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The association between clinical parameters and retinal nerve fiber layer thickness in patients with multiple sclerosis

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KEYWORDS :

Introduction

Multiple sclerosis (MS) is an autoimmune disorder characterized by demyelinization, inflammation, axonal/neuronal loss and gliosis of white matter of central nervous system (CNS) with multifactorial etiology including genetic, environmental and immunological factors [1]. Optic neuritis is a common pathology that may affect nearly half of the patients with MS and also may lead to thinning of the retinal nerve fiber layer (RNFL) due to the neuroinflammation of the optic nerve (2). Spain et al (3) reported that RNLF measured by optical coherence tomography (OCT) may be correlated with disease duration and EDSS scores in patients with untreated MS. In another study RNLF was found to discriminate patients with sub types of MS including clinically isolated syndrome patients; relapsing remitting MS patients; secondary progressive MS (4).

In current study, we aimed to evaluate if there is a possible the association between clinical parameters and retinal nerve fiber layer thickness in patients with MS.

Methods

This is a prospective cohort study of fortyfour consecutive MS patients. The study was approved by the Ethics Committee of local ethics committee of the institution. This is a tertiary research and education hospital in middle of Turkey and most of the health services are free of charge and supported by the central government of Turkey. The diagnosis of MS was based on standard clinical and neuroimaging criteria. (5). Study group was formed from the MS patients (n= 44; age range= 17 to 47 years old; 10 male and 35 female) and control group from the healthy patients (n= 35; age range= 18 to 57 years old; 17 male and 18 female). There was no optic neuritis in both study and the control group patients.

Patients with autoimmune diseases, acute disseminated encephalomyelitis, chronic inflammatory diseases such as brucellosis and stroke, other causes of vision loss (glaucoma, maculopathies, amblyopia), other optic neuropathies, and those who were unable to undergo reliable OCT testing were excluded from the study.

Related medical records were reviewed, including age and gender of the patients, disease duration, disease-specific therapies (e.g., immunomodulatory agents) and their duration, and MS disease. RNLF thickness of both eyes were measured by using OCT (Stratus OCT-3, Carl Zeiss Meditec Inc., Dublin, CA, USA). All scans were done using an internal fixation target in the OCT device. The fast RNFL scan protocol consisted of three consecutive 360° circular scans with a diameter of 3.4 mm centered on the optic disc with a total of 2225 A-scans.

The values of RNFL thickness between the groups were compared. The subsequent analyses were performed as correlation analysis between RNFL thickness and clinical characteristics (gender, EDSS, type and duration of medications).

Statistical Analyses

Mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogornov Smirnov test. Chi-square (χ^2) test Student's t test and Mann Whitney U test have evaluated associations between the categorical and continuous variables. Spearman's correlation coefficient was used in prder to find out a correlation between RNFL thickness and clinical parameters. The mean values of the four groups were analyzed by using one way ANOVA followed Post-Hoc test Bonferroni for multiple comparison. ROC curve analysis was also performed to find out if RNFL thickness may be a discriminative parameter for our patient group. Variables were included in the backward stepwise procedure. All other analyses were performed employing SPSS version 15 (SPSS Inc, Chicago, Illinois). A p value of 0.05 or less was accepted as significant.

Results

The demographic and clinical characteristics of the patients are depicted in table 1. The mean age of the patients in the MS group was 37.66± 9.76 years old and 52.11±6.40 years old in the control group. There was statistically significantly different between the groups in terms of age ($p<0.001$). The mean RNFL thickness was statistically significantly lower in patients with MS ($p< 0.05$). There was no statistically significantly difference between right and left eyes RNFL thickness in the MS group ($p>0.05$). ROC curve analysis demonstrated that RNFL thickness may be a discriminative parameter in the patients with MS. The AUC and cut off value (sensitivity-specificity %) of RNFL thickness was; 0.668 and 98.6 µm (87.5-75.0); respectively (Figure 1).

According to the correlation analysis we performed in patient group there was a negative correlation between RNFL thickness and treatment (cc: -0.220; p: 0.039) and a positive correlation between RNFL thickness and duration of the disease (cc:0.346; p:0.046). We found no correlation between RNFL thickness and gender, EDSS of the patients (Table 2).

Subsequent analysis was performed by using Bonferroni method. The patients were divided into four groups according to the medications (Interferon beta 1b, interferon beta, interferon beta 1-alpha and glatiramer acetate) in order to investigate the affect of drugs on RNLF thickness. There was no statistically significant difference in terms of RNFL thickness between the groups according to the Bonferroni method (Table 3).

Discussion

To best of our knowledge, this is the first study evaluating the effect of different drugs on RNFL thickness in MS patients. We found RNFL thickness as a discriminative parameter in MS patient with a cut off value of 98.6 µm. Also there was a correlation between drug therapy and duration of the disease and RNFL thickness, the type of the drug was not found to have an impact on RNFL thickness. Based on our results, RNFL thickness may be a part of MS diagnosis.

MS is a chronic disorder of CNS and pathophysiology is characterized by inflammation, axonal loss and neurodegeneration of the white matter. MS lesions are also seen at optic nerves, periventricular white matter, brainstem, spinal cord, and cerebellum. In postmortem evaluation, in 94-99% of patients with MS, optic nerve lesions were

observed. Inflammation, demyelination, gliosis, axonal injury, and decrease in RNFL thickness were reported to be the findings of optic nerve lesions (6, 7).

RNFL thickness is assessed by optical coherence tomography (OCT) is a non-invasive technique and since has been first used by Parisi et al (8) it has matured into an interesting and highly sensitive method for imaging of neurodegeneration (9, 10).

In a study by Fisher et al.[11] RNFL thickness were evaluated in three groups (MS patients with optic neuritis, without optic neuritis and control group). They found the least RNFL thickness in MS patients with optic neuritis and MS patients without optic neuritis have also lower RNFL thickness than control group. We also found similar results to this study.

Spain et al.[3] also noted reductions in RNFL thickness in MS patients. They also found correlation between RNFL thickness and EDSS and disease duration. Similar to this study, we found correlation between disease duration but there was no correlation between EDSS in our study.

RNFL thickness was also evaluated in different types of patients with MS. Costello et al.[4] measured RNFL values over two years in 35 patients (70 eyes) with optic neuritis in different types of MS including; clinically isolated syndrome (CIS), relapsing remitting MS (RRMS); and secondary progressive MS (SPMS). In this study, authors reported RNFL thickness as a structural marker, which can help distinguish MS subtypes. We also found RNFL thickness as a discriminative parameter in MS patients in our study.

In the study reported by Spain et al.[3], they have found a correlation between disease duration and EDSS and RNFL thickness in untreated MS patients. The difference of our study may be related to the treatment of our patients, therefore we did not find a correlation between RNFL thickness and EDSS in our study.

In conclusion, we think that RNFL thickness may be a promising parameter in assessing the status of a patient with MS. The limitations of our study are small number of patients may have hindered the statistical power of comparisons and non-randomized study design. Future randomized controlled studies evaluating the RNFL thickness with treated and untreated patients with MS may strengthen the predictive role of RNFL thickness.

Conflict of interest

We declare we have no conflict of interest

Table 1. Comparison of the demographic and laboratory parameters between the groups

	Patients with MS (n=45)	Patients without MS (n=35)	p
Age	37.66± 9.76	52.11±6.40	<0.001
Gender Male Female	 10 35	 17 18	0.654
EDSS	1.53±1.27	-	
Duration of MS	3.32±2.63	-	
RNFL thickness (µm)	84.90±15.53	92.80±8.95	<0.001

Table 2. Correlation between RNFL thickness and clinical parameters in MS patients

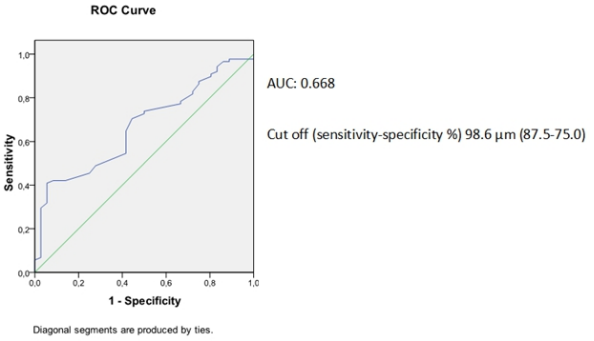
	Treatment	Duration of the disease	EDSS	Gender
RNFL thickness (µm)	CC=-0.220 P:0.039	CC=0.346 P:0.046	CC=0.002 P=0.987	CC=-0.049 P=0.647

Table 3. Results of compared the means of four groups by using ANOVA followed Bonferroni test

	aInterferon beta 1b	bInterferon beta	cInterferon beta 1-alpha	dGlatiramer acetate	Bonferroni Test (p)
RNFL thickness (µm)	93.20±15.49	89.43±19.34	88.87±15.55	86.41±14.39	>0.05

p values were calculated from ANOVA test, Bonferroni post-hoc test was used after ANOVA test

Figure1. ROC curve demonstrating the AUC of RNFL thickness in MS patients



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