JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1213743
J Contemp Med 2023;13(2):170-175

Original Article / Orijinal Araştırma

The Contribution of Diffusion Tensor Imaging to Conventional Magnetic Resonance Imaging in the Diagnosis of Multiple Sclerosis Patients

Multipl Skleroz Hastalarının Tanısında Difüzyon Tensör Görüntülemenin Konvansiyonel Manyetik Rezonans Görüntülemeye Katkısı

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Abstract

Aim: The aim of this study is to investigate whether anisotropic diffusion is superior to conventional magnetic resonance imaging for understanding the pathophysiology of multiple sclerosis (MS) disease by Fractional anisotropy (FA) measurements.

Material and Method: In our study, FA measurements were made from the plaque, the peri-plaque area, the normal appeared white matter contralateral to the plaque and normal appearing white matter areas in MS patients and from the normal white matter in the control group. 3D tractography maps were made in all MS patients and it was evaluated whether white pathways were affected by MS disease.

Results: When the degree of anisotropy was compared to the control group, the degree of plaques was found lowest. Increase was observed in peri-plaque, the normal appeared white matter contralateral to the plaque and normal appearing white matter, respectively. The active plaque FA value was found to be lower than the chronic plaque FA value, and the chronic plaque FA was found to be lower than the normal white matter FA value. It has been shown that plaques traced along axonal pathways in MS patients cause interruption in axonal pathways.

Conclusion: Progressive decrease in anisotropy from normal appearing white matter to peri-plaque white matter and plaque level indicates myelin damage. This suggests that the white matter that appears normal on T2 images on conventional MR is not actually normal. Based on these results, it was thought that diffusion tensor imaging would be useful in evaluating the burden of disease in MS patients.

Keywords: Multiple sclerosis, diffusion tensor imaging, fractional anisotropy, magnetic resonance imaging

Öz

Amaç: Bu çalışmanın amacı Fraksiyonel anizotropi (FA) ölçümleri ile multipl skleroz (MS) hastalığının patofizyolojisini anlamada anizotropik difüzyonun konvansiyonel manyetik rezonans görüntülemeye üstün olup olmadığını araştırmaktır.

Gereç ve Yöntem: Çalışmamızda MS hastalarında plak, periplak , plağın karşısında normal görünen beyaz cevher ve normal görünen beyaz cevher alanlarından, kontrol grubunda ise normal beyaz cevherden FA ölçümleri yapıldı. Tüm MS hastalarında 3 boyutlu traktografi haritaları yapıldı ve beyaz yolakların MS hastalığından etkilenip etkilenmediği değerlendirildi.

Bulgular: Anizotropinin derecesi kontrol grubu ile karşılaştırıldığında en düşük değer plakta saptanırken; periplak, plağın karşısında normal görünen beyaz cevher ve normal görünen beyaz cevherde anizotropinin sırasıyla arttığı izlenmiştir. Aktif plak FA, kronik plak FA'dan; kronik plak FA, normal beyaz cevherde FA'dan düşük saptanmıştır. MS hastalarında aksonal yollar boyunca izlenen plakların aksonal yollarda kesintiye neden olduğu gösterilmiştir.

Sonuç: Normal görünen beyaz cevherden plak düzeyine doğru anizotropideki progresif artış myelin hasarını göstermektedir. Bu da konvansiyonel MR'da T2 görüntülerde normal görünen beyaz cevherin aslında normal olmadığını düşündürmektedir. Bu sonuçlara dayanarak MS hastalarında hastalık yükünün değerlendirilmesinde Difüzyon tensör görüntülemenin faydalı olacağı düşünülmüştür.

Anahtar kelimeler: Multipl skleroz, difüzyon tensör görüntüleme, fraksiyonel anizotropi, manyetik rezonans görüntüleme

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Received *(Geliş Tarihi)*: 02.12.2022 **Accepted *(Kabul Tarihi)*:** 11.01.2023

INTRODUCTION

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system (CNS) in young adults. Inflammation, demyelination and axonal damage are responsible for the pathology of the disease. Accordingly, the most prominent pathological finding of MS is cerebral or spinal plaques containing demyelination.[1] Cortex and deep gray matter are also affected in MS. Irreversible white matter damage and severe demyelination as a result of axonal loss is the main determinant of long-term disability in multiple sclerosis.[2,3] Magnetic resonance imaging (MRI) is a sensitive imaging modality for identifying plaques critical to the diagnosis of MS and evaluation of treatment response.[4] MRI helps in the diagnosis of MS by detecting demyelinating plaques in the periventricular, juxtacortical, and infratentorial areas. Until now, these demyelinating plaques were thought to be responsible for MS pathology. However, this technology is limited due to a lack of pathologic specificity and a poor correlation with disability. Studies performed with diffusion tensor imaging (DTI) in the postmortem period, it has been determined that tissue damage is not only in plaques, but also in white and gray matter in MS patients.[5,6] Therefore, it can be thought that conventional MRI has a limited role in the diagnosis and follow-up of MS when compared with DTI. Diffusion tensor imaging (DTI) is an advanced imaging method that can quantitatively show changes in brain tissue, unlike MRI, which has been increasingly used in MS recently.[7]

The movement of free water protons in the brain along the applied gradient is measured with diffusion-weighted imaging. In isotropic tissues where diffusion is independent of tissue alignment, information about all diffusion properties of the tissue can be obtained with a single Apparent diffusion coefficient (ADC) measurement. However, ADC measurement is insufficient in anisotropic tissues where diffusion is dependent on tissue alignment and myelin is dense.[8,9] It is important to determine the diffusion size with DTI, since the places where the anisotropic diffusion is greater indicate the white matter pathways. While diffusion-weighted MR is the method that shows the information of the diffusion rate of molecules in a single direction; Diffusion tensor MR imaging provides information about the direction of molecules as well as their velocity. However, it does not give any information about the rate. In addition, features such as density of axons, average axon diameter, myelin sheath thickness and directions of pathways in white matter pathways in DTI affect diffusion in that tissue and provide important information about the structure of pathways.

In this study; It was aimed to quantitatively demonstrate diffusion abnormalities of the plaque, the peri-plaque area, the normal appeared white matter contralateral to the plaque and normal appearing white matter areas that in MS patients with FA measurements with DTI. Determine the location of DTI imaging in terms of active and chronic plaque separation by evaluating FA measurements in active and chronic plaques in MS patients. In addition, to determine whether anisotropic diffusion is superior to conventional MR imaging and whether axonal pathways are affected by obtaining 3D tractography maps from DTI images in MS patients.

MATERIAL AND METHOD

The study is a prospective study conducted at Ankara Hospital of Başkent University between February 2012 and August 2013. Patients diagnosed with MS using clinical and laboratory methods using Mc- Donald criterias in neurology department and referred to our clinic for brain MRI were included in the patient group. People who were found to be neurologically healthy as a result of the examination performed by the Neurology department were included as the control group. The patient group was between the ages of 18-72 (mean 38±12); a total of 54 patients, 39 women and 15 men, and a total of 56 healthy individuals in the control group, 32 women and 24 men, aged 20-56 years (mean 31±7) were included.

MRI was performed in all patients with a 1.5 Tesla MR device (Siemens, Germany, Avanto) using a head coil in the supine position. Fluid attenuated inversion-recovery (FLAIR) in sagittal and transverse planes, TSE T2-weighted sequences in transverse and coronal planes and axial TSE T1-weighted sequences were taken from MS patients and control group. Postcontrast sagittal and transverse TSE T1-weighted and coronal fat-suppressed T1-weighted sections were obtained only from MS patients. DTI was administered to all MS patients and the control group. Images in DTI were acquired using the (EPI) sequence 30 directions were used to obtain tensor images.

In our study, FA measurements were made from plaque, peri-plaque, normal-appearing white matter (NAWM) and the normal appeared white matter contralateral to the plaque (CP-NAWM) in MS patients. The adjacent white matter, where the plate ends, was accepted as the peri-plaque area and the measurement was made. CP-NAWM was measured as the white matter area corresponding to the symmetry of the plaque in the opposite cerebral hemisphere. In MS patients, contrast retaining plaques considered active plaque, and non-contrast retaining plaques were considered as chronic plaques. FA measurements were made from active and chronic plaques. In the control group, FA measurements were made from normal white matter (NWM). After determining the location of the lesion in T2 or FLAIR-weighted sequence in MS patients, measurements were made manually using region of interest (ROI). The measurement we made from the MS patients included in our study is shown in **Figure 1**.

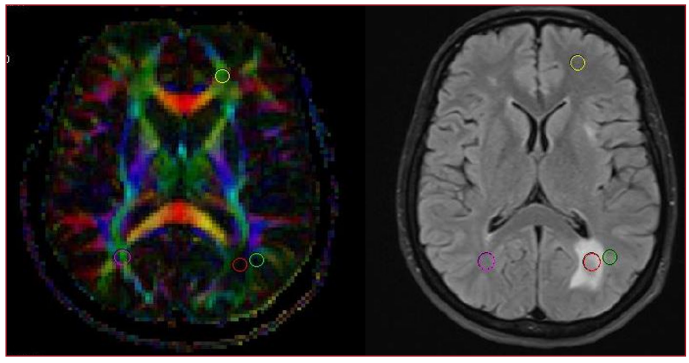


Figure 1: Demonstration of FA measurement in MS patients

A: Color FA map, B: Axial FLAIR images show the measurements we made using ROI. FA measurements from the plate adjacent to the left lateral ventricle (red ROI), periplaque area (green ROI), CP-NAWM area (pink ROI) and NAWM (yellow ROI) are shown

Since quantitative measurements will be made in DTI, plaques below 5 mm were not included in the study in order to avoid artifact and partial volume effects. In addition, if the white matter area that we will evaluate across the plate is not normal, no measurement was made from this area. Measurements made in MS patients were statistically compared among themselves and with the control group.

In MS patients, 158 chronic plaques (54.5%), 23 active plaques (7.9%), a total of 181 plaques (32%), 54 NAWM (9%), 171 peri plaques (30%), 150 CP-NAWM (27%) were evaluated. 56 NWM were evaluated in the control group.

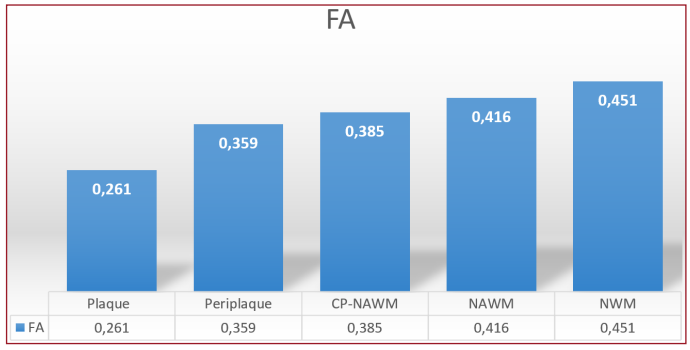
Our study was approved as a thesis project by the Ethics Committee of the Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee of Başkent University in 2012, with the decision of the ethics committee numbered KA13/43.

Statistical analysis

As descriptive statistics, mean ± standard deviation in numerical variables and number values in categorical variables are given. Kolmogorov Smirnov test was used to examine whether the numerical data were normally distributed. For the comparison of two independent groups in terms of numerical variables, the "significance test of the difference between the two means" was applied, for the comparison of more than two groups, "One-way Analysis of Variance (ANOVA) if the variances were homogeneous," and if the variances were not homogeneous, "Welch Analysis of Variance" was applied. Spearman rho correlation coefficient was used to examine the amount of correlation between variables. It was considered statistically significant when P<0.05. All analyzes were performed in IBM SPSS (Statistical Package for the Social Sciences) Statistics 21 program.

RESULTS

In MS patients, 158 chronic plaques (54.5%), 23 active plaques (7.9%), a total of 181 plaques (32%), 54 NAWM (9%), 171 peri plaques (30%), 150 CP-NAWM (27%) were evaluated. 56 NWM were evaluated in the control group. When plaque, peri plaque, CP-NAWM, NAWM and control group NWM FA were compared in MS patients; value of the plaque FA (0.261±0.113) was the lowest. Other FA values increased in the following order: peri plaque (0.359±0.115.), CP-NAWM (mean FA 0.385±0.120), NAWM (mean FA 0.416±0.082), and NWM (mean FA 0.451±0.098). The difference between the mean FA values of plaque, periplaque, CP-NAWM, NAWM and control group NWM in MS patients is shown graphically (**Graph 1**). In our study, the difference between plaque (p<0.001), peri-plaque (p<0.001), CP-NAWM (p<0.001), NAWM (p<0.001) and NWM FA (p<0.001) values was statistically significant (**Table 1**).



Graph 1: Graph of mean FA values measured in MS patients and control group

Table 1: FA values in different localizations of MS patients and statistical comparison of FA values measured among themselves and with the control group

	FA	± SD	P
Plaque	0,261	0,113	p<0.001
Peri-plaque	0,359	0,115	p<0.001
CP-NAWM	0,385	0,120	p<0.001
NAWM	0,416	0,082	p<0.001
NWM	0,451	0,098	p=0,047

NWM: Normal white matter, NAWM: Normal-appearing white matter, CP-NAWM Normal-appearing white matter opposite the plaque, p< 0.05 statistically significant

Although active plaque FA value was lower than chronic plaque, it was not statistically significant (p=0.165) (**Table 2**). While 21 of MS patients were clinically active, 34 were not clinically active. While there was active plaque in the MRI of 7 of the clinically active patients, no active plaque was detected in 14 of them. FA was measured from 44 chronic plaques of 14 clinically active patients whose active plaque was not detected by conventional MR imaging. While the FA value of 24 of 44 chronic plaques was lower than the mean FA value (FA value of 0.230), the FA value of 20 chronic plaques was found to be higher than the mean FA value. Based on this result, we cannot comment on the activity of MS disease by evaluating the chronic plaques of patients who are clinically active and could not detect active plaque in conventional MRI.

Table 2: Mean and p values of active and chronic plaque FA measurements in MS patients

	Active Plaque	Chronic Plaque	p
FA	0,230 ± 0,090	0,265 ± 0,115	0,165

FA: Fractional anisotropy, p< 0.05 statistically significant

In all MS patients, the starting point of the mesencephalon was determined and 3D tractography maps were made. It was evaluated whether the white matter pathways of the patients whose tractography maps were obtained were affected by MS disease. It has been shown that plaques traced along axonal pathways in MS patients cause interruption in axonal pathways (**Figure 2**). However, it has been shown that in some patients the plaques are not during the drawn tractography pathways and therefore do not cause a significant pathology in the axonal pathways.

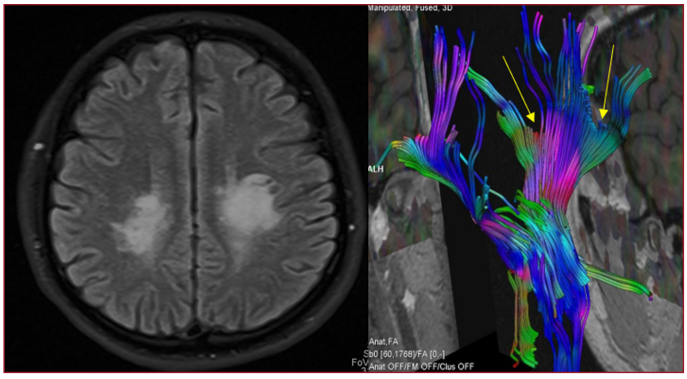


Figure 2: Demonstration of MS lesions by tractography

A: Axial FLAIR, B:3D tractography images of a 22-year-old male MS patient is shown. Large MS plaques observed in both periventricular white matter in the axial and sagittal FLAIR sequence have been shown to cause interruption of the axonal pathways in tractography images (yellow arrows)

DISCUSSION

Multiple Sclerosis (MS) is the most common chronic inflammatory, demyelinating disease of the central nervous system. It is a disease characterized by demyelinating plaques in the white matter.[1] Axonal injury in the NAWM is thought to be responsible for the pathology of MS disease, as well as demyelinating plaques.[3] Conventional MRI is the most commonly used imaging method in the diagnosis and follow-up of MS today. Although conventional MRI is very sensitive to show macroscopic lesions, it is insufficient to show hidden microscopic changes in NAWM. Inconsistency between the distribution of lesions and clinical findings in conventional MRI may be an indicator of this. DTI is an advanced MRI application that can focus on plaques and NAWM, which are thought to be responsible for MS pathology, with ROI analysis, and can evaluate tissue pathology quantitatively and objectively.[10]

In our study, when plaque, peri-plaque, NAWM, CP-NAWM and control group FA measurements were compared in MS patients; plaque FA was found to be lower than the others. Peri-plaque, CP-NAWM, NAWM and NWM FA measurements were also observed to increase in this order. Rachel E. Maia de Andrade.[11] measured plaque, peri-plaque, CP-NAWM, NAWM and NWM FA and plaque FA was the lowest; Peri-plaque, CP-NAWM, NAWM and NWM FA measurements were also found to increase in the same order. Alexande Guo et al.[12] obtained similar results in their study, but they did not evaluate CP-NAWM. In another study by Alexande Guo et al.[13], they showed that plaque FA was the lowest and peri-plaque and CP-NAWM measurements increased in this order, but they did not compare the results with the control group and NAWM. Sijens PE et al.[14] compared only plaque FA value with the control group and showed that plaque FA was lower than the control group NWM FA. Bing Hu et al.[15] compared plaque with NAWM and NWM FA values and obtained results similar to our study.

In our study, it was determined that the FA measurements obtained from the peri-plaque area, CP-NAWM and NAWM, which were normal in conventional MRI, were higher than the plaque but lower than the control group, and there was a statistically significant difference between them. Rachel E. Maia de Andrade.[11] and Alexande Guo et al. in two separate studies.[12,13] found that peri-plaque FA was higher than plaque FA and lower than the measurements made from white matter and the control group. In the literature, there are studies similar to our study showing that the NAWM FA value in MS patients is lower than the white matter of the control group and there is a statistical difference between them.[11,12,16-18]

In our study, the difference between FA values of plaque ($p<0.001$), peri-plaque ($p<0.001$), CP-NAWM ($p<0.001$), NAWM ($p=0.047$) and NWM ($p=0.047$) was found to be statistically significant. In the literature, Alexande Guo et al.[13] Rachel E. Maia de Andre et al.[11] Bing Hu et al.[15] and Sijens PE et al.[14] found similar findings.

The fact that the anisotropy at the plaque level was lower than in other localizations in our study indicates that plaques are mainly responsible for MS pathology. Detection of anisotropy in the peri-plaque area higher than plaque and lower than NAWM suggests that the peri-plaque area is affected, although not as much as plaque. There are many studies showing abnormalities in FA values of normal-appearing white matter in the peri-plaque area with Diffusion Tensor Imaging.[19-21] Therefore, FA is more sensitive than conventional MRI for the assessment of WM integrity in MS. Tievsk et al.[22] found a significant decrease in the ratio of N-acetylaspartate/creatine, which is considered as the marker of neuronal and axonal injury, in NAWM adjacent to the plaque in a different study they conducted with MR spectroscopy. This study supports the hypothesis that white matter that appears normal on conventional MRI with DTI is not normal. It also shows that the white matter area that appears normal on conventional MR is actually not normal and is affected.

When active and chronic plaque FA measurements are evaluated; although active plaque FA was observed to be lower than chronic plaque, no statistically significant difference was observed between active and chronic plaque FA ($p=0.165$) values. Filippi et al.[16], with 4728 chronic plaques and 128 active plaques, and Tievsk et al.[22] in another study, found the FA value in active plaque to be lower than in chronic plaque. However, unlike our study, they showed that

the difference between them was statistically significant. Lorenzo Testaverde et al.[23] in their study of 7 active plaques and 14 chronic plaques, they found the FA value of chronic plaque to be lower than that of active plaque, unlike our study and the literature. However, similar to the studies in the literature, they found the FA value of active and chronic plaque to be lower than NAWM and NWM, and they found a statistically significant difference between active, chronic plaque, NAWM and NWM FA values. The reason why the FA values between active and chronic plaques were not statistically significant in our study, unlike the literature, may be due to our small number of active plaque evaluations. However, DTI are not sufficient to distinguish between active and chronic plaques since there was no statistically significant difference between active plaque and chronic plaque FA values in our study.

Limitations

In our study, the normal-appearing white matter area opposite the plaque was evaluated. If this area is not normal in T2 signal, it was not included. In addition, since the ROI of small plates is limited to drawing, plates smaller than 8 voxels (78mm) were not included. The number of active plaques is less than chronic plaque; For this reason, it may cause inadequacy in statistical calculations.

CONCLUSION

In MS patients, abnormal findings were detected in FA values in plaque and all white matter areas. Progressive decrease in anisotropy from normal-appearing white matter to peri-plaque white matter and plaque level suggests myelin damage and white matter abnormalities extending beyond plaque. In addition, the decrease in anisotropy we detected in the white matter areas of MS patients compared to the control group indicates that the white matter that appears normal on T2 images in conventional MR is not actually normal but is affected by MS disease.

Unlike conventional MR, DTI provides more objective data by providing quantitative information about MS lesions and abnormalities in the white matter area. In addition, it gives information about the abnormalities in the white matter that appears normal on conventional MR and the areas other than the lesions observed in T2W, which gives an advantage in understanding MS pathologies. Based on these results, it was thought that DTI would provide more objective and quantitative information than conventional MR in the evaluation of disease burden in MS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved as a thesis project by the Ethics Committee of the Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee of Başkent University in 2012, with the decision of the ethics committee numbered KA13/43.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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