are shown in Table 2.

The mean FA values of all ROIs are presented in Figure 1. There were significant differences in the FA values of the NAWM in the bilateral temporal lobe (P = 0.016) and the CCG (P = 0.017) between the CIS and HC groups. The patients with RRMS had lower FA values in the left (P = 0.015) and right temporal lobe (P =0.025) and CCS (P =0.032). No differences were found in all regions between the CIS and RRMS groups (all P values >0.050) (Table 3).

The mean MD values of all ROIs are given in Figure 2. No differences in the MD values between the right- and left-sided ROIs were seen in either the patients or the controls (all P values >0.050) except the CCG between the RRMS and HC groups (P = 0.002) (Table 4).

Discussion

This study demonstrated the early-stage invisible alterations that cannot be detected by conventional MRI techniques in patients with CIS and RRMS using DTI. To do so, the FA and MD values were measured in both cerebral hemispheres, the CCG, the CCS, and the NAWM. The changes in the NAWM were detected in the temporal lobe and CC.

MS is a progressive, inflammatory, demyelinating, and degenerative disease of the CNS. Since the disease leads to increasing disability, both curative therapy efforts and pathogenesis are studied comprehensively from the CIS stage (when the first clinical findings are seen) till the RRMS stage (11). MS is

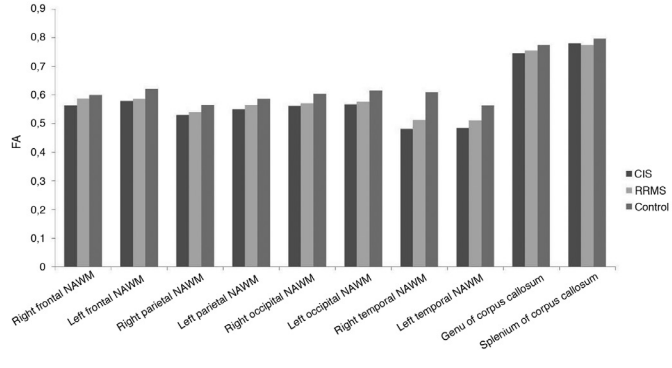

Figure 1. The mean fractional anisotropy values of white matter regions of interest in the clinically isolated syndrome, relapsing-remitting multiple sclerosis, and healthy control groups

CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, NAWM: Normal-appearing white matter, FA: Fractional anisotropy

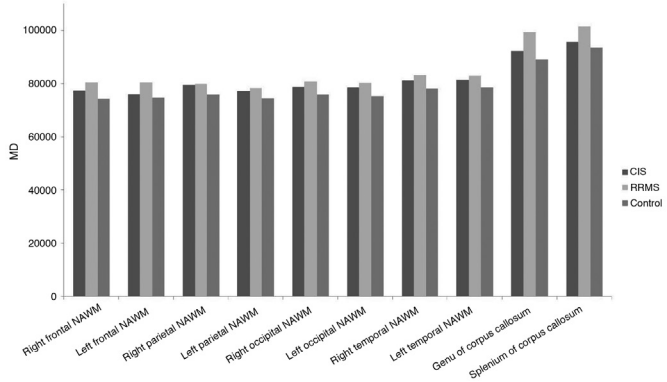

Figure 2. The mean diffusion values of white matter regions of interest in the clinically isolated syndrome, relapsing-remitting multiple sclerosis, and healthy control groups

CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, NAWM: Normal-appearing white matter, MD: Mean diffusion

Table 2. Statistical analysis results of the FA and MD values in ROIs performed by two observers

	r	*P*
FA - right parietal NAWM	0.959	<0.001
FA - left parietal NAWM	0.981	<0.001
FA - right frontal NAWM	0.976	<0.001
FA - left frontal NAWM	0.968	<0.001
FA - right occipital NAWM	0.959	<0.001
FA - left occipital NAWM	0.951	<0.001
FA - right temporal NAWM	0.971	<0.001
FA - left temporal NAWM	0.998	<0.001
FA - genu of corpus callosum	0.978	<0.001
FA - splenium of corpus callosum	0.988	<0.001
MD - right frontal NAWM	0.943	<0.001
MD - left frontal NAWM	0.952	<0.001
MD - right parietal NAWM	0.964	<0.001
MD - left parietal NAWM	0.974	<0.001
MD - right occipital NAWM	0.971	<0.001
MD - left occipital NAWM	0.916	<0.001
MD - right temporal NAWM	0.972	<0.001
MD - left temporal NAWM	0.990	<0.001
MD - genu of corpus callosum	0.979	<0.001
MD - splenium of corpus callosum	0.995	<0.001

FA: Fractional anisotropy, MD: Mean diffusion, NAWM: Normal-appearing white matter

prevalent in young adults, and there is no curative therapy since the pathogenesis is not yet known. It affects not only the patient but also the whole family, and it leads to serious social problems. MS initially exerts 85%–90% relapse and remission, but it consequently leads to disabilities in most patients (12).

The onset of the disease emerges as a CIS related to the optic nerve, brainstem, or spinal cord in 85% of young adults with MS. Subsequently, MS develops in 30%–70% of patients with CIS (13). When MS is in the CIS stage, different locations in the cerebral white matter can be affected. Brainstem and cerebellum affection in the cerebral hemisphere is seen not only in MS but also in other diseases. Occult lesions are currently bypassed due to routine and conventional histochemical and MRI methods. However, recent studies that use advanced MRI techniques have stated that the first damage was shown in the NAWM (when the cranial MRI was normal, but the pathological alterations related to MS had already begun) (14).

Diffusion-weighted MRI depends on the principle of the molecular motion of water, and it provides quantitative data about tissue structure (15). Although it is not known whether myelin is the reason for anisotropy, there is a diffusion limitation due to the focal acute plaque edema and demyelination. Additionally, there can be an axonal loss in chronic plaques and an increase in diffusion due to extracellular distance enlargement because of glycolysis. High MD and lower FA values were detected in the demyelination areas when using the DTI technique. Similar alterations have been observed in the NAWM, indicating myelin destruction. MS lesions are pathologically heterogeneous, and they have shown variable diffusion index values (16). When the lesions were compared to the contralateral NAWM, they had high MD and low FA values (17). These values indicated deterioration in tissue organization and myelin damage that increased the extracellular area. In postmortem studies that were conducted using DTI, these values were affected by both the destruction of the axon and myelin (18).

Studies that compared the histopathological evaluations using DTI have shown that both myelin destruction and inflammatory changes led to statistically significant alterations in parameters such as MD and FA (19,20). Some studies have compared

Table 3. Statistical analysis results of the FA values between the CIS, RRMS, and healthy control groups

	Kruskal–Wallis *P* value	**Post-hoc *P* value**		
		CIS-control	**RRMS-control**	**CIS-RRMS**
Right frontal NAWM	0.242	0.100	0.644	0.167
Left frontal NAWM	0.342	0.121	0.270	0.711
Right parietal NAWM	0.549	0.438	0.289	0.885
Left parietal NAWM	0.718	0.420	0.568	0.711
Right occipital NAWM	0.465	0.292	0.282	0.723
Left occipital NAWM	0.718	0.107	0.131	0.573
Right temporal NAWM	**0.017***	**0.016***	**0.025***	0.157
Left temporal NAWM	**0.016***	**0.016***	**0.015***	0.288
Genu of corpus callosum	0.081	**0.017***	0.187	0.234
Splenium of corpus callosum	0.066	0.072	**0.032***	0.499

The sign "*" indicates a statistical significance of $P < 0.050$. CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, NAWM: Normal-appearing white matter, FA: Fractional anisotropy

Table 4. Statistical analysis results of the MD values between the CIS, RRMS, and healthy control groups

	Kruskal–Wallis *P* value	**Post-hoc *P* value**		
		CIS-control	**RRMS-control**	**CIS-RRMS**
Right frontal NAWM	0.100	0.172	0.054	0.394
Left frontal NAWM	0.267	0.515	0.115	0.450
Right parietal NAWM	0.173	0.067	0.124	0.723
Left parietal NAWM	0.231	0.215	0.097	0.962
Right occipital NAWM	0.255	0.137	0.145	0.872
Left occipital NAWM	0.112	0.067	0.059	0.923
Right temporal NAWM	0.222	0.154	0.108	0.872
Left temporal NAWM	0.272	0.121	0.169	0.898
Genu of corpus callosum	0.081	0.153	**0.002***	0.058
Splenium of corpus callosum	0.066	1.000	0.124	0.253

The sign "*" indicates a statistical significance of $P < 0.050$. CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, NAWM: Normal-appearing white matter, MD: Mean diffusion

histopathological evaluations with DTI findings, while others have shown a correlation between MD and FA values using serological markers checked in the peripheral blood and CSF (21). The defined correlation emerged as MD values increased and FA values decreased in areas where there is a pathological issue. Thus, utilizing DTI, non-invasive information can be obtained and calculated regarding neuronal integrity at the molecular level in the CNS with parameters such as FA and MD (22).

Although a white matter loss was seen in the later stages of the demyelinating process by conventional imaging techniques, DTI studies indicated that the decrease in FA values and the increase in MD values were observed in some parts of the brain even in the early stages of CIS. For instance, a decrease in FA values detected using DTI in the CCG and CCS was shown in the early stages before a definitive diagnosis of MS (23).

Prospective DTI studies have been conducted with patients with CIS and are characterized by the involvement of the optical nerve or brainstem. In these studies, the decrease in FA values and the increase in MD values were found in areas such as the cerebral peduncle, internal capsule, CCG, and CCS (24). This study showed a similar decrease in FA values at the level of the CCG in the CIS and RRMS groups (P = 0.020). Although we observed low values at the CCS, these differences were not statistically significant. We believe that this is because of the more stringent axonal network at the level of the CCS.

Zhao et al. (24) conducted a study in which they compared 24 patients (admitted to the hospital with brainstem findings, although they had normal conventional MR results) with 24 healthy individuals regarding their CCS levels; they detected increases in the MD values and decreases in the FA values. This study included 10 patients with CIS and 29 patients with RRMS, and similar results were obtained.

In most of the studies in which the CC was evaluated by the DTI technique, measurements were done from sagittal sections and by dividing the CC into parts (25,26). This study only took measurements from axial sections of the CCG and CCS, and our measurements were similar to the results of other studies.

The level of cognitive involvement of patients with MS was correlated with DTI findings (27,28,29,30,31). Benedict et al. (32) conducted two distinct studies with 55 and 60 MS patients (1.5 T and 3 T), and they compared clinical tests that measured the level of affected areas and DTI findings. The found that low FA and high MD values in the measurements of the cerebral white matter and thalamus were shown to be closely related to the level of cognitive affection (32). Llufriu et al. (33) conducted a study with 67 MS patients and found that in addition to cortical affection, alterations in the white matter negatively influenced cognitive processes.

Note that psychiatric disorders can accompany MS (34). In our study, we did not compare examinations of temporal lobe white matter with psychiatric examination data. The study by Bruno et al. (35) compared 36 patients with bipolar disorder without a history of neurological disease and 28 healthy individuals; they detected a decrease in FA values and an increase in MD values in the inferior frontal area and medial temporal lobe in the bipolar disorder group. This was linked to neuronal disorganization rather than axonal loss (35). There is no such study on the temporal lobe of patients with MS using the DTI technique; therefore, this topic needs to be investigated.

This study's findings, except for those concerning the CCS, are compatible with the literature. If we accept that RRMS is a milder form of MS and CIS (a demyelinating disease that is the early stage of MS), we can assume that differences in the CCS may emerge in the later stages of the disease. The CCS has a more stringent network compared with the CCG. However, this difference can also occur due to factors such as technical parameters (Tesla, gradient number, slice thickness, etc.), the number of participants, and the stage of the disease.

Study Limitations

Potential limitations of this study include the following: 1) this study was cross-sectional, and 2) sample sizes in each group were relatively small, which might reduce the power of the group comparison.

Conclusion

This study's results indicate structural alterations in the NAWM of crucial brain regions such as the temporal lobe and the CC that may represent an MRI structural marker related to MS. Increased knowledge about the pathophysiological mechanisms that cause MS can lead to improved therapy processes and imaging techniques. The clinical usage of these new developments is slow because there should be larger and long-term studies to evaluate these techniques. Additionally, long-term studies should measure the changes in the brains of the same individuals over time.

Ethics

Ethics Committee Approval: Approval for the study was received from the Clinical Research Ethics Committee of Dokuz Eylul University Non-Interventional Clinical Research Ethics Committee (decision no: 2013/21-02, date: 06.06.2013).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ö.A., E.İ., F.İ., E.A., Design: Ö.A., E.İ., F.İ., E.A., Data Collection or Processing: Ö.A., A.Ç., O.K., E.İ., F.İ., E.A., Analysis or Interpretation: Ö.A., B.Ç., A.Ç., O.K., E.A., Literature Search: Ö.A., B.Ç., A.Ç., O.K., E.A., Writing: Ö.A., B.Ç., A.Ç., O.K., E.İ., F.İ., E.A.

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