Diffusion Tensor Magnetic Resonance Imaging in Patients with Multiple Sclerosis and Its Relationship with Disability

Ş. TEMEL¹, H.D. KEKLIĞKOĞLU¹, G. VURAL¹, O. DENİZ¹, K. ERCAN²

¹Department of Neurology, ²Department of Radiology, Yıldırım Beyazıt University Atatürk Education and Research Hospital; Ankara, Turkey

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SUMMARY – Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. Diffusion tensor magnetic resonance imaging (DTI) can yield important information on the *in vivo* pathological processes affecting water diffusion. The aim of this study was to quantitatively define water diffusion in normal-appearing white matter (NAWM) distant from the plaque, in the plaque, and around the plaque, and to investigate the correlation of these changes with clinical disability. Conventional MRI and DTI scans were conducted in 30 patients with MS and 15 healthy individuals. Fractional anisotropy maps and visible diffusion coefficients were created and integrated with T2-weighted images. Regions of interest (ROIs) were placed on the plaques on the same side, white matter around the plaques and NAWM on the opposite side. Only the white matter of healthy individuals in the control group, and FA and ADC values were obtained for comparison. The highest FA and lowest ADC were detected in the control group at the periventricular region, cerebellar peduncle and at all ROIs irrespective of location. There was a significant difference in comparison to the control group at all ROIs in patients with MS ($p < 0.001$ for all comparisons). No significant correlation between diffusion parameters and expanded disability state scale (EDSS) scores was found in patients with MS. DTI may provide more accurate information on the damage due to the illness, compared to T2A sequences, but this damage may not be correlated with the clinical disability measured by EDSS score.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease that generally occurs in young adults and is more frequently seen in women¹. No prominent correlation exists between the number of lesions and the severity of the clinical picture² detected by magnetic resonance imaging (MRI) (that is commonly used in the diagnosis and follow-up of MS). The presence of a generalized disorder even in normal-appearing brain tissues and serious axonal injury regions were reported in recent histopathological studies in very early phases of the disease³. Although demyelination, axonal damage, gliosis and remyelination could be shown microscopically in the central nervous system of patients with MS, it is not

easy to detect these features *in vivo* by neuroimaging methods. T2-weighted (T2A) and T1-weighted (T1A) MRI sequences with gadolinium uptake provide evidence on white matter MS lesions with a high sensitivity, and are helpful in the diagnosis of MS⁴. Conventional MRI cannot demonstrate other histopathological features of MS apart from the relationship between inflammation and gadolinium uptake⁵. One of the major reasons for the weak correlation between conventional MRI and disability may be due to the inadequacy of conventional MRI in reflecting the pathology in MS^{6,7}.

Not only is MS a disease affecting the brain in a diffuse pattern, but there are also microscopic abnormalities in the normal-appearing white matter and tracts². The sensitivity of conventional MRI in detecting these microscopic

Figure 1 Determination of ROIs. A) T2A image. B) Plaque, the area around the plaque and the T2A image on which ROIs were placed on normal-appearing white matter (NAWM). C) Plaque, the area around the plaque and the FA map on which NAWM and ROIs are placed.

lesions is rather low. Non-conventional MRI techniques were recently developed to measure the pathological changes not detected with routine MRI sequences. Diffusion tensor imaging (DTI) is one of the newly developed MRI techniques with sufficient power to increase the sensitivity in detection of microstructural architectural changes in normal-appearing brain tissues⁸. DTI is an important imaging technique which can yield quantitative *in vivo* information and orientation of brain white matter tracts non-invasively.

The damage in the white matter, which appears normal with quantitative MRI techniques, may have an important clinical significance, as it contributes to the disability of patients with MS⁹. We aimed to investigate the relationship between the microstructural changes in normal-appearing white matter and disability, by measuring quantitative water diffusion changes in normal-appearing white matter using DTI in patients with MS.

Material and Methods

This study was approved by the Ethics Committee of our hospital and informed consent from all patients recruited was collected before participating in the study. A total of 30 patients (18 females and 12 males) who were being fol-

lowed-up with a diagnosis of MS at the time of the study and 15 healthy volunteers matched for age and sex were enrolled.

All patients underwent a detailed neurological examination and those diagnosed with MS according to McDonald's criteria, having a relapsing-remitting clinical course (RRMS) were included in this study^{4,10}. Conventional cranial MRI, DTI and cervical MRI examinations were done in all patients after a remission period of three months, and their functional capacities were evaluated with the Expanded Disability Status Scale (EDSS). The presence of a neurological disturbance of at least 24 hours duration was considered a new attack and these patients were followed-up; MRI and simultaneous EDSS evaluations were collected after three months of remission.

All MRI sequences of MS patients and the control group were obtained with a 1.5 T super conductive magnet (Philips Achieva) MRI device using an 8-16 channel standard headgear. The conventional cranial MRI examination included axial T1A, axial T2A, coronal T2A, axial FLAIR, sagittal FLAIR, and MRI sequences with MTC contrast. T2A sequence parameters were analyzed as FOV: 210×210, slice thickness: 5 mm, gap: 1 mm, TR: 5291 mS, TE: 110 mS. FLAIR sequence parameters were FOV: 210×210, slice thickness: 5 mm, gap: 1 mm, TR: + 1000 mS, TE: 120 mS. Diffusion-weighted

Figure 2 T2 (A) and DT MR images (B: FA map, C: ADC map) of a patient with MS.

images (DWI) sequences were: FOV: 210×210, slice thickness: 5 mm, gap: 1 mm, TR: 3142 mS, TE: 72 mS. Different images in six directions of $b = 1000 \text{ s/mm}^2$ and one $b = 9 \text{ s/mm}^2$ image were obtained for DWI. These seven DWIs were obtained for every section. DTIs were obtained from DWIs with 2/2.03/2 mm voxel dimensions, 2 mm slice thickness and 0 mm gaps. DTI images were integrated with T2A axial images. DTI data were transferred to the workstation and apparent diffusion coefficient (ADC) maps were created with fractional anisotropy (FA). Three separate regions of interest (ROI) were defined for each plaque to be examined. The first of these ROIs was selected to include the plaque that was seen in T2A images. The voxel dimensions, FA value, ADC value, fiber voxel dimensions, fiber FA value and fiber ADC values were calculated. The second ROIs were selected to be included in the normal-appearing area that completely surrounded the plaque in the T2A images. The second ROIs were around the plaque. These ROIs were very close to the plaques, and surrounded them for 360°. The voxel dimensions, FA value, ADC value, fiber voxel dimensions, fiber FA value and fiber ADC values were calculated again for the ROI around the plaque. To determine the ROI around the plaque, if the area surrounding the plaque was a grey matter region, cerebrospinal fluid (CSF) or a white matter area

which did not appear normal, these areas were skipped, and the required calculations were made for this area. The third ROI was determined in a normal-appearing white matter area away from the plaque. These regions were matched with the related plaque, and were selected on the opposite hemisphere white matter from the same structure. A ROI having the same voxel dimensions as the plaque selected for this area and the voxel dimensions, FA value, ADC value, fiber voxel dimensions, fiber FA value and fiber ADC value were calculated in this ROI. If this area, selected from the opposite hemisphere and matched with the plaque, was seen to have abnormal signal intensity in T2A images, then another ROI area very close to this one but without signal abnormalities in T2A images was determined. The location of this determined plaque and normal-appearing white matter ROIs were classified according to their location in one of the following regions: periventricular white matter, cerebellum, brain stem, cerebellar peduncle, and subcortical white matter. In the control group, ROIs with similar plaque locations and similar voxel dimensions as the patient population were determined and their voxel dimensions, FA value, ADC value, fiber voxel dimensions, fiber FA value and fiber ADC values were determined. Figure 1 shows how these ROIs were determined.

Figure 3 FA and ADC maps of a healthy individual from the control group.

Table 1 Mean FA, ADC, fiber FA, fiber ADC, voxel count and p values of the ROIs from the periventricular region in the patient and control groups.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.370 ± 0.120	0.500 ± 0.100	<0.001
Mean ADC	1.080 ± 0.075	0.780 ± 0.0800	<0.001
Number of voxels	13 ± 8.4	14 ± 6.9	0.908
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.430 ± 0.080	0.500 ± 0.100	<0.001
Mean ADC	0.910 ± 0.110	0.780 ± 0.0800	<0.001
Number of voxels	25 ± 11.3	14 ± 6.9	<0.001
<i>NAWM/Control group ROI</i>			
Mean FA	0.460 ± 0.100	0.500 ± 0.100	0.014
Mean ADC	0.850 ± 0.156	0.780 ± 0.0800	<0.001
Number of voxels	13 ± 8.2	14 ± 6.9	0.998
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.510 ± 0.07	0.560 ± 0.04	<0.001
Mean ADC	0.940 ± 0.041	0.780 ± 0.0800	<0.001
Number of voxels	167 ± 134	271 ± 206	0.001
<i>NAWM fiber/Control group ROI fiber</i>			
Mean FA	0.540 ± 0.067	0.560 ± 0.04	0.015
Mean ADC	0.860 ± 0.128	0.780 ± 0.0800	<0.001
Number of voxels	143 ± 135	271 ± 206	0.001

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

Table 2 Mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the cerebellums of the patient and control groups.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.413 ± 0.125	0.281 ± 0.022	0.021
Mean ADC	0.826 ± 0.071	0.705 ± 0.028	0.021
Number of voxels	16 ± 7.9	17 ± 7.6	0.882
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.518 ± 0.097	0.281 ± 0.022	0.021
Mean ADC	0.751 ± 0.048	0.705 ± 0.028	0.248
Number of voxels	29 ± 12.7	17 ± 7.6	0.144
<i>NAWM/Control group ROI</i>			
Mean FA	0.666 ± 0.112	0.281 ± 0.022	0.021
Mean ADC	0.750 ± 0.053	0.705 ± 0.028	0.191
Number of voxels	16.5 ± 7.7	17 ± 7.6	0.882
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.507 ± 0.086	0.312 ± 0.044	0.021
Mean ADC	0.981 ± 0.125	0.752 ± 0.047	0.021
Number of voxels	125 ± 88	43.5 ± 25.9	0.248
<i>NAWM fiber/Control group ROI fiber</i>			
Mean FA	0.617 ± 0.062	0.312 ± 0.044	0.021
Mean ADC	0.841 ± 0.069	0.752 ± 0.047	0.083
Number of voxels	205.5 ± 95	43.5 ± 25.9	0.083

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

In the comparison of values calculated from patients and the control group, the location of the ROIs was determined and comparisons were made between ROIs of similar dimensions on the same areas. In addition, T2 spinal images of every patient were obtained. The evaluation was not done determining the ROIs individually, but rather whether a lesion was “present” or “not present”.

These radiological evaluations were done by a neurologist and a radiologist blinded in terms of the clinical findings and laboratory tests of patients.

The statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS) for Windows version 16.0 software. Shapiro Wilks test was used to determine the distribution of variable groups and non-parametric statistical methods were used for variables showing skewed distribution, whereas parametric statistical methods were used for normally distributed variables. Cross-table

analyses were preferred for the comparison of variables (chi square and Fisher's Exact Test). Pearson test was used to seek correlations between variables. $p = 0.05$ was considered the limit of statistical significance.

Results

Eighteen of the patients were females (60%) and 12 were males (40%), while nine of the healthy controls were females (60%) and six were males (40%). There were no significant differences between the patient and control groups' age and gender distributions.

The EDSS scores of the MS patients varied between 0.0 and 7.5. Spinal involvement was present in 13 out of 18 female patients (72.2%), while eight out of 12 male patients had spinal involvement (66.6%). Spinal involvement was more prevalent in women than men but the difference was not significant ($p = 1$). T2

Table 3 Mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the brain stems of the patient and control groups.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.536 ± 0.144	0.606 ± 0.076	0.142
Mean ADC	0.817 ± 0.176	0.787 ± 0.054	0.845
Number of voxels	9 ± 3.8	11 ± 4.1	0.374
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.565 ± 0.090	0.606 ± 0.076	0.025
Mean ADC	0.873 ± 0.164	0.787 ± 0.054	0.283
Number of voxels	16 ± 11.8	11 ± 4.1	0.106
<i>NAWM/Control group ROI</i>			
Mean FA	0.512 ± 0.075	0.606 ± 0.076	0.064
Mean ADC	0.830 ± 0.148	0.787 ± 0.054	0.434
Number of voxels	8.5 ± 3.4	11 ± 4.1	0.324
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.586 ± 0.063	0.614 ± 0.0194	0.143
Mean ADC	0.820 ± 0.229	0.771 ± 0.028	0.380
Number of voxels	77.5 ± 99	288 ± 69	0.003
<i>NAWM fiber/Control group related ROI fiber</i>			
Mean FA	0.596 ± 0.072	0.614 ± 0.0194	0.283
Mean ADC	0.954 ± 0.092	0.771 ± 0.028	0.079
Number of voxels	171 ± 121	288 ± 69	0.019

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

and DT MR images and FA and ADC maps of a patient with MS are shown in Figure 2A-C. The FA and ADC maps of a healthy individual from the control group are shown in Figure 3. The mean FA, ADC, fiber FA, fiber ADC, voxel count and p values of the ROIs from the periventricular region in the patient and control group are listed in Table 1. An analysis of Table 2 shows that the mean FA increases and mean ADC decreases as the distance from the plaque increases. In addition, the highest mean FA and lowest mean ADC are seen in the control group. The mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the cerebellums of the patient and control group are shown in Table 2. The mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the brain stems of the patient and control groups are shown in Table 3. The mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the cerebellar peduncles of the patient and control groups are shown in Table 4. The mean FA,

mean ADC, mean fiber FA, mean fiber ADC, mean number of voxels and p values of ROIs in the subcortical white matter of the patient and control groups are shown in Table 5. The mean plaque FA, plaque ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the subcortical white matter of the patient and control groups are shown in Table 5. The mean FA, mean ADC, area around the plaque FA, area around the plaque ADC, NAWM, FA, NAWM ADC, plaque fiber FA and plaque fiber ADC values and mean number of voxels of ROIs of the patients and healthy individuals are shown in Tables 1-5. The mean FA, mean ADC, mean fiber FA, mean fiber ADC, mean voxel numbers and p values of all ROIs of the patient group and healthy individuals, independent of location differences are shown in Table 6. Table 7 shows that the mean FA increases and the mean ADC decreases as the distance from the plaque increases. In addition, the highest mean FA and the lowest mean ADC are seen in the control group. The correlation between

Table 4 Mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the cerebellar peduncles of the patient and control groups.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.470 ± 0.12	0.620 ± 0.08	0.002
Mean ADC	0.820 ± 0.112	0.730 ± 0.053	0.021
Number of voxels	10.08 ± 5.82	11.42 ± 5.65	0.505
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.530 ± 0.12	0.620 ± 0.08	0.053
Mean ADC	0.790 ± 0.115	0.730 ± 0.053	0.061
Number of voxels	20 ± 9	11.42 ± 5.65	0.014
<i>NAWM/Control group ROI</i>			
Mean FA	0.560 ± 0.109	0.620 ± 0.08	0.184
Mean ADC	0.750 ± 0.108	0.730 ± 0.053	1.000
Number of voxels	11.25 ± 5.78	11.42 ± 5.65	0.908
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.570 ± 0.08	0.600 ± 0.037	0.126
Mean ADC	0.800 ± 0.138	0.760 ± 0.062	0.260
Number of voxels	138.83 ± 106.77	204.33 ± 78.69	0.083
<i>NAWM fiber/Control group ROI fiber</i>			
Mean FA	0.580 ± 0.050	0.600 ± 0.37	0.299
Mean ADC	0.780 ± 0.075	0.760 ± 0.062	0.402
Number of voxels	121.58 ± 79.29	204.33 ± 78.69	0.038

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

plaque mean FA, plaque mean ADC, plaque mean fiber FA, plaque mean fiber ADC values, without regard to location is shown in Table 7.

The correlation between the mean FA, mean ADC, mean fiber FA, mean fiber ADC values of NAWM are shown in Table 8. The following conclusions may be drawn from Table 8: 1) A significant positive correlation between mean plaque FA and mean plaque fiber FA ($r = 0.647$) and a significant negative correlation between mean plaque FA and other parameters; 2) A significant positive correlation between mean plaque ADC and mean plaque fiber ADC ($r = 0.548$); 3) A significant negative correlation between mean plaque fiber FA and mean plaque fiber ADC ($r = -0.508$).

The correlations between plaque mean FA, plaque mean ADC, plaque mean fiber FA, plaque mean fiber ADC, NAWM mean FA, NAWM mean ADC, NAWM mean fiber FA and NAWM mean fiber ADC and EDSS scores are shown in Table 9. No significant correlation was present between these parameters and EDSS

score. The following conclusions may be drawn from Table 9: 1) There was a significant negative correlation between mean NAWM ADC and mean NAWM FA and NAWM mean fiber FA; 2) There was a significant positive correlation between mean NAWM FA and NAWM mean fiber FA, whereas there was a significant negative correlation between NAWM mean FA and NAWM mean ADC; 3) There was a significant negative correlation between NAWM mean fiber ADC and NAWM mean FA and NAWM mean fiber FA, whereas there was a significant positive correlation between NAWM mean fiber ADC and NAWM mean ADC.

Discussion

Our understanding of MS has increased considerably since MRI became available. Although it has certain limitations, this tool has become indispensable in the diagnosis of the disease and follow-up of its activity, along with

Table 5 Mean FA, ADC, fiber FA, fiber ADC, number of voxels and p values of ROIs in the subcortical white matter of the patient and control groups.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.380 ± 0.11	0.460 ± 0.08	<0.001
Mean ADC	1.110 ± 0.02	0.800 ± 0.055	<0.001
Number of voxels	12.25 ± 5.83	12.10 ± 4.88	0.888
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.440 ± 0.09	0.460 ± 9.08	0.191
Mean ADC	0.910 ± 0.150	0.800 ± 0.055	<0.001
Number of voxels	25 ± 7	12.10 ± 4.88	<0.001
<i>NAWM/Control group ROI</i>			
Mean FA	0.500 ± 0.10	0.460 ± 0.08	0.074
Mean ADC	0.800 ± 0.099	0.800 ± 0.055	0.310
Number of voxels	11 ± 6.5	12.10 ± 4.88	0.963
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.490 ± 0.07	0.480 ± 0.08	0.456
Mean ADC	0.920 ± 0.115	0.800 ± 0.055	<0.001
Number of voxels	143 ± 115	12.10 ± 4.88	0.779
<i>NAWM fiber/Control group related ROI fiber</i>			
Mean FA	0.510 ± 0.08	0.480 ± 0.04	0.006
Mean ADC	0.850 ± 0.113	0.800 ± 0.055	<0.001
Number of voxels	90 ± 96	12.10 ± 4.88	0.035

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

MR diagnostic criteria^{11,12}. There is no prominent contrast between the white matter, grey matter and CSF. In addition, different signals, especially those originating from the grey matter-white matter and white matter-CSF junctions reach a voxel at these locations. This conceals the lesions in nearby regions or at least makes them seem less prominent. Imaging techniques with different “operating sets” are required to delineate lesions in different areas. For example, no lesion can be detected in T1-weighted images unless a “black hole” develops. Although T2A is the golden standard in detecting lesions in the periventricular and other white matter areas, this sequence cannot disclose lesions in the CSF-white matter junctions and infratentorial region. Additionally, FLAIR and proton-weighted MRI techniques are required to visualize lesions in these areas. The grey and white matter lesion burden of MS patients is determined with the help of all of these non-conventional techniques¹³⁻¹⁵.

A correlation between the lesion burden de-

termined with MRI in patients with MS and disability has been investigated in many studies and most have reported no such correlation^{16,17}. All these data suggest that disability is not dependent solely on the white matter and grey matter lesion burden shown with conventional MRI techniques. Diffuse-global damage was shown in NAWM of the brains of patients with MS in post-mortem studies¹⁸. Acute generalized axonal damage was reported, along with demyelination in patients with MS in both chronic and early phases^{19,20}. DTI may be useful in detecting these lesions as a novel MRI technique²¹⁻²⁵.

Voxel-based morphometry (VBM) is recommended as a useful method of defining the pathological changes that occur in the brain²⁶. However, VBM is insufficient in detecting changes in white matter, primarily because of the weak correlation between white matter T1 signal intensity and white matter integrity. In contrast to this approach that depends on T1A images, DTI yields more detailed information

Table 6 Mean FA, mean ADC, mean fiber FA, mean fiber ADC, mean voxel numbers and p values of all ROIs of the patient and control groups independent of location differences.

	<i>Patient group</i>	<i>Control group</i>	<i>P value</i>
<i>Plaque/Control group ROI</i>			
Mean FA	0.400 ± 0.13	0.510 ± 0.110	<0.001
Mean ADC	1.080 ± 0.26	0.790 ± 0.09	<0.001
Number of voxels	13.13 ± 7.22	13.11 ± 6.1	0.974
<i>Area around the plaque/Control group ROI</i>			
Mean FA	0.460 ± 0.100	0.510 ± 0.110	<0.001
Mean ADC	0.910 ± 0.14	0.790 ± 0.09	<0.001
Number of voxels	25 ± 11.3	13.11 ± 6.1	<0.001
<i>NAWM/Control group ROI</i>			
Mean FA	0.465 ± 0.100	0.510 ± 0.110	<0.001
Mean ADC	0.850 ± 0.156	0.790 ± 0.09	<0.001
Number of voxels	13 ± 8.2	14 ± 6.9	0.998
<i>Plaque fiber/Control group ROI fiber</i>			
Mean FA	0.510 ± 0.08	0.530 ± 0.08	0.024
Mean ADC	0.940 ± 0.041	0.810 ± 0.07	<0.001
Number of voxels	167 ± 134	271 ± 206	0.001
<i>NAWM fiber/Control group ROI fiber</i>			
Mean FA	0.540 ± 0.08	0.530 ± 0.08	0.002
Mean ADC	0.880 ± 0.12	0.810 ± 0.07	<0.001
Number of voxels	145 ± 117	271 ± 206	0.001

ROI: region of interest; FA: fractional anisotropy; ADC: apparent diffusion coefficient.

on the white matter composition, by allowing identification of *in vivo* fiber tracts. For this reason, DTI started to be used in the investigation of neurodegenerative diseases. The fast changes in DTI technique have opened new pathways in the examination of the white matter in live brain tissues and aroused interest in this technique²⁷⁻²⁹.

DTI is a technique which shows the direction of the restricted movement of water molecules in tissues and expresses this quantitatively. Free movement of water molecules is called "brownian movement" and the mathematical counterpart of movement in different directions is called "tensor". Theoretically, water displaces equally in all directions in an environment without macromolecules, i.e. diffusion is isotropic. The movement of water is assumed to be in this manner with the DWI technique. On the other hand, the movement of water molecules in some directions in *in vivo* conditions is limited by macromolecules and cellular structure and diffusion becomes unisotropic.

Some structures in the CSF contain a large amount of fat blocking the diffusion of water molecules, thus causing an increase in 'visualization' of pathways of white matter in DTI, enabling us to obtain non-invasive quantitative information in *in vivo* conditions. Isotropic and unisotropic data are determined by ADC and FA values. ADC represents the amount of unisotropy in tissues; FA represents the ratio of the unisotropic portion of diffusion in tissues to all diffusion^{30,31}. DTI detects microstructural changes in white matter by measurement of molecular diffusion orientations and thus enables examination of the entire brain. Well-organized white matter tracts possess high FA because diffusion is considerably limited by the cellular organization of the tracts. When white matter is damaged, FA decreases due to decreased unisotropic diffusion³²⁻³⁴.

The first diffusion imaging study in patients with MS was published by Larsson et al.³⁵ and many studies have been done since then³⁶⁻³⁸. In all these trials, an increase in ADC was shown

Table 7 Correlations between plaque mean FA, plaque mean ADC, plaque mean fiber FA and plaque mean fiber ADC.

		Plaque mean ADC	Plaque mean fiber FA	Plaque mean fiber ADC
Plaque mean FA	R	−0.763	0.647	−0.529
	P	<0.001	<0.001	<0.001
Plaque mean ADC	R	1	−0.397	0.548
	p		<0.001	<0.001
Plaque mean fiber FA	r	−0.397	1	−0.508
	p	<0.001		<0.001

FA: fractional anisotropy; ADC: apparent diffusion coefficient.

Table 8 Correlation between mean FA, mean ADC, mean fiber FA, mean fiber ADC values of NAWM.

		NAWM mean FA	NAWM mean ADC	NAWM mean fiber FA
NAWM mean ADC	r	−0.558	1	−0.424
	p	<0.001		<0.001
NAWM mean fiber FA	r	−0.626	−0.424	1
	p	<0.001	<0.001	
NAWM mean fiber ADC	r	−0.355	0.673	−0.436
	p	<0.001	<0.001	<0.001

FA: fractional anisotropy; ADC: apparent diffusion coefficient; NAWM: normal-appearing white matter.

Table 9 Correlation analysis between EDSS scores and other parameters:

	<i>r</i> value	<i>P</i> value
Plaque mean FA	0.007	0.97
Plaque mean ADC	0.219	0.244
Plaque mean fiber FA	−0.001	0.996
Plaque mean fiber ADC	0.039	0.839
NAWM mean FA	−0.291	0.118
NAWM mean ADC	0.178	0.347
NAWM mean fiber FA	−0.216	0.253
NAWM mean fiber ADC	0.126	0.507

EDSS: expanded disability state scale; FA: fractional anisotropy; ADC: apparent diffusion coefficient; NAWM: normal-appearing white matter.

in lesions of MS patients in comparison with the white matter of healthy controls. In fact, these increased ADC values were found in experimental autoimmune encephalomyelitis lesions, an animal model of MS. When compared with the ADC values determined in lesions of patients with MS, the highest ADC values were reported to be in T1 hypointense lesions, which do not present contrast enhancement, and which are referred as “black holes”. The tissue destruction occurring in these lesions for a long time is believed to permit movement of water, and limit diffusion. Consequently, DWI

techniques may yield information on the severity of tissue damage in patients with MS and may help in determination of clinical disability^{8,29,33,37-39}. The contemporary approach is to calculate the diffusion tensor, which is a mathematical matrix to better define the movements of all water molecules^{2,38}. Various mathematical combinations of the three vectors used to calculate the tensor allow derivation of quantitative diffusion indicators, which are independent of factors such as patient position, and which do not change rotationally. The principle advantage of DTI use in clinical studies is that it is a

technique that measures diffusion characteristics of human brain objectively, quantitatively and reliably³⁸.

We examined periventricular and subcortical white matter in a similar number of supratentorial regions, infratentorial regions and brain stem, cerebellum and cerebellar peduncle with DTI of the patient and control groups. According to the findings of our study, the mean FA of patients in plaque, area around the plaque and NAWM areas in the periventricular region was significantly lower than the mean FA of ROIs of the control group. In addition, the mean ADCs of patients in all plaques, area around the plaque and NAWM areas were significantly higher than the mean ADCs of the control groups ROIs. In the subcortical white matter, the mean FA of the patient group was highest in the NAWM and lowest in the plaque, the mean ADC was highest in the plaque and lowest in the NAWM, as expected. But the calculated mean FA value of the control group was higher in subcortical white matter than the plaque and area around the plaque, differently from the periventricular white matter. It was lower than NAWM, and the mean ADC values were lower than those at the plaque and area around the plaque, differently from the periventricular white matter that was higher than NAWM. The differences between the subcortical white matter plaque mean FA, plaque mean ADC, mean ADC in the area around the plaque were significant. We obtained different results from ROIs in the infratentorial region, cerebellar peduncle, brain stem and cerebellum. The mean FA of the control group in areas examined in the cerebellum were lower than the plaque, area around the plaque and NAWM mean FA of the patient group. On the other hand, when the mean ADC value of cerebellum was examined, the highest ADC value was found in the plaque and the lowest ADC in the area around the plaque, and the mean ADC value of the control group was lower than all mean ADC values of the patient group. Only four of our patients had one plaque located in the cerebellum. These paradoxical findings may be due to the small number of regions examined, selection of ROIs in the control group not exactly symmetrical with the patient group, and inhomogeneous distribution of white matter fibers in the cerebellum. In the ROIs in the brain stem, the mean FA value of the patient group was lower than the controls, and the mean ADC values were higher but these differences were significant only at the areas

around the plaque. An interesting finding from the ROIs we examined at the brain stem was the mean FA at the ROIs in NAWM which was found to be lower than the mean FA at the plaque. These findings suggest that the inflammatory response may indicate differences according to regions. The findings from ROIs examined at the cerebellar peduncle were exactly in accordance with the findings of periventricular area ROIs. The mean FA of plaque, area around the plaque and NAWM of the patient group was lower, and mean ADC was higher than the controls; but this difference was only significant for the comparison of plaque with the control group. When all ROIs were compared, independent of location differences, the findings were completely in accordance with the periventricular location findings. The lowest mean FA was found at the plaque, while the highest mean FA was in the control group, the highest mean ADC was at the plaque, and the lowest mean ADC was in the control group, and all comparisons were significant.

In conclusion, in all ROIs examined, without regard to location, the mean FA value at the periventricular white matter and cerebellar peduncle was lowest at the plaque, followed by the area around the plaque, NAWM and control group ROIs. The mean ADC in these three regions was highest at the plaque, followed by the area around the plaque, NAWM and control group ROIs. In addition, when all locations of the patient group were examined separately, the mean FA showed an increase and mean ADC showed a decrease as the distance from the plaque increased in all locations except the brain stem and the mean values calculated without regard to location.

After MRI was introduced and started to be used in the diagnosis of MS, no correlation was observed between the lesion burden shown especially in T2A sequences and clinical disability. This has directed investigators to histological studies of MS, which was formerly considered solely a demyelinating disease. These studies suggested that long-term disability and axonal damage may be correlated⁴⁰. With the help of these histological studies, it was found that the disease was not present only at the lesions seen at MRI, but microscopic changes are also present in NAWM away from the lesions, and that these affect the brain globally. Some groups found a significant decrease in N-acetylaspartate (NAA) levels and the NAA-creatine ratio, which is a marker of axonal and neuronal damage in NAWM in patients with MS^{2,40}. His-

tological studies reported axonal loss in NAWM^{41,42}. A recent study reported acute axonal loss in the areas around the demyelinating plaque. Some other studies also reported the presence of myelin degradation products around the reactive chronic plaques and acute plaques⁴³⁻⁴⁵. Thus, the disease process in MS is present not only in the plaque that is seen in conventional MRI, but also in NAWM areas^{27,43,46}. With the exception of some locations, our findings are in accordance with these histopathological studies. If it becomes possible to measure myelin and axon degradation *in vivo* with imaging techniques alone without histological examinations, it may also be an important marker of therapeutic response to therapeutic agents. For this reason, the DTI technique described above has become an important focus of interest. Although it is not in routine use, it has started to be used for many neurodegenerative diseases including MS.

Many investigators have used DTI to detect the pathological changes in MS and search for a correlation between these changes and disability^{37,43-45,47,48}. Guo et al. found that the FA values in the white matter were lowest in the plaque, higher than the plaque in the white matter around the plaque, and still higher in NAWM in comparison to the other two areas. The difference between the mean ROI FA in the control group and mean FA at both NAWM and the plaque was significant, while the highest ADC measured at the plaque was followed by the ADC around the plaque, NAWM ADC and control group ADC. In addition, measurements of anisotropy were claimed to be more sensitive than diffuse measurements in shedding light on the pathological process in MS^{8,43}. MS plaques may either show enlargement in time concentrically around the perivenular focus, or may show regression. Although the areas where the regression of MS plaques appears to be normal, the ADC values of the areas around the plaque may be higher than NAWM ADC values, as axonal damage and myelin loss continue histologically in these areas⁴³. These investigators also reported a strong correlation between MRI spectroscopy of anisotropy measurements in regions away from the plaque borders with findings obtained from histological studies. Our results also show a progressive increase in the mean FA with increasing distance from the plaque, in a concentric manner around the venules, and a progressive decrease in mean ADC. In the same study, the FA in the area around the plaque was significantly

lower than the control group white matter and NAWM, as in our study. The FA values at the plaque, area around the plaque and NAWM were significantly lower than those in controls, as in our study. This indicates that the white matter damage around the plaque is not as severe as the damage inside the plaque. The diffusion abnormalities at the focal lesions are more prominent than those at the NAWM, but the superiority of this method is that it can also show the damage at the NAWM. The mean FA of the plaque was 0.400 in patients with MS in a study by Thievsky et al.⁵¹, while it was 0.440 in a study by Bammer et al.³¹, and 0.540 by Werring et al.²⁷. The mean plaque FA found in the present study is in accordance with the results of Thievsky et al.⁴⁸, Bammer et al.³¹ and Werring et al.²⁷. The FA values of infratentorial and supratentorial NAWM ROIs of patients with MS were reported to be lower than the controls by Ciccarelli et al.³⁷.

Although it is not known which pathological processes change DTI parameters in MS, it is thought to be less related to inflammation and demyelination. Pathological changes detected in MS lesions such as edema, demyelination, cellular infiltration, and axonal loss are also found in NAWM. But myelin and axonal loss are thought to be more related to DTI changes⁸. The mechanism causing ADC increase in DTI is a loss of structural barriers, while the mechanism causing FA decrease is the change in movements of water molecules, with a change in the physiological organization of the structural barriers. Reactive gliosis may also contribute to the decrease in FA⁵⁰. Fiber, which is one of the DTI parameters, may be obtained in tractography. Some recent studies showed that lesions may cause interruption in white matter fiber tracts, similar to brain tumors^{8,51,52}. Fiber tractography may play a potential role in measuring the amount of axon loss and demyelination in NAWM and different lesion types. The damage in the white matter tracts may be directly shown by tractography⁸. The mean fiber ADC values we measured in our study were highest in the plaque, followed by the NAWM, except the cerebellum ROIs, in which very few regions were examined, and these values were lowest in the control group. The mean fiber FA values were lowest in the plaque, followed by the NAWM, except the cerebellum and subcortical areas, and highest in the control group. Statistical significance was detected in both mean FA and mean ADC values in the comparison of plaque and NAWM areas of the

periventricular region of patients and controls. The subcortical white matter NAWM mean fiber ADC value was statistically significantly higher than that in the control group.

The correlation analysis showed a significant correlation between mean plaque FA and mean plaque fiber FA, whereas there was a significant negative correlation between mean plaque FA and mean plaque ADC and mean plaque fiber ADC. There was a positive correlation between mean plaque ADC and mean plaque fiber ADC and a significant negative correlation between mean plaque fiber FA and mean plaque fiber ADC.

In the NAWM correlation analysis, a weak negative correlation was found between mean NAWM ADC, mean NAWM FA and mean NAWM fiber FA. There was a significant positive correlation between mean NAWM FA and mean NAWM fiber FA, whereas there was a significant negative correlation between mean NAWM FA and mean NAWM ADC. A weak negative correlation between mean NAWM fiber ADC and mean NAWM FA and mean NAWM fiber FA was found, and a significant positive correlation between mean NAWM fiber ADC and mean NAWM ADC. This analysis suggests that separate DTI measurements of fiber FA and ADC may yield more accurate results.

Both mental and physical disabilities of different grades of severity from mild to severe develop in patients with MS in time. It is still not clearly known why disabilities of different severity develop in a similar time frame. The disability of MS is probably due to the changes in the plaque, area around the plaque and NAWM, loss of volume, and cerebral atrophy. We detected changes not only at the plaque, but also in the area around the plaque and NAWM with DTI. These changes may be indirect signs of underlying histopathological processes. It is hard to comment on the correlation between these findings and the functional changes as it has not been possible to correlate only DTI findings, i.e. FA and ADC values, with disability.

Although many tests are used to detect the disability, EDSS is the most frequently used but presents some limitations⁵³. Although more than 45% of patients considered to have benign

MS have cognitive disability, the EDSS score of these patients is 3.0 or lower. This shows that EDSS scoring may underestimate some functional effects of the disease^{54,55}. Another limitation is the ignorance of upper extremity functions. A few spinal lesions in appropriate locations may cause paraplegia in a patient with MS, which is equal to seven points on the EDSS score even without cerebral lesions. These limitations may have caused conflicting findings on the correlations between plaque, area around the plaque and NAWM changes and disability.

A study by Filippi et al.⁵⁴ in 2001 found a mild correlation between the plaque and NAWM mean FA and mean ADC values and the EDSS score of patients with SPMS, whereas no correlation was detected with the EDSS score in patients with RRMS.

Ciccarelli et al.³⁷ found a correlation between FA value at the cerebral peduncle and EDSS and pyramidal function scores in all patients with MS. This correlation was stronger in patients with RRMS in comparison with other subtypes.

We did not find a correlation between diffusion parameters and EDSS scores. Although there was a statistically significant difference in many DTI parameters between patients and controls, the lack of a correlation between these and EDSS may be due to the small sample size and presence of mild clinical disability in our patients. On the other hand, we do not know how much disability may be caused by the changes we detected with DTI in the plaque, area around the plaque and NAWM. Further, EDSS may not determine clinical disability accurately because of its own limitations in evaluating disability. This suggests that other scales may be needed to assess the functional capacities of MS patients.

In conclusion, we detected changes not only in the plaque itself, but also in the area around the plaque and NAWM using the DTI technique, but these changes were not correlated with EDSS scores. Further studies and new tests of disability are needed to understand the meaning of changes detected by DTI in the plaque, area around the plaque, and NAWM, and their correlation with disability.

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Hava Donmez Kekliğkoğlu, MD
 Yıldırım Beyazıt University Ataturk E.
 and R. Hospital Ankara/Turkey
 Ataturk E. and R. Hospital, Neurology
 Department Bilkent-Ankara/Turkey
 Tel.: 090 312 2912525/4111
 Fax: 090 312 3118054
 E-mail: havadonmez@hotmail.com