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Assessment of structural and functional visual outcomes in relapsing remitting multiple sclerosis with visual evoked potentials and optical coherence tomography

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ABSTRACT

The purpose of this study is to consider the clinical utility of optical coherence tomography (OCT) and find a correlation with VEP. Effects of different disease modifying treatments (DMT) were further evaluated by measuring OCT parameters and whether a correlation exists between the RNFL thickness, disease duration and expanded disability status scale (EDSS) were also assessed. 13 patients were on interferon beta-1a (IFN), 14 patients were receiving glatiramer acetate (GA), 19 patients were not being treated with any DMT and 21 healthy controls were included the study. During OCT examination, retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness was found to be lower in all MS groups but macular volume (MV) was lower only in GA group than controls. Although, P100 latencies were longer than controls in all MS groups, there was no statistically significant difference between IFN and w/o DMT groups. Patients with ON history, P100 latencies were found significantly longer than those without ON. VEP amplitudes were found lower with ON history patients than those without ON, however this was not statistically significant. EDSS strongly correlated with P100 latency, RNLF, GCC but no correlation was observed with VEP amplitude and MV. Our results show that RNFL, GCC and MV were all decreased in MS patients with or without DMT comparing to controls and it is more prominent in eyes with ON. Further follow-up studies are warranted to understand the pathophysiology of CNS axonal degeneration and involvement of optic nerves.

1. Introduction

Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disorder of the central nervous system (CNS) characterized by demyelination and axonal degeneration [1]. Acute optic neuritis (ON) due to an inflammatory demyelinating lesion of the optic nerve is often seen in association with MS [2]. Although functional recovery usually follows the acute episode of visual loss, persistent visual deficits are common. In vivo measurements of thinning of the retinal nerve fiber layer (RNFL) suggest that the extent of axonal loss is associated with the degree of persistent visual dysfunction following optic neuritis [3–5]. Retinal axonal loss begins early in the course of MS in the absence of clinically evident ON and retinal thinning is nearly identical between MS subtypes [6–8].

The mechanisms responsible for the formation of lesions in different patients and in different stages of the disease as well as those involved in the induction of diffuse brain damage are complex and heterogeneous. This heterogeneity is reflected by different clinical manifestations of the disease, such as relapsing or progressive MS [9,10]. Because of the complex immunopathological mechanisms involved, the evidence for the effectiveness of different therapeutic strategies varies widely between the different agents. Up to date, several therapies for MS exist, however many possible therapies are still under investigation. Monitoring the progression of disease activity, effectiveness of therapies carry great importance in the management of patients with MS. MS diagnosis and prognosis require integrating clinical findings with the assessment of magnetic resonance imaging (MRI) and other paraclinical methods including visual evoked potentials (VEP), and elimination of alternative disorders that might mimic MS [10,11]. To date, biomarkers or imaging techniques remain insufficient to estimate prognosis and provide evidence for development of neuronal loss and atrophy [12].

Optical coherence tomography (OCT) is a new method assessing the impact of MS on the thickness of the RNFL by measuring the echo time delay and intensity of back-reflection of light from different structures in the eye. OCT is a noninvasive and reproducible tool and might present valuable data for axonal degeneration [13–18].

The purpose of this study is to consider the clinical utility of OCT and find a correlation with VEP, and in assessment of relative effect of different disease modifying treatments (DMT) on MS patients by measuring

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RNFL thickness, macular volume (MV) and ganglion cell complex (GCC) volume. Furthermore, we aimed to determine whether a correlation exist between the RNFL thickness, disease duration, expanded disability status scale (EDSS).

2. Methods

This study was carried out in the setting of an MS center at Bakırkoy Training and Research Hospital for Psychiatric and Neurological Diseases, Istanbul. The study was approved by the local ethical committee and written informed consent was received from all patients. The study was performed according to the tenets of the Declaration of Helsinki for research involving human subjects. Our study included patients with clinically definite MS according to McDonald criteria with or without a history of optic neuritis and the patients were selected randomly [11]. Patients had relapsing remitting disease course (RRMS). Patients who did not have any relapses or corticosteroid treatment within 3 months prior to the study were included. Patients who were not able to cooperate or patients with additional ocular comorbidities were excluded from the study. Study group was divided into 4 groups respectively: 1) Patients on glatiramer acetate (GA) treatment 2) Patients treated with IFNB1-a (IFN) intramuscular and 3) Patients with no DMT who had refused therapy and 4) Healthy controls. The patients who received DMT for at least 1 year were included. Routine neurological exam was performed and EDSS scores were evaluated. All patients' right and left eyes were also assessed by VEP and RNFL thickness was measured.

2.1. VEP studies

VEP studies were performed using KeyPoint device in a dark and quiet room. Active and reference electrodes were placed on the Oz and Fz in respectively, according to 10–20 system. 16 × 12 checkerboard (white and black) pattern reversed stimulation was applied. Subject was seated 100 cm distance from the monitor screen and fixed the gaze at a red dot on the center of the screen. Stimulus rate was 2 Hz. The filter bandpass was 0.5 Hz–1 kHz, sensitivity was 5 microvolt/division (μV/D) and sweep was 30 millisecond/division (ms/D). At least 100 artifact free responses were averaged and two runs were performed for right and left eye of each patient. N75, P100 and N135 latencies and N75/P100 amplitudes were measured [19].

2.1.1. Optic coherence tomography

OCT images were obtained using the Optovue RTVue Fourier domain OCT (RTVue-100, 2007, version 3.0, Optovue Inc., Fremont, CA, USA). The patients were also selected on the basis of their ability to maintain steady fixation at the OCT, and each scan was accurately checked to avoid misaligment of foveal imaging. All retinal scans were performed by the same examiner. Throughout scanning, the subject kept each eye constantly fixed on an internal target provided by the equipment. Each eye underwent the Nerve Head Map, 4 mm diameter (NHM4), Macular Map, 5 × 5 mm (MM5), Ganglion Cell Complex (GCC) scan protocols. All scans had signal strength of at least 50 (range, 30–79.4) and no artifacts. MM5 scan protocol measure the macular retinal thickness map with 5 × 5 mm square grid centered on fixation. Macular volume within 5 mm was measured. NHM4 scan measures the average parapapillary RNFL thickness. GCC scan protocol measures the GCC layer which encompasses RNFL, ganglion cell bodies and inner plexiform layer. It has one horizontal line with 7 mm scan length, followed by 15 vertical lines with 6 mm scan length and 0.5 mm interval, centered 1 mm temporal to fovea.

2.1.2. Statistical analysis

Descriptive statistics were applied to the demographic features of the cohort. Analysis was performed with SPSS program for Windows. Besides standard descriptive statistical calculations (mean and standard deviation), one way ANOVA was used in the comparison of groups, post Hoc Bonferroni multiple comparison test was utilized in the comparison of subgroups, unpaired *t*-test and chi square test was performed during the evaluation of quantitative data. Pearson correlation was used to describe correlations. $P < 0.05$ that was considered statistically significant.

3. Results

Demographical and clinical findings of the study showed on Table 1. Age and sex was similar between three MS groups and controls ($p = 0.826$, $p = 0.986$). 13 patients were on IFN, 14 patients were receiving GA and 19 patients were not being treated with any DMT. Although disease duration was similar between three MS groups, EDSS was significantly different and in post hoc analysis EDSS was higher in GA groups than those of without DMT groups (w/o DMT) ($p = 0.031$ and $p = 0.033$ respectively). Out of 92 eyes of 46 MS patients, 36 eyes had ON history and ON history was similar between three MS group ($p = 0.318$) (Table 1).

3.1. VEP results

There was a significant difference P100 latencies between four groups ($p < 0.0001$, Table 2). In post hoc analysis, P100 latencies in GA group were found significantly longer than those of IFN, w/o DMT and control grups ($p < 0.0001$ for all). Although, P100 latencies were longer than controls in all MS groups, there was no statistically significant difference between IFN and w/o DMT groups ($p = 0.007$ for IFN, $p < 0.0001$, for GA and $p = 0.001$ for w/o DMT).

VEP amplitudes were also found significantly different between four groups ($p = 0.005$, Table 2). While there was not any significant amplitude difference between IFN, w/o DMT and control groups, GA group had lower amplitude than control group ($p = 0.003$).

3.2. OCT results

RNLF thickness was found to be lower in all MS goups when compared with control group ($p = 0.001$ for IFN and $p < 0.0001$ for GA and w/o DMT groups, Table 2). Similarly, GCC thickness was also lower in all three MS groups than controls ($p = 0.001$ for IFN and $p < 0.0001$ for GA and $p < 0.0001$ w/o DMT groups). MV was also lower in GA

Table 1
Demographic and clinical characteristic of the study.

	IFN	GA	w/oDMT	Controls	F	p
N (F/M)	13(9/4)	14(9/5)	19(12/7)	14/7		0.986
Age (mean ± SD)	34.7 ± 8.5	37.4 ± 10.6	36.6 ± 9.5	35.1 ± 7.5	0.299	0.826
Disease duration (month)	59.5 ± 39.3	87.1 ± 56.4	71.4 ± 49.7		1.129	0.333
Eye of ON history	7	12	17			0.318
Duration of therapy (month)	22.00 ± 18,45	27.54 ± 13.78				0.401
EDSS	1.2 ± 0.7	1.9 ± 1.2	1.03 ± 0.7		3.754	0.031

IFN = Interferon GA = Glatiramer acetate w/o DMT = Without disease modifying therapy F = Female M = Male SD = Standart deviation ON = Optic neurit EDSS = Expanded Disabilitiy Status Scale.

Table 2
The latencies and amplitudes of VEP responses and OCT results of the study.

	IFN	GA	w/o DMT	Controls	F	p
N	26	28	38	42		
P100 latency	113.8 ± 13.3	135.6 ± 27.6	114.12 ± 12.8	100.8 ± 3.5	27.950	<0.0001
VEP amplitude	6.44 ± 3.6	5.22 ± 3.8	7.31 ± 3.0	8.47 ± 4.3	4.559	0.005
RNFL	103.3 ± 12.7	97.25 ± 18.9	100.86 ± 13.6	117.3 ± 11.0	14.733	<0.0001
GCC	95.25 ± 8.3	88.91 ± 11.9	93.63 ± 11.9	104.9 ± 6.6	16.544	<0.0001
MV	5.810 ± 0.22	5.593 ± 0.48	5.920 ± 0.82	6.128 ± 0.22	6.335	<0.0001

N:number eyes evaluated VEP = Visual evoked potential RNLF = Retinal nerve fiber layer.
GCC = Ganglion cell complex MV = Macular volume.

Table 3
VEP and OCT results among patient group with and without ON.

	ON (+)	ON (−)	F	p
VEP latency	127.9 ± 25.16	115.8 ± 16.38	4.503	0.013
VEP amplitude	5.58 ± 3.23	6.98 ± 3.61	1.428	0.063
RNLF	94.17 ± 14.63	104.5 ± 14.29	0.004	0.001
GCC	87.54 ± 11.03	96.07 ± 10.13	0.185	<0.0001
MV	5.592 ± 0.31	5.916 ± 0.72	0.488	0.013

group ($p < 0.0001$), however, it was not significantly different between IFN, w/o DMT and control groups.

In subgroup analysis of MS patients with ON history, P100 latencies were found significantly longer than those without ON ($p = 0.013$, Table 3). VEP amplitudes were found lower with ON history patients than those without ON however this was not statistically significant ($p = 0.063$).

During OCT evaluation, RNLF, GCC and MV were significantly thinner in eyes with ON history than without ON ($p = 0.001$, $p < 0.0001$ and $p = 0.013$, respectively), Table 3).

Disease duration was strongly correlated with EDSS and GCC; and weak correlated with P100 latency of VEP responses and macular volume. EDSS found strongly correlated with P100 latency, RNLF, GCC and weak correlated with VEP amplitude and MV. Similarly, ON history was strongly correlated with P100 latency, RNLF, GCC and weak correlated with MV, but not correlated with VEP amplitude. RNLF, GCC and MV, P100 latencies and amplitudes of VEP responses found strongly correlated with each other. (Table 4).

4. Discussion

During disease course neuronal degeneration, axonal transection has been demonstrated in MS lesions [9,10]. Axonal loss is responsible for disease progression and the development of disability and new strategies are warranted for monitoring MS and preventing neuronal degeneration and disability. However up to date no sensitive and specific markers for predicting and preventing disability exist. As a part of the disease process, optic nerve may also be involved and close correlation has been observed between OCT findings and the histological evaluation of RNFL [19]. Recent studies have suggested that reduced RNFL thickness may be a potentially MS outcome measure and serve as a surrogate marker for MS disability [20–22]. Our study showed that RNLF, GCC and MV were all reduced in the MS group with or without DMT when compared with controls and the abnormal findings were more prominent for eyes with ON history. These results were consistent with previous published studies [4,7,8,13,14,16,21,23]. It has also been suggested that VEP represents a summed potential from all stimulated neuronal structures and assesses functional integrity of visual pathways. Therefore some authors have proposed that its clinical benefit may be limited for ON [24,25]. There has also been some conflicting results between OCT and VEP parameters in literature. Parisi et al reported that there was reduction in VEP amplitude in ON eyes, but no correlation existed with RNLF thickness. On the other hand, Noval et al found strong correlation between RNFL thickness and VEP amplitudes and they suggested that VEP amplitudes reflect an indirect sign of the axonal loss [23,24]. In our study VEP latencies and amplitudes were also strongly correlated with RNLF, GCC and MV (Table 4). In our previous studies also suggested that while at initial presentation no VEP response was obtained in a patient with ON, on follow up, prolongation latency and reduced amplitude of VEP response were found [26]. This suggests that VEP might be more sensitive to capture remyelination while OCT seems to reveal axonal loss.

Up to date debate about the efficacy and monitoring the effects of immunomodulatory drugs has existed. Literature has suggested that OCT measures of RNFL thickness may also aid in assessment of treatment efficacy and effects of DMT during disease course and also for monitoring MRI activity [27–29]. Our study also looked into the effects of DMT on RNFL thickness and no statistically significant difference was observed between treated and non treated patient group. However our study is a cross-sectional study and further follow up may capture additional findings.

A recent study by Serbecic et al showed that RNLF reduction could be found in both RRMS and SPMS patients but in patients with ON this reduction might be a reflection of the optic nerve involvement [30]. A question relating to this phenomenon is risen and RNFL reduction may also be caused by secondary axonal degeneration due to distant focal lesion in the visual pathways or by diffuse progressive axonal degeneration due to compartmentalized ongoing CNS inflammation. If this is the pathological process behind the RNFL reduction then OCT evaluation may fail to show the disease progression. Conflicting data regarding abnormal RNFL in the fellow eye or in patients without ON also exists thus more follow-up studies regarding monitoring disease process and DMT effects are warranted.

Table 4
Correlation analysis of the study.

	Disease duration	EDSS	ON history	RNLF	GCC	MV	VEP latency
EDSS	0.394[b]		−0.042				
VEP latency	0.347[a]	0.366[b]	−0.2[b]	−0.540[b]	−0.592[b]	−0.327[b]	
VEP amplitude	−0.131	−0.248[a]	0.195	0.410[b]	0.332[b]	0.271[b]	−0.459[b]
RNLF	−0.250	−0.347[b]	0.333[b]				
GCC	−0.448[b]	−0.361[b]	0.373[b]	0.805[b]			
MV	−0.323[a]	−0.223[a]	0.259[a]	0.428[b]	0.475[b]		

[a] Correlation is significant at the 0.05 level.
[b] Correlation is significant at the 0.01 level.

In conclusion, our results show that RNFL, GCC and MV decreased in MS patients with or without DMT comparing to controls and it is more prominent in eyes with ON. These results may be related to involvement of the optic nerve or axonal degeneration of central nervous system as a consequence of MS disease course. For better understanding the pathophysiology, follow-up long term studies are needed.

Conflict of interest

There are no conflicts of interest.

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First (BT) and second authors (AS) have contributed equally in this study.

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