

Apparent Diffusion Coefficient Variabilities of the Optic Nerve in Multiple Sclerosis: Optic Nerve Head and Intraorbital Segment

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ABSTRACT

To investigate the diffusion alterations in the optic nerve head/intraorbital segment in Multiple sclerosis (MS) patients (with or without a history of optic neuritis) in comparison with healthy controls.

MS group consisted of 57 patients who had previously been diagnosed with MS. A total of 234 eyes which consisted of 114 eyes of the MS patients and 120 eyes of the healthy controls, were investigated. In 16 of the MS patients had the history of optic neuritis in one eye. The control group was selected from healthy subjects who were matched with MS patients group in terms of gender and age. Echo planar imaging (EPI) sequence was benefitted to attain diffusion-weighted images (DWI). The optic nerve head/intraorbital segment apparent diffusion-coefficient (ADC) values of two groups were compared.

The difference between the optic nerve head/intra-orbital segment ADC values of control group and MS patients was found statistically considerable ($P=0.009$, $P=0.006$, respectively). The difference between the optic nerve head/intra-orbital segment ADC values of MS patients without optic neuritis and control group was also found statistically considerable ($P=0.016$, $P=0.026$, respectively). It was found that there is a positive correlation between the ADC values and duration of the disease in MS patients ($R=0.485/0.428$, $P<0.01$).

The ADC values of the optic nerve head/intraorbital segment measured by ocular DWI may have potential for MS patients in the future and this method deserves additional validation in the disease staging and more work to predict patients at risk of optic neuritis.

Key Words: Multiple sclerosis, optic nerve, magnetic resonance imaging, diffusion-weighted imaging

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease. This disease has some effects on the central nervous system (1-4). Demyelination and iron-related abnormalities are the accepted underlying pathological mechanism (5, 6). Impaired vision is one of the most prevalent symptoms of MS, and the visual system can be affected in all anatomical sites. Of these sites, the optic nerve is the best described, since inflammatory demyelinating optic neuritis may be the initial presenting feature in patients with MS (7,8).

In order to diagnose optic neuritis in patients with MS, conventional magnetic resonance imaging (MRI) techniques have been benefitted (2, 9-12). Diffusion-weighted imaging (DWI) is a kind of MRI techniques. This technique is sensitive to the movement of water molecules (13).

DWI is a method developed based on the randomly selected movement of water molecules in the tissue, and therefore can be used to examine the structural properties of tissues. Apparent diffusion coefficient (ADC) values are derived from DWI and give significant data about the textures. The ADC value which is calculated from DWI, is a quantitative parameter. By drawing the region of interest (ROI), it is possible to calculate the ADC values of different tissues on the map (14, 15). DWI measurements can measure the amount of diffusion in the optic nerve, evaluate damage to axons, and predict visual results (13, 16-18).

There are many studies evaluating the optic nerve DWI on MS and optic neuritis (7-9, 12, 13, 16, 19-23). In this study, we aimed to investigate the optic nerve DWI on MS and optic neuritis, with a different perspective, by examining the diffusion differentiations in the optic nerve

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Fig. 1. 48-year-old female MS patient, The optic nerve head ADC measurement from the area including optic nerve 3 mm behind the globe

head/intraorbital segment in MS patients (with or without a history of optic neuritis) in comparison with healthy controls.

Materials and methods

Participants: This study was carried out with regarding to the Helsinki Declaration. In this context, the hospital ethics committee approved this study and gave permission to gather patients' data for examination. Brain diffusion MRIs which had recorded in computer automation system between January 2014 and April 2018 in our clinic were examined.

MS diagnosis was established utilizing the revised McDonald criteria (24), and patients with relapsing-remitting MS were included in the study. Patients who underwent once the episode of a history of optic neuritis were included in the study (patients without a residual visual deficit). Images obtained from optic neuritis patients were examined at least after 3 months from their episode of acute optic neuritis. The diagnosis of optic neuritis was carried out upon the patient's typical history and clinical findings by an ophthalmologist (25). In case of patients' first presentation with optic neuritis, MS patients were eligible for examination. The patients with a normal ophthalmological examination and without any other sign, comprised control group.

Patients with systemic disease affecting the eye such as diabetes mellitus, Behçet's disease, systemic hypertension, and other neurodegenerative diseases were excluded from the study in both MS patients and control group. Patients with a history of ophthalmic surgical intervention, accompanying glaucoma, or



Fig. 2. Three consecutive ADC measurements in the intraorbital segment of the optic nerve

advanced retinal or macular disease were also excluded from the study.

Diffusion-weighted imaging examination:

Diffusion-weighted imaging was performed with 1.5 Tesla MRI device (Model: Philips MRI Systems, Achieva Release 3.2 Level 2013, Manufacturer: Philips Medical Systems Nederland B.V). All images were made using the internal diameter of a 24 cm head coil as a conductor. In order to attain diffusion-weighted images (DWI), EPI sequence was benefitted. Orbital level DWI images were obtained for the parallel alignment of the optic nerve and its head. In order to calculate the ADC values in this study, the selected b-values of 0 and 1000 s/mm² were utilized. DWI was carried out using following parameters: TR/TE, 3469/92 ms; field of view (FOV), 150×150×66 mm; flip angle, 90°; matrix, 100 × 149; number of acquisitions, 4 and slice orientation, axial planes. In the axial plane, 20 slices were attained with 3 mm slice thickness and 0.3 mm intersection gap. With the help of these images, the ADC maps were reconstructed. In order to calculate values and trace images, magnitude images were carried from the MRI system to an separate work station.

Two radiologists (M.H.Ş., N.A.) who had more than 8-9 years of experience, attended the study for the examination of patient and control groups. Then both the two specialists carried out the examination of the quality of DWIs. For further analysis, they selected DWI images, with minimum distortion arising from susceptibility artifacts and ghosting, by consensus. Two specialists made their selection decision by consensus. The ADC values of optic nerve intraorbital segment and optic nerve head were obtained from both patient and control groups. ADC values of the optic nerve intraorbital segment and the optic nerve head were used measurement with a circular region of

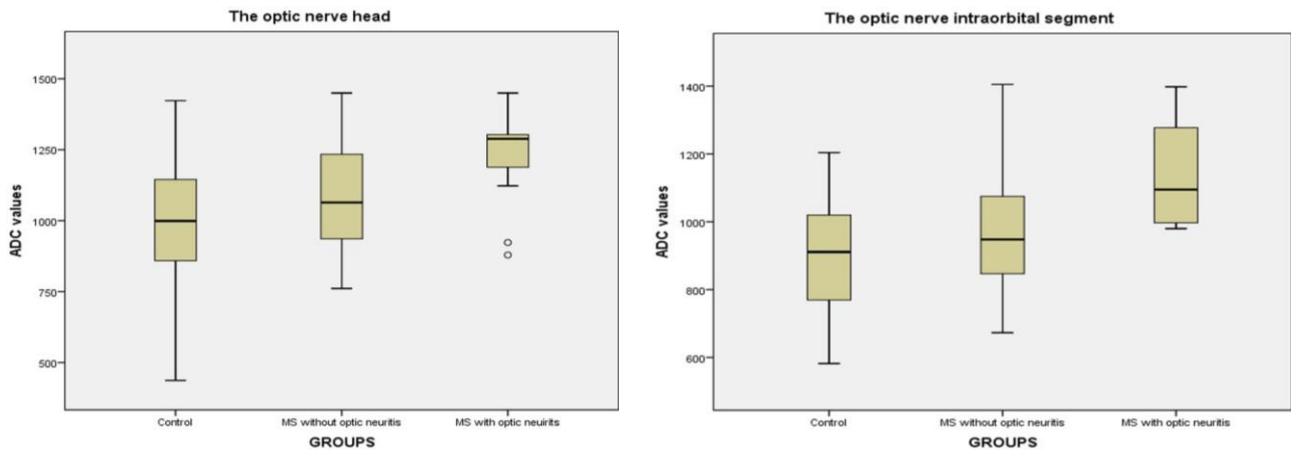


Fig. 3. Box plots show the distributions of the ADC values ($\times 10^{-6}$ mm²/s) of all groups. A, For the optic nerve head. B, For the intraorbital segment

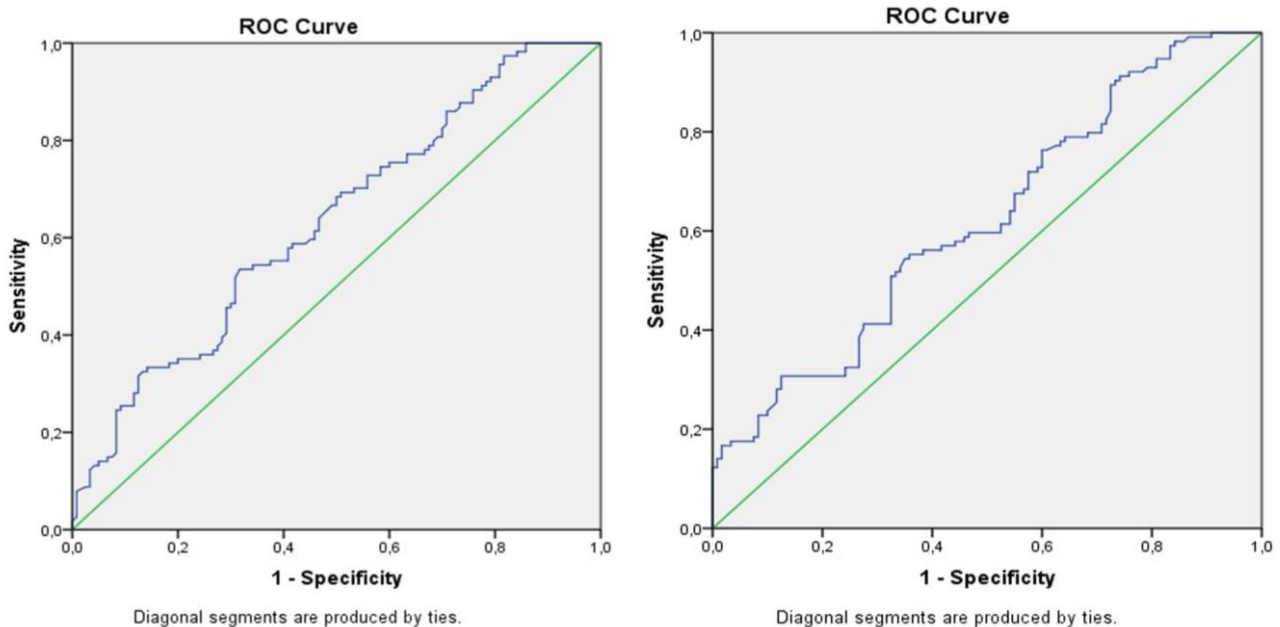


Fig. 4. The receiver operating characteristic curves of ADC values ($\times 10^{-6}$ mm²/s) in differentiating MS from the control group. A, For the optic nerve head. B, For the intraorbital segment. The blue curve represents the receiver operating characteristic curve, and the green line represents the diagonal line used as a reference

interest (ROI) area in the interval of 1.2-1.5 mm². Calculation of ADC values were carried out from the ADC map automatically. The optic nerve head ADC values for each optic nerve were obtained a single measurement from the area including optic nerve 3 mm behind the globe (Figure 1). The optic nerve intraorbital segment ADC values for each optic nerve were obtained with at least three measurements, and mean value of ADC was obtained by calculating the average of three measurements (Figure 2). The mean of ADC values was used for statistical comparisons.

Statistical Analysis: We used the SPSS software package program (SPSS, Chicago, Illinois, USA), version 20.0, for the statistical analyses. Median (range) or mean \pm standard deviation (SD) were used to express the results of the data analysis. Categorical variables such as gender were compared between groups with the chi-square test.

The groups showed normal distribution, and the variances were homogeneous. One-way ANOVA test was utilized to evaluate differences between the groups. For binary comparisons, Tukey post hoc analysis was done. The independent t-test was

Table 1. Gender, age and duration of MS patients, characteristics of all groups

	MS totally (n=57, 114 eyes)		Control group (n=60, 120 eyes)	P value
	MS with optic neuritis (n=16, 16 eyes)	MS without a history of optic neuritis (n=57, 98 eyes)		
Gender (M:F)	7:9	17:40	20:40	P> 0.05*
Age (year)(range)	45.5 ± 12 (21-64)	39.5±9.5 (21-64)	40.6±11.2 (21-64)	P> 0.05**
The mean duration of the disease ±SD (range)	6.8±3.6 years (1-15)	5.3±3.6 years (1-18)		0.111**

Values are expressed as mean ± standard deviation (SD) and range. MS—Multiple sclerosis, M-Male, F- Female. * P values according to Chi square analysis. **P values according to post hoc Tukey test. *** P values according to the independent t test

utilized to compare duration of disease in MS groups. Pearson's correlation was performed between duration of MS disease and the ADC values. A *p* value less than the level of 0.05 was accepted as statistically considerable. Paired t-test was used for comparisons within the group.

A receiver operator characteristic curve was plotted to assess the diagnostic value of MS patients' ADC values. The ADC cut-off value that maximizes the accuracy for the diagnosis of MS was established on the receiver operator characteristic curve.

Results

Evaluation involved 57 MS patients (17 males, 40 females), whose mean age was 40.37±10 years (range, 21–64 years), and 60 control subjects (40 males, 20 females), whose mean age was 40.6±11.2 years (range, 21–64 years). A total of 234 eyes which consisted of 114 eyes of the MS patients and 120 eyes of the healthy controls, were considered. In 16 of the MS patients, it was diagnosed a history of optic neuritis in one eye (Table 1). Patient and control groups were compatible in terms of age and gender as well (*P*>0.05).

The ADC values of the optic nerve head were found 1100.6±189 10⁻⁶ mm²/s and the optic nerve intraorbital segment ADC values were found 990.4±175 10⁻⁶ mm²/s in all patients with MS. In the control group, the ADC values of the optic nerve head were found 999.5 ± 202 10⁻⁶ mm²/s, and the optic nerve intraorbital segment ADC values were found 899.3 ± 156 10⁻⁶ mm²/s. The difference between the optic nerve head/intra-orbital segment ADC values of control group and MS patients was statistically considerable

(*P*=0.006, *P*=0.009, respectively) (Table 2). The difference between optic nerve head/intra-orbital segment ADC values of MS patients without optic neuritis and control group was also statistically considerable (*P*= 0.016, *P*= 0.026, respectively).

In MS patients who had a history of optic neuritis, the ADC values of the optic nerve head were found 1242 ± 159 10⁻⁶ mm²/s, and the optic nerve intraorbital segment ADC values were found 1131 ± 140 10⁻⁶ mm²/s (Table 2). Differences between MS without optic neuritis and MS with optic neuritis in terms of the optic nerve head/intra-orbital segment ADC values was found to be considerable (*P*<0.001, *P*=0.005, respectively). Box plots show the distributions of the ADC values of all groups in Figure 3.

Significant differences were found in ADC values between two eyes in optic neuritis patients (the optic nerve head ADC, *P*= 0.019, the optic nerve intraorbital segment ADC, *P*= 0.001). There were statistically significant differences between the optic nerve head and intraorbital segment ADC values of all groups (*P*<0.01).

The average disease duration was 5.53±3.6 years (range, 1–18 years) in all MS patients. (Table 2). A positive correlation between duration of the disease and the ADC values in MS patients was found (the optic nerve head ADC, *R*=0.485, *P*<0.01, the optic nerve intraorbital segment ADC, *R*=0.428, *P*<0.01).

The receiver operator characteristic curve analysis gave a value of the optic nerve head of 0.632 (95% CI=0.566-0.694) and the optic nerve intraorbital segment of 0.621 (95% CI=0.555-0.683). For the MS patients ADC value of 1090 10⁻⁶ mm²/s in the optic nerve head had a low sensitivity (53.5%), specificity (68.3%), a negative predictive value of 60.7% and a positive predictive value of 61.5%.

Table 2. Comparison of the optic nerve head/intraorbital segment ADC values between MS patients (with or without a history of optic neuritis) and control groups

Groups	The optic nerve head Mean ADC values (ADC × 10 ⁻⁶ mm ² /s)	P value	The optic nerve intraorbital segment Mean ADC values (ADC × 10 ⁻⁶ mm ² /s)	P value
MS with optic neuritis (n=16 eyes)	1242.4±159 (879-1450)	0.005	1131±140 (980-1398)	0.001
MS without a history of optic neuritis (n=98 eyes)	1077.5±184 (761-1450)		967.4±170 (673-1405)	
MS totally (n=114 eyes)	1100.6±189 (761-1450)	0.009	990.4±175 (673-1405)	0.006
Control groups (n=120 eyes)	999.5 ±202 (437-1423)		899.3 ±156 (582-1204)	

MS – Multiple sclerosis, ADC – Apparent diffusion-coefficient. ADC values are expressed as mean ± standard deviation (SD) and range, **P values according to post hoc Tukey test

The cut off ADC value of 969 10⁻⁶ mm²/s in the optic nerve intraorbital segment had also a low sensitivity, specificity, negative predictive value, and positive predictive value: 55.2%, 64.1%, 60.1%, and 59.4% respectively (Figure 4).

Discussion

Optic neuritis which is an immune-mediated inflammatory condition of the optic nerve, is a widespread localized inflammatory demyelination in MS patients. Optic neuritis may be result in acute visual loss as a result of acute demyelination of the optic nerve. Approximately, at any point of the course of disease, one half of the MS patients experience acute visual loss. After resolution of inflammation, although this visual loss significantly recovers, there may be a residual visual deficit. Histopathological research of the optic nerve in MS has showed that prominent axonal loss occurs and the optic nerve cross-sectional area decreases after optic neuritis (8, 26, 27). This study proposed that DWI can be utilized to quantitatively assess the optic nerve damage in MS.

Iwasawa et al (22) first applied DWI specifically in order to evaluate optic neuritis in MS patients. In their study, these researchers used diffusion measurement to assess the damage stem from optic neuritis. Abdoli et al (19) carried out a research on MS patients' MRI diffusion values of active demyelinating lesions. These researchers reported that these values were associated with neurological symptoms in active lesions with DWI restriction. Wan et al (13) and Lu et al (23) reported that in acute optic neuritis, low ADC values related with MS. The results of their study

were matched with previous studies proving that acute optic neuritis showed reduced ADC values and diffusion restriction in MS patients (16, 22). In acute optic neuritis, the diffusion restricting and ADC reducing the mechanism may be related with ischemic factors or cytotoxic edema. However, this study proved higher ADC values in the optic nerve in patients with or without a history of optic neuritis in patients with MS. Hickman et al (21) measured ADC values of the optic nerve 1 year after the first episode of the acute optic neuritis. These researchers found that ADC values of the optic nerve were higher in patients group than the control group. According to the results of their study, in the chronic, post-inflammatory optic nerve lesion, the ADC was giving a surrogate measure of axonal disruption. Hakyemez et al (28) proposed that the rise in ADC values may be associated with increasing in the level of interstitial water arising from neuronal cell death. Accordingly, results of this study were also regarded to be suggestive of disruption in the optic nerve. Despite several number of studies that investigated the relationship between MS and optic nerve disruption on DWI have been conducted (6, 16, 21-23, 29), there have not been any previous study in the literature that investigated the changes at the optic nerve head/intraorbital segment in patients with MS.

With DWI, there can have difficulties in evaluating the canalicular and intracranial segments of the optic nerve due to anatomical localization, but intraorbital segment and the optic nerve head can be examined with higher precision (30). Seeger et al (30) reported that it is possible to detect optic neuritis, with high sensitivity, in the intraorbital segment without the need for contrast.

This study revealed that the ADC values increased in MS patients without optic neuritis when compared to the ADC values of the control group, suggesting subclinical optic neuritis in MS. Optical coherence tomography may be used to assess the damage in the optic nerve caused by the thickness of the optic nerve fiber layer. In MS patients without a history of optic neuritis, it has been found that the thickness of the retinal nerve fiber layer may possibly be lost (26, 31-33). Furthermore, it has been revealed that the ADC values have considerable correlation with duration of MS disease (the optic nerve head/intraorbital segment, $R=0.428$, $P<0.01$, $R=0.485$, $P<0.01$, respectively). In MS patients, it has been found that the longer the course of disease leads to the greater the likelihood of optic neuritis and associated visual loss (8, 26, 27). These results may explain the increased ADC values in MS patients associated with the chronic process. Although the operator characteristic curve which was used for distinguishing MS and healthy control, indicated only 53.5-55.2% sensitivity and 68.3-64.1% specificity, it was encouraging parameter of MRI for assessing the optic nerve by structure damage.

There were some limitations in this study. The first limitation was the relatively small size of the sample which caused some bias between each group. Secondly, the small size of the optic nerve, it was very challenging to carry out ADC measurement of optic nerve. In addition, there was likely to be a partial volume effect of neighbor structures significantly different diffusion characteristics, such as the cerebrospinal fluid and vitreous humor surrounding the optic nerve. Thirdly, there was no comparison between optical coherence tomography findings and the ADC values. Fourthly, there was no repeatability between intra- and inter- operators to assess whether there is a significant ADC dependence with the selection of ROI. Nevertheless, the results of this study were meaningful. Additionally, it was found that comprehensive studies required that include correlation of optical coherence tomography and clinical findings. In addition, in patients with optic neuritis in our study, there were no residual visual defects, the study involving patients with residual visual defects would be interesting.

In this study, the mean of ADC values of patients with or without a history of optic neuritis in patients with MS was higher than in the control groups. These results reveal that, in the post inflammatory chronic nerve lesions coming after optic neuritis, the ADC value gives a surrogate

measure of functionally relevant axonal pathway fragmentation. However, an increase that is seen in ADC value in the MS patients without optic neuritis may be related with the existence of subclinical optic neuritis. These results suggest that the ADC values of the optic nerve head/intraorbital segment which are measured by ocular DWI may provide great opportunity for MS patients in the future and this technique deserves additional validation in the disease staging and more work to predict patients at risk of optic neuritis.

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