ORIGINAL ARTICLE

Relationship between Structural and Functional Assessment of the Visual System in Mildly Disabled Relapsing-Remitting Multiple Sclerosis Patients

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ABSTRACT

Studies that explored the anterior visual pathway in the patients with multiple sclerosis (MS) have demonstrated contradictory results about the correlation between structural and functional status of optic nerve and retina. We aimed to investigate the functional and structural findings in our cohort of mildly disabled relapsing-remitting MS patients. A total of 134 eyes (80 eyes of the patients with MS and 54 eyes of the control group) were investigated. Eyes of MS patients were divided into two groups—as eyes with history of optic neuritis (ON group) and without history of optic neuritis (NON group). Ophthalmological investigation including visual evoked potentials, standard automated perimetry, and optical coherence tomography were performed for all participants. Retinal and macular thicknesses were significantly decreased in ON and NON groups compared with controls. Also, visual evoked potential latencies and visual field loss were worse in the both MS groups compared with control group. We did not find any correlation between visual evoked potentials and retinal or macular thickness values but visual field parameters were correlated between retinal and macular layer loss in the NON group. According to our results and some previous studies, although both functional and structural changes were detected in patients with MS, functional status markers do not always show parallelism (or synchrony) with structural changes, especially in eyes with history of optic neuritis.

Keywords: Multiple sclerosis, optical coherence tomography, perimetry, retinal nerve fibre layer thickness, visual evoked potentials

INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative disease that involves autoimmune inflammatory demyelination and axonal degeneration in the central nervous system. In recent years, several studies have demonstrated the existence of neuroaxonal degeneration in the different stages of MS.^{1–3} The investigation of the retina and optic nerve head (ONH) is an ideal basis for visualizing the processes of neuroaxonal degeneration and understanding the mechanisms of brain tissue injury in neurodegenerative diseases, because the retinal cell axons do

not contain a myelin sheath until they penetrate the lamina cribrosa.⁴

One technique for structural investigation of the retina is optical coherence tomography (OCT), which is a noninvasive technique that allows direct visualisation and measurement of retinal nerve fibre layer (RNFL) thickness, macular volume, and optic disc parameters. In recent years, OCT has been widely used for visualisation of axonal loss in neurodegenerative diseases such as MS, Parkinson's disease, and Alzheimer's diseases.^{5,6}

Also conventional techniques such as visual evoked potentials (VEPs) and standard automated

perimetry (SAP) for visual field (VF) examination can provide accurate measurements of the functional state of the visual system, particularly the optic nerve. VF examination is a subjective test for determination of visual function loss. VEP provides an objective functional assessment of the anterior visual pathway and as a gold standard; VEP P100 wave latency and amplitude are used for assessing the extent of demyelination and axonal damage, respectively.⁷

Several studies have investigated the functional and structural state of the visual pathway in patients with MS, using OCT, VEP, and/or VF examination, and have shown good correlations between structural and functional status even in the early stages of the disease, both with or without a previous history of optic neuritis (ON).^{8–10} Controversially, other researchers have not found correlations between functional and structural measurements.¹¹ For these reasons, we designed a study to investigate both functional and structural investigation using OCT, VEP, and VF examination in our cohort of relapsing-remitting (R-R) MS patients with mild disability and with or without history of optic neuritis.

MATERIALS AND METHODS

This study was performed at the Departments of Neurology and Ophthalmology of Kafkas University, Medical Faculty, Kars, Turkey. The study adhered to the tenets of the Declaration of Helsinki. It was approved by the local ethics committee (2011/13) and all of the patients gave written informed consent.

A total 40 MS patient with Expanded Disability Status Scale (EDSS) scores ≤ 4.5 , admitted to our outpatient clinic between January 2011 and December 2012 were included into the study. Twety-seven age- and gender-matched subjects, who were hospital staff with no history of MS and ophthalmological diseases, formed the control group. A total of 134 eyes (80 eyes of patients with MS and 54 eyes of the control group) were investigated. Eyes of MS patients were divided into two groups: eyes with a history of optic neuritis (ON group) and without a history of optic neuritis (NON group). History of optic neuritis was based on data from hospital records and information from the patients and their relatives about visual disturbances compatible to ON as blurry vision and visual loss that had lasted several days and spontaneously improved. Demographic variables, including age, gender, and neurological status, including EDSS scores, were determined for all of the patients. We did not include data for disease duration in our study, because some patients were not able to give reliable data on the onset of the disease. We defined our MS patients as mild disabled because previous studies have classified EDSS ≤ 5 as mild disability.³ All patients were

under immunomodulatory treatment (interferons or glatiramer acetate) and were in remission at the time of the examination.

The inclusion criteria for the study were MS based on revised McDonald's criteria, intraocular pressure < 21 mm Hg, visual acuity (VA) $\geq 20/30$, and refractive error < 5 D equivalent sphere or 3 D of astigmatism.¹² Patients who had a history of any diagnosed ocular or neurological conditions other than MS were excluded from our study. Patients with ON that had occurred within 6 months prior to examination were excluded from the study. Both eyes of the patients and controls were examined.

Pattern reversal VEPs were recorded using a Neuropack M1 MEB-9200 (Nihon-Kohden, Tokyo, Japan) device with full correction of refraction, in accordance with previous recommendations.¹³ Checkerboard pattern stimulation was performed on a single eye with occlusion of the other eye. The analysis time was 250 ms and sensitivity was $20 \mu\text{V}/\text{division}$. The low-cut filter was 1 Hz and the high-cut filter was 100 Hz. Two hundred noise-free sweeps were averaged and the average P100 wave value was used for analysis. The P100 wave latency and amplitude were recorded for each eye.

VF examinations were performed using the Octopus 900 (Haag-Streit International, Koeniz, Switzerland) perimeter after near-vision refractive correction by the "G1 Octopus" program. The test was applied after near-vision refractive correction. The VF was studied using the dynamic strategy, background illumination 31.4 asb, and examination area within central 30° , using a III white target stimulus. Mean deviation (MD) and pattern standard deviation (PSD) were recorded for each patient and control subject. MD scores represent the average of the differences from normal expected value for the patient's age, and are used to detect of diffuse VF loss.² PSD indicates the homogeneity of defect distribution in the VF, and thus measures localised damage.¹⁴ Patients with unreliable perimetry results with fixation loss $> 15\%$ or false positives and false negatives $> 15\%$ were excluded from the study.

OCT was performed through undilated pupils using the RTVue version 4.0 (OPTOVUE, Fremont, CA, USA). Only scans that reached signal strength of at least ≥ 6 , which indicate a high-quality scan, were accepted for analysis. The RNFL scan pattern completes four circular scans in 0.15 seconds at a diameter of 3.45 mm, targeted around the ONH. Peripapillary RNFL thickness was measured in each eye as an average. Ganglion cell complex (GCC) thickness, which includes the nerve fibre layer, ganglion cell layer, and inner plexiform layer in the macular region, was obtained by GCC scan protocol; this consists of one horizontal scan followed by 15 vertical scans, centred 1 mm temporal to the fovea. Macular thickness included average thickness, focal loss volume

(FLV), and global loss volume (GLV) values. FLV provides a quantitative measurement of the amount of significant GCC loss. FLV is the total sum of significant GCC loss (in volume) divided by the map area, which provides a percentage of significant tissue loss for volume. GLV is the sum of the pixels where the fractional deviation map value is <0 , and then divided by the total area to give a percent loss of GCC thickness. Optic nerve head volume (NHV) and optic disc area (ODA) measurements were obtained using a protocol that consists of 12 radial line scans and 13 concentric rings, centred on the disc.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Base 13.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are given as median or mean $\pm$ SD, and minimum and maximum values; categorical variables are shown as frequencies and percentages. Normal distributions were determined using the Shapiro-Wilk test. For comparisons of variables between two groups, Mann-Whitney *U* tests were used; for comparisons between three groups, Kruskal-Wallis test were used. Bonferonni corrected Mann-Whitney *U* tests were used to determine differences between two groups if a significant difference was found on the Kruskal-Wallis test. Spearman correlation coefficient used to determine the relationship between continuous variables. A *p* value below 0.05 was accepted as significant. Exact *p* values are provided for all test results.

RESULTS

A total of 40 MS patients (14 males, 26 females) with a mean age of 34.75 (range between 23 and 50) and mean EDSS scores of 2.43 ± 1.31 and 27 healthy individuals (11 males, 16 females) with a mean age of 33.97 ± 5.76 (range between 20 and 45) were included into the study. The demographic and clinical features of MS patients and healthy subjects are shown in Table 1.

Comparisons of RNFL, VEP, and VF parameters were performed between both MS groups (ON and NON) and healthy controls (Table 2). VEP latencies were significantly longer in ON and NON groups compared with controls ($p < 0.001$ for both). VEP latencies were longer in the ON group compared with the NON group ($p < 0.001$). Also, average RNFL thicknesses were significantly lower in the ON and NON groups compared with the control ($p < 0.001$ for both) group; they were also significantly lower in eyes in the ON group compared with the NON group ($p < 0.001$). There were no statistically significant differences in VEP amplitudes and NHV and ODA

TABLE 1 Demographic and clinical characteristics of MS patients and healthy controls.

	Patients (<i>n</i> = 40)	Controls (<i>n</i> = 27)	<i>p</i>
Gender (M/F)	14 (35%)/26 (65%)	11 (40.7%)/16 (59.3%)	0.500
Age (years)			
Mean $\pm$ SD	34.75 ± 6.57	33.97 ± 5.76	0.063
Median	35 (23–50)	34.05 (20–45)	
(min–max)			
EDSS			
Mean $\pm$ SD	2.43 ± 1.31		
Median	2 (1–4.5)		
(min–max)			

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale. $p \leq 0.05$ was accepted as significant.

parameters among both MS groups and healthy controls.

The average GCC thicknesses were significantly lower in both ON and NON groups than in controls ($p < 0.001$ for both). GCC values were significantly lower for the ON group than for the NON group ($p < 0.001$).

Macular and retinal volume loss parameters, represented as FLV and GLV, were significantly higher in both MS groups compared with the healthy group ($p < 0.001$ for both); FLV and GLV were higher in eyes with ON than in the NON group ($p < 0.001$).

Statistical analysis of VF data, such as MD and PSD, demonstrated that the MS groups had higher significant visual fields loss compared with the control eyes, but MD and PSD values did not differ between ON and NON groups.

Also, correlations between significant structural and functional parameters in both MS groups are shown in Table 3 and Table 4.

DISCUSSION

In the present study, we investigated the structural and functional status of the retina and optic nerve in mildly disabled MS patients with and without history of ON, and compared the results with age- and gender-matched healthy controls. In addition, we studied correlation between the functional and structural parameters of the patient's eyes. Apart from other studies, we added macular loss parameters such as FLV and GLV, which had not been investigated in previous studies with MS.

The results of our study generally support the results of previous studies investigating structural and functional changes in MS eyes with and without a history of ON.^{15–22}

MS eyes with a previous history of ON have significant loss of RNFL thickness compared with the eyes of healthy controls and clinically unaffected eyes in the patients with MS.^{9,15,22,23} According to a review,

TABLE 2 Ophthalmologic findings in NON, ON, and control groups.

Parameter	ON	NON	Control	<i>p</i>
VEP lat (ms)				<0.001 ^{a,b,c}
Mean $\pm$ SD	139.16 $\pm$ 15.28	111.03 $\pm$ 15.64	100.26 $\pm$ 7.54	
Median (min–max)	139.5 (106.8–174.6)	108.5 (86.7–152.4)	100.65 (86.5–114.3)	
VEP amp (μ V)				0.067
Mean $\pm$ SD	6.45 $\pm$ 2.58	8.23 $\pm$ 3.69	8.32 $\pm$ 3.75	
Median (min–max)	6.25 (2.5–11.7)	7.65 (3–19.9)	8 (2.6–15.8)	
RNFL (μ m)				<0.001 ^{a,b,c}
Mean $\pm$ SD	88.17 $\pm$ 10.98	107.86 $\pm$ 9.63	114.89 $\pm$ 10.46	
Median (min–max)	89.07 (58.35–108.98)	107.53 (89.47–124.86)	109.8 (102.94–137.45)	
NHV (mm ³)				0.180
Mean $\pm$ SD	0.25 $\pm$ 0.15	0.30 $\pm$ 0.15	0.30 $\pm$ 0.21	
Median (min–max)	0.18 (0.02–0.50)	0.25 (0.03–0.80)	0.22 (0.09–0.96)	
ODA (mm ²)				0.184
Mean $\pm$ SD	1.84 $\pm$ 0.40	1.86 $\pm$ 0.37	1.78 $\pm$ 0.31	
Median (min–max)	1.83 (0.61–2.55)	1.85 (0.59–2.45)	1.74 (1.35–2.55)	
GCC (μ m)				<0.001 ^{a,b,c}
Mean $\pm$ SD	80.58 $\pm$ 7.26	95.32 $\pm$ 8.39	101.12 $\pm$ 7.01	
Median (min–max)	80.07 (63.08–94.50)	95.62 (79.9–115.82)	99.21 (90.07–124.08)	
FLV (%)				<0.001 ^{a,b,c}
Mean $\pm$ SD	5.80 $\pm$ 3.64	1.76 $\pm$ 3.06	0.44 $\pm$ 0.34	
Median (min–max)	6.03 (0.79–17.26)	0.84 (0–18.77)	0.39 (0.01–1.35)	
GLV (%)				<0.001 ^{a,b,c}
Mean $\pm$ SD	15.30 $\pm$ 6.10	4.80 $\pm$ 4.45	1.89 $\pm$ 1.70	
Median (min–max)	16.50 (3.24–31.24)	2.86 (0.002–14.30)	1.01 (0.20–5.82)	
MD (decibels)				<0.001 ^{a,b}
Mean $\pm$ SD	–7.5 $\pm$ 6.1	–4.98 $\pm$ 4.81	–0.80 $\pm$ 1.50	
Median (min–max)	–6.4 (–25.1–0.9)	–3.30 (–19.40–1.0)	–0.50 (–5.20–0.60)	
PSD (decibels)				<0.001 ^{a,b}
Mean $\pm$ SD	5.6 $\pm$ 2.2	4.52 $\pm$ 2.43	2.05 $\pm$ 0.58	
Median (min–max)	5.9 (2.0–8.6)	3.90 (1.40–9.20)	1.95 (1.20–3.50)	

MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; NHV = optic nerve head volume; ODA = optic disc area; GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume; MD = mean deviation; PSD = pattern standard deviation; ON = eyes with history of optic neuritis; NON = eyes without history of optic neuritis. $p \leq 0.05$ was accepted as significant.

According to post hoc analysis:

a: Statistically significant difference between the control and NON groups.

b: Statistically significant difference between the control and ON groups.

c: Statistically significant difference between the ON and NON groups.

TABLE 3 Correlation between VEP latencies and OCT parameters in ON and NON groups.

Group	RNFL	GCC	FLV	GLV
VEP latencies ON				
Correlation coefficient	–0.046	–0.017	0.301	0.099
Significance (2-tailed)	0.811	0.928	0.106	0.601
VEP latencies NON				
Correlation coefficient	0.147	–0.161	0.020	–0.129
Significance (2-tailed)	0.307	0.265	0.894	0.384

VEP = visual evoked potential; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume; ON = eyes with history of optic neuritis; NON = eyes without history of optic neuritis.

MS eyes with a history of ON have greater RNFL and GCC thinning than without ON and eyes of healthy controls.²⁴ Although these data are generated from the general population of MS patients, it is generally similar to our results that only patients with the

TABLE 4 Correlation between VF and OCT parameters in ON and NON groups.

Group	RNFL	GCC	FLV	GLV
MD ON				
Correlation coefficient	0.202	0.316	–0.295	–0.458*
Significance (2-tailed)	0.284	0.089	0.113	0.011
PSD ON				
Correlation coefficient	–0.168	–0.305	0.321	0.390*
Significance (2-tailed)	0.376	0.102	0.083	0.033
MD NON				
Correlation coefficient	0.345*	0.388**	–0.354*	–0.329*
Significance (2-tailed)	0.016	0.006	0.014	0.022
PSD NON				
Correlation coefficient	–0.331*	–0.377**	0.308*	0.313*
Significance (2-tailed)	0.022	0.008	0.033	0.030

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

VF = visual fields; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume; MD = mean deviation; PSD = pattern standard deviation; ON = eyes with history of optic neuritis; NON = eyes without history of optic neuritis.

relapsing-remitting subtype of MS and relatively mild disability were included.

The usefulness of VEP for evaluation of abnormalities in the anterior visual pathway in MS patients has been reported in several previous studies dating back several years.^{10,11,25–28} Weinstock-Guttman et al. evaluated 37 MS patients and found prolonged P100 latency in 75% of them.²⁵ Also, some studies found increased P100 latency in MS eyes: not only in patients with ON, but also in those without a history of previous ON.^{10,11,26–28} In our study, we found significant prolonged P100 latency similar to the results of the above studies. Most of the previous studies have demonstrated a decrease in P100 wave amplitudes in MS eyes compared with controls.^{10,26,29} In contrast, we found that P100 wave amplitudes were similar both in MS and healthy groups. Mild disability and thus absence of severe axonal loss may explain unaltered amplitudes in our MS patients.

Even so, Naismith et al. showed that VEP remains the preferred test for detecting clinical and subclinical ON and more sensitive in ON than OCT, and some previous studies in MS patients demonstrated a correlation between VEP parameters and RNFL thickness.^{10,30,31} In contrast to these studies, we did not find significant correlation between RNFL thickness and VEP P100 latencies or amplitudes (Table 3). In addition, other study supports our results, showing no correlation between VEP and RNFL thickness.¹¹ It is possible that different samples of patients may justify varying results.

Similar to our study, some previous research has found abnormal VF parameters in most MS patients, even without a prior history of ON.^{28,32–34} Although MS eyes had significantly worse values compared with healthy eyes, there were no significant differences found between eyes with and without a history of ON. This can be explained by the fact that VF loss in MS eyes without a previous history of ON may be due to subclinical ON attacks or retrograde degeneration of retinal ganglion cells from postchiasmal lesions, which could affect both eyes.³³

Some previous studies have shown significant correlations between VF values and RNFL thickness. Cheng et al. reported significant correlations between visual function, measured by SAP, and RNFL thickness, measured by OCT, in ON eyes but not in eyes without a history of ON.³⁵ Also, Costello et al. found a significant correlation between RNFL thickness and MD in MS eyes with severe damage.³⁶ Significant correlations between averaged RNFL thickness and VF loss have also been confirmed by other researchers.^{28,37} On the other hand, a study by Noval et al. demonstrated significant correlation between RNFL thickness and visual field loss at 1.5 and 3 months after ON, but not after 6 months.³⁸ The differing results of the above studies may be based on different study designs, MS subtypes, disability scores, and

durations of the disease. We also found a significant correlation between RNFL thickness and VF loss, but only in NON eyes, not in ON eyes (Table 4). It is possible that RNFL and VF parameters did not show synchronous changes, especially in eyes, which were the direct impact of the demyelination and degeneration, due to ON. In support of this suggestion, our study found no statistically significant differences in VF parameters between both MS groups, whereas RNFL thicknesses differed from each other in all three groups. Although both RNFL and VF losses develop even in mildly disabled patients, we believe that RNFL changes are more sensitive and selective indicators of ON than are VF defects.

Another structural indicator of the visual pathway that was assessed in some studies is macular thickness. We used the term “GCC” to denote the macular region that includes the nerve fibre, ganglion cell, and inner plexiform layers. GCC values were lower in the ON group than in the NON and healthy groups. Our mean values resemble the average reference values from recent investigations of macular region OCT.²⁴ Further, our study found significant correlations between GCC and VF MD with PSD in the NON group, but not in the ON group. We also found no significant correlations between GCC and VEP latencies for either of the MS groups.

To our knowledge, only one previous study assessed ONH parameters in MS patients in a similar way to our study.²⁷ Iester et al. enrolled the optic nerve head shape in 23 MS patients with a history of ON using scanning laser ophthalmoscopy; they did not find significant differences on ONH parameters between MS eyes with ON and an available normative database, and between MS eyes with ON and the unaffected fellow eye.²⁷ Although these results support ours with respect to unaltered optic nerve values, future research may be required to clarify the changes in ONH in MS.

Macular parameters such as FLV and GLV were included in our study have not been examined in previous researches with MS patients. These parameters have been used mainly for the investigation of glaucomatous eyes. In brief, GLV represents the average amount of GCC loss over the entire GCC map. FLV measures focal loss using a pattern deviation map, similar to PSD in the VF.^{38,39} We explored these parameters because some authors consider that MS-associated ON may share some pathogenetic, structural, and functional similarities with glaucomatous optic neuropathy.^{33,35} Global and focal losses in the GCC map were significantly higher in the ON group compared with NON and control groups. Also, the NON group had worse values than the control group. These data confirm results that have been discussed above about GCC changes in ON, NON, and healthy eyes. We did not find statistically significant correlations between VEP latency and FLV with

GLV, as in the case of the correlation between VEP and GCC. Also, we found significant correlations between GLV and VF values in both MS groups, whereas FLV was correlated with VF MD and PSD only in the NON group.

The present study had limitations, such as the relatively small number of participants, which may limit interpretation of the results. We examined only patients with the R-R subtype of MS with mild disability and we cannot generalise our results to the larger population of MS patients. Also, VEP and VF examinations are tests that depend on the attention and cooperation of patients.

In summary, we can say that structural and functional parameters were worse in MS eyes with a history of ON compared with NON and control eyes, and also in NON eyes compared with controls, as we expected. These results are similar to previous studies. In contrast to some other studies, we did not find significant correlations between structural and functional parameters in ON eyes, whereas NON eyes showed good correlations among most parameters. This probably occurred because eyes with a history of ON can show some differences in retinal and macular cell loss, unlike eyes without ON; in the eyes that have been directly impacted by inflammation due to ON, glial tissue replace dead retinal nerve cells more aggressively than in fellow unaffected eyes. In addition, it is important to consider pathological changes in posterior (postchiasmal) visual pathways in MS, which affect functional tests, especially VF examination. For all these reasons, such functional status markers as VEPs and VF parameters do not always show parallelism (or synchrony) with RNFL or GCC changes.

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