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Relapsing-Remitting Multiple Skleroz Hastalarında Difüzyon Tensor Görüntüleme Bulguları: Bir Vaka-Kontrol Çalışması

Diffusion Tensor Imaging Findings In Relapsing-Remitting Multiple Sclerosis Patients: A Case-Control Study

İsa Çam[1], Hande Biçkin[2], Yonca Anik[1], Hüsnü Efendi[2]

1Kocaeli Üniversitesi Tıp Fakültesi Radyoloji Ana Bilim Dalı, Kocaeli, Türkiye
2Kocaeli Üniversitesi Tıp Fakültesi Nöroloji Ana Bilim Dalı, Kocaeli, Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Bu çalışmada, Multiple Skleroz (MS) hastalarında çeşitli normal görünen beyin anatomik lokalizasyonların Difuzyon Tensor Görüntüleme (DTG) bulgularını incelemek amaçlanmıştır. Ek olarak, MS hastalarında yapısal, fonksiyonel ve klinik hasarı yorumlamak için beyaz ve gri cevherin hacimsel analizi ve bu bulguların Genişletilmiş Özürlülük Durumu Ölçeği (Expanded Disability Status Scale; EDSS) ile korelasyonu yapıldı.*

YÖNTEM ve GEREÇLER: *Çalışmamıza McDonald 2010 kriterlerine göre tanı almış 32 relapsing remitting MS hastası ve 24 sağlıklı kontrol dahil edildi. Hasta ve kontrol grubuna 3T DTG-traktografi ve volumetrik Manyetik rezonans görüntüleme (MRG) ile hasta grubuna rutin kranial MRG incelemesi yapıldı. Çeşitli anatomik alanlardan traktografi ölçümlerinden ortalama difüzyon (MD) ve fraksiyonel anisotropi (FA) değerleri kaydedildi. MS hastalarının EDSS skorları kaydedildi ve DTI parametreleri ve volumetrik analiz ile korele edildi.*

BULGULAR: *FA ve MD ölçümlerinde tüm MS hastalarında incelenen korpus kallozum genu, korpus ve splenium, forniks, bilateral forceps major, forceps minor, inferior longitudinal fasikül, prefrontal korteks, talamus alanlarında FA değerleri kontrol grubuna göre düşük saptanır iken MD değerleri aynı alanlarda kontrol grubuna göre yüksek olarak bulunmuştur. Gri ve beyaz cevher volüm değeri açısından hasta grubu kontrol grubundan istatistiksel olarak anlamlı derecede düşük bulunmuştur. Volumetrik analiz ve DTG analizinden FA değerlerinde, MS grubu ile EDSS arasında anlamlı korelasyon izlenmedi. Bilateral forseps majör, prefrontal korteks, globus pallidusta MD değerleri ile EDSS arasında anlamlı bir korelasyon saptandı.*

TARTIŞMA ve SONUÇ: *DTI-traktografi ve volumetrik MRG gibi yeni MRG yöntemleri MS'de aksonal dejenerasyon tutulumunun değerlendirilmesinde önemli katkılar sağlayacaktır.*

Anahtar Kelimeler: *Multipl skleroz, Difüzyon Tensör Görüntüleme, beyaz cevher, gri cevher.*

ABSTRACT

INTRODUCTION: *The aim of this study is to determine Diffusion Tensor Imaging (DTI) findings of normal-appearing brain anatomic localizations in Multiple sclerosis (MS) patients. Additionally, volumetric analysis of white and gray matter and correlation with EDDS were performed to interpret structural, functional, and clinical damage in MS patients.*

METHODS: *32 patients with relapsing remitting MS diagnosis according to McDonald 2010 criteria and 24 healthy volunteers as the control group were included. 3T DTI-tractography and volumetric Magnetic resonance imaging (MRI) were performed in each group and conventional cranial MRI in MS group as well. Mean diffusivity (MD), fractional anisotropy (FA) values of tractography measurements of from various anatomic locations were obtained. EDSS were recorded in MS patients and correlated with DTI parameters and volumetric analysis.*

RESULTS: *FA and MD measurements from corpus callosum genu, body and splenium, fornix, bilateral forceps major, forceps minor, inferior longitudinal fasciculus, prefrontal cortex, thalamus areas revealed that FA values were decreased and MD values were increased in MS patients compared with that of the healthy control group. Grey and white matter volume values were significantly lower in MS patients group. Volumetric analysis and FA values from DTI analysis were not significantly correlated with EDSS in MS group. There was a significant correlation between MD values and EDSS in bilateral forceps major, prefrontal cortex, globus pallidus.*

DISCUSSION AND CONCLUSION: *Advanced MRI techniques such as DTI-tractography and volumetric MRI seem to make remarkable contributions to the evaluation of axonal degeneration in MS.*

Keywords: *Multiple sclerosis, Diffusion Tensor Imaging, white matter, gray matter.*

İletişim / Correspondence:

İsa Çam
Kocaeli Üniversitesi Tıp Fakültesi Radyoloji Ana Bilim Dalı, Kocaeli, TürkiyeE-mail: serkanbakirdogen@hotmail.com
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INTRODUCTION

Multiple sclerosis (MS); is a chronic inflammatory, demyelinating, disease of the central nervous system (CNS), characterized by demyelinating plaques in white matter. Cortex and deep gray matter can also be affected (1). Besides demyelination axonal degeneration seems to be the main reason for neurologic disability (2). Conventional magnetic resonance imaging (MRI) plays an important role in MS diagnosis via demonstrating MS lesions and change in lesion nature (3).

In the past few years, MS has been demonstrated to be characterized by both focal white matter (WM) damage and diffuse damage identified by using non-conventional MRI techniques, including magnetization transfer imaging and diffusion tensor imaging, or estimated via brain volume quantification (3,4). Especially normal appearing white matter (NAWM) damage is prominent in progressive period (5).

Diffusion tensor imaging (DTI) is a technique on demonstrating white matter tracts quantitative analysis MS lesions are heterogeneous and show variable diffusion index (6). In general plaques display increased mean diffusivity (MD) and decreased fractional anisotropy (FA) values compared with that of normal white matter and NAWM in DTI (6,7). This is attributed to increased extracellular space due to disorganization caused by myelin and axonal damage. Alteration normal-appearing white matter tracts, in DTI parameters are reported in a few reports (8,9). In this study DTI values of white matter tracts, white and gray matter volumes were determined and correlated with Expanded Disability Status Scale (EDSS) in MS patients. In addition, white and gray matter volumes and DTI parameters were compared to that of healthy volunteers.

MATERIAL AND METHODS

A total of 32 MS patients were included in the study. There were 20 female, 12 male patients; age range 21-53 years. All MS patients were diagnosed as relapsing remitting MS according to McDonald 2010 criteria. A total of 24 healthy volunteers (11 male, 13 female) were included as the control group. The MS patient group included patients who had not undergone a new attack until 1 month before the date of the study and who did not receive corticosteroid therapy. Patients with further disability, accompanying other cerebral lesions and systemic disease were not included. Patients with an EDSS score of 6 or less were enrolled. The control group's age and gender parameters were matched with the patient group. Exclusion criteria were pregnancy, heart battery carriers, psychiatric disorders, alcohol-substance usage, claustrophobic patients and patients with prosthesis that are not compatible with MRI.

This prospective study protocol was approved by the institutional review board. (KAEK 14/18 Project no: 2015/320). Written informed consent was obtained from all participants. MS patients were examined initially by the clinician in the MS clinic. Expanded Disability Status Scale (EDSS) scores were calculated and then patients were referred to Kocaeli University Radiology Department for MRI.

All MRI examinations were obtained at a single academic center. Scanning was performed via 3T Philips MRI unit (Philips Medical Systems Achieva 1 2008-07-18 Release 2.3.6.7, Software 22) using the 8-channel headband in supine. Study protocol included an axial plane with 2 mm slice thickness SE EPI sequence DTI and sagittal, axial and coronal 3D T1 FFE along with routine conventional contrast enhanced cranial MRI sequences according to the MS protocol for the patient group. In the control group, only axial plane DTI and sagittal, axial and coronal 3D T1 FFE sequences were obtained.

MRI analysis: Post-processing was performed on the 3T Philips workstation. (Release 2.5.3.0 2007-12-03, Philips Medical Systems, Netherlands B.V.) Total gray matter and white matter volumes were calculated with full automated neuroimaging software. On DTI analysis fiber tractography images were obtained. FA, color FA, Apparent Diffusion Coefficient (ADC), exponential ADC maps were done. Corpus callosum genu, corpus and splenium, fornix, bilateral superior longitudinal fasciculus (SLF) (Figure 1), inferior longitudinal fasciculus (IFL) (Figure 2), bilateral forceps major, forceps minor, corticospinal tract (CST) (Figure 3), uncinate fasciculus (UF), prefrontal cortex, globus pallidus, thalamus, putamen MD (ADC) and FA values were recorded manually by ROI plotting.

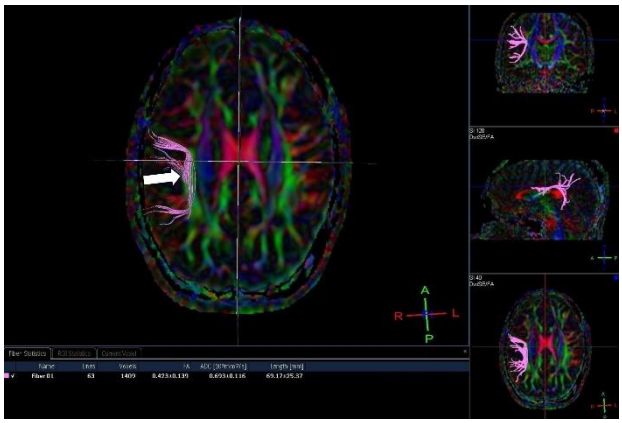

Figure 1.Tractography, FA and MD values of the right superior longitudinal fasciculus.

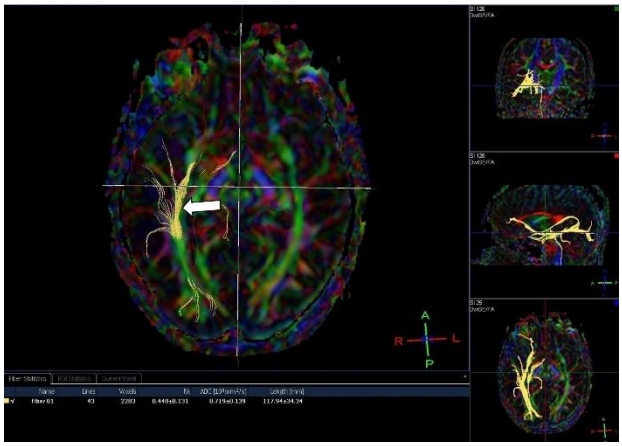

Figure 2.Tractography, FA and MD values of the right inferior longitudinal fasciculus

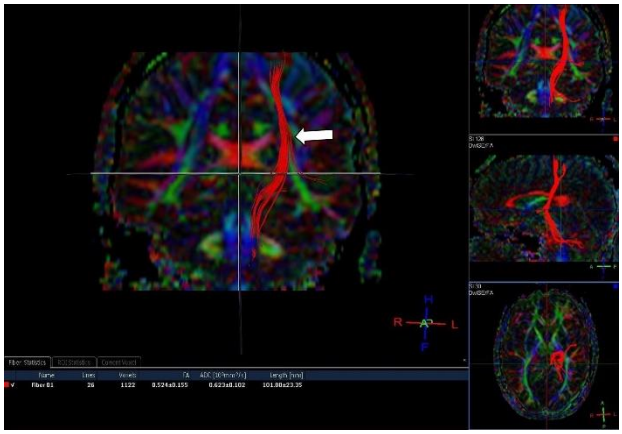

Figure 3. Tractography, FA and MD values of the left corticospinal tract.

ROI drawing was designed to cover the anatomical area but to be large enough not to affect the partial volumetric effect.

Volumetric analysis: 3D FFE T1 weighted images were studied on the workstation. Total gray matter and white matter volumes in patient and control groups were calculated with fully automated neuroimaging software.

Statistical analysis was performed using the SPSS 13.0 for Windows package program. The age, gender, mean values, and standard deviations of all cases in the patient and control groups were evaluated by simple descriptive test. Normality of distribution was evaluated by the Kolmogorov-Smirnov test. DTI and volumetric analysis values of MS patients and control groups were evaluated by T test and One-way ANOVA- Post Hoc test. In addition, Pearson test was used for assessing the correlation among EDSS scores and volumetric analysis and DTI values. $p < 0.05$ was considered as significant.

RESULTS

The mean age of the patients was 37.8 ± 9.43 years versus the control group 33.6 ± 11.02 years. There was no statistically significance of age and gender parameters among the patients and the control group. (p:0.177 and p:0.539, respectively).

EDSS distribution in the patient group was between 0 and 6, and the mean was calculated as 1.64 ± 1.81.

In all anatomic localizations, the FA mean values were lower in the patient group compared to that of the control group, and the MD mean values were higher.

Statistically, between patient group and the control group FA mean values (Table 1) were found significant; p:0.033 in the corpus callosum genu section, p<0.001 corpus callosum body section, p: 0.022 in the splenium, p<0.001 in the fornix, p:0.016 in the right forceps major, p:0.005 in the left forceps major, p:0.046 in the right forceps minor, p:0.041 in the left forceps minor, p:0.032 in the right ILF, p:0.005 in the left ILF, p:0.003 in the right prefrontal cortex, p:0.016 in the left prefrontal cortex, p:0.013 in the right thalamus and p:0.011 in the left thalamus.

Between patient group and the control group MD mean values (Table 2) were also significant; p<0.001 in the corpus callosum genu section,

p:0.004 in the body section, p:0.001 in the splenium, p<0.001 in the fornix, p<0.001 in the right forceps major, p:0.03 in the left forceps major, p<0.001 in the right forceps minor, p:0.025 in the left forceps minor, p:0.004 in the right SLF, p:0.013 in the left SLF, p:0.011 in the right ILF, p: <0.001 in the left ILF, p:0.007 in the right prefrontal cortex, p:0.048 in the left prefrontal cortex, p:0.001 in the bilateral thalamus. No significant correlation was found between FA values and EDSS. There was a significant correlation between MD mean values and EDSS in bilateral forceps majör (right p:0.042, left p:0.019) prefrontal cortex (right p:0.011, left p:0.035), globus pallidus (right p:0.034, left p:0.042).

The gray matter mean volume value was 0.711 ± 0.09 L in the patient group versus 0.832 ± 0.08 L in the control group; that is significantly lower at p<0.001. The white matter mean volume value of the patient group was 0.517 ± 0.06 L versus the control group 0.631 ± 0.07 L; that is also statistically significantly lower at p<0.001 (Table 2). However no statistically significant correlation has been observed between EDSS and brain gray-white matter volume in the patient group. Details are given in Table 4.

Table 1. Comparison of FA measurements of patient group and healthy group. IFL: inferior longitudinal fasciculus.

Anatomic localization	Patient group (n=32)	Control Group (n=24)	p value
Corpus callosum genu section	0.499±0.08	0.541±0.02	0.033
Corpus callosum body section	0.516±0.08	0.552±0.01	<0.001
Corpus callosum splenium	0.546±0.09	0.594±0.02	0.022
Fornix	0.389±0,06	0.453±0.04	<0.001
Right forceps major	0.427±0.07	0.471±0.03	0.016
Left forceps major	0.435±0.07	0.484±0.03	0.005
Right forceps minor	0.406±0.07	0,438±0,02	0.046
Left forceps minor	0.411±0.06	0.442±0.02	0.041
Right ILF	0.436±0.07	0.471±0.02	0.032
Left ILF	0.444±=0.07	0.493±0.02	0.005
Right prefrontal cortex	0.397±0.03	0.456±0.02	0.003
Left prefrontal cortex	0.394±0.09	0.446±0.02	0.016
Right thalamus	0.439±0.06	0.459±0.03	0.013
Left thalamus	0.431±0.06	0.451±0.03	0.011

Table 2. Comparison of MD (10^{-3} mm^2/s) measurements of patient group and healthy group. SLF: superior longitudinal fasciculus, IFL: inferior longitudinal fasciculus.

Anatomic localization	Patient group (n=32)	Control Group (n=24)	p value
Corpus callosum genu section	0.737±0.08	0.652±0.02	<0.001
Corpus callosum body section	0.762±0.13	0.670±0.03	0.004
Corpus callosum splenium	0.793±0.12	0.670±0.03	0.001
Fornix	1.270±0.19	1.056±0.14	<0.001
Right forceps major	0.693±0.06	0.639±0.02	<0.001
Left forceps major	0.696±0.09	0.651±0.02	0.03
Right forceps minor	0.722±0.06	0.662±0.02	<0.001
Left forceps minor	0.691±0.05	0.662±0.03	0.025
Right SLF	0.680±0.05	0.642±0.02	0.004
Left SLF	0.671±0.05	0.638±0.02	0.013
Right ILF	0.758±0.09	0.697±0.06	0.011
Left ILF	0.753±0,09	0.693±0.05	<0.001
Right prefrontal cortex	0.731±0.09	0.671±0.03	0.048
Left prefrontal cortex	0.694±0.05	0.667±0.02	0.048
Right thalamus	0.671±0.06	0.622±0.01	0.001
Left thalamus	0.673±0.06	0.624±0.02	0.001

Table 3: Gray and white matter volume values of patient and control groups.

	Patient group (n=32)	Control group (n=24)	p value
Gray matter volume (L)	0.711±0.09	0.832±0.08	<0.001
White matter volume (L)	0.517±0.06	0.631±0.07	<0.001

Table 4: Comparison of brain gray-white matter volume and EDSS in the patient group.

Patient group	EDSS	
	r	p
Gray matter volume	-0.247	0.174
White matter volume	-0.094	0.609

DISCUSSION

Multiple sclerosis (MS); is a chronic inflammatory, demyelinating, and neurodegenerative disease characterized by plaques of focal demyelination (1). Conventional MRI has a crucial role in detecting MS lesions, and showing changes in the nature of the lesions (3). EDSS is a method, first defined by Kurtze (10), used to detect disability in MS. Eight functional systems are assessed and that gives neurologists the ability to calculate the functional system score. MS lesions are hyperintense on T2 weight MRI due to prolonged T2 relaxation time, The newly formed T2 hyperintense lesion shows developing inflammation and lesion size reaches the largest diameter at 4 weeks in the acute phase. By limiting inflammation and developing remyelination, lesion sizes shrink in the next 6-8 weeks.

DTI is an important technique that noninvasively demonstrates the quantitative information of the white matter pathways of the brain and the orientation of the tracts. Tractography is the calculation of white matter structure with DTI data. Other imaging modalities are not as useful as DTI in establishing the pathological process of microstructural damage in the brain in vivo (11). The use of DTI in demyelinating diseases, particularly MS, is common. Decrease in FA values and increase in MD values were found in demyelination. In general, the plaques demonstrate increased MD and decreased FA values as compared to the normal white matter of the contralateral side (6,7). This shows disorganization and extracellular space, which is the result of myelin and axonal destruction.

NAWM is known to be affected in MS (9). It has been demonstrated that NAWM of patients with MS have increased ADC and reduced FA (8,9,12,13). As authors of these studies indicated, we observed a remarkable increase in the mean ADC and a decrease in the mean FA in the white matter tracts. The change in DTI measures is supposed to indicate the reduced white matter tract integrity and axonal injury both locally and distally. The directional information of water molecule diffusion is employed to produce virtual 3D white matter tracts (14) in diffusion tractography which is a supplementary of DTI. Tractography permits white matter to be collected into white matter pathways with functional specificity and, therefore, allows evaluation of disease procedure as regards functional systems. It has been found in the adult MS population that white matter tracts involved more commonly than in healthy controls (15,16).

Lin et al (15) reported that there was a notable increase in the mean ADC along the corticospinal tracts and the corpus callosum (17) in patients with MS, which correlated with disability. Contrary to data of these studies on MS, we could not find any correlation between FA values of white matter tracts and EDSS scores in the patients with MS. However, we observed a significant correlation between MD values and EDSS in only a few localizations.

It has been shown in several studies carried out on patients with MS that brain atrophy is seen as a final outcome of all subtypes in MS, and is between 47% and 100% (18,19,20). Due to its high sensitivity and accuracy in detecting volumetric changes of the brain, Magnetic resonance imaging volumetry has become an applicable component in the assessment of disease (21). It permits whole-brain volume to be measured, as well as the volume of particular brain lobes and gyri (22).

Multiple sclerosis has been considered to be a white matter (WM) disease of the CNS. Foci of demyelination in WM are often demonstrated using MRI and remain a distinctive feature of the disease. GM is also reported to be affected in pathologic studies, and appears to be a large component in all of the pathologies resulting from MS. This injury contains extensive demyelination, neuron apoptosis, and atrophy deteriorating the cortex and deep GM structures (22). Usually atrophy of the corpus callosum and dilatation of the ventricles are seen. Some studies have shown that the relationship between brain atrophy and EDSS is more significant than the relationship between lesion load and EDSS (18,23). Ge et al. (24) in 2000 showed that brain atrophy was higher in MS patients than in the control group. While there was a negative correlation between brain atrophy and EDSS score in SPMS patients, no significant correlation was found in RRMS patients (24). Contrary to these studies, a number of studies have revealed no direct correlation between brain volume changes and patient's clinical state and rate of disability (21,23,25). Unrelated to

the disease, there may be other factors influencing brain volume changes in MS patients. Further investigations are needed to identify it.

In the present study, both gray and white matter atrophy was significant in the MS group compared with that of the healthy volunteers (both $p<0.001$). However, there was no significant correlation among atrophy and EDSS.

This study has some limitations. First of all, is the limited number of patients, thus some anatomical localizations did not reach significance with being very close. Correlations between MS lesion load and DTI parameters in MS patients were not evaluated.

In conclusion, the current study indicates decreased FA values and increased mean MD values in the ROIs of normal-appearing white matter tracts in patients with MS, which suggest that diffuse damage exists even in early-onset MS. Nevertheless, future studies should consist of large prospective cohorts in order to confirm the involvement of major white matter structures in patients with MS in correlation with functional assessment.

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Conflicts of interest
The authors declare that there is no conflict of interests regarding the publication of this paper

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