Journal of the Neurological Sciences 335 (2013) 182–185

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

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ARTICLE INFO

Article history:
Received 17 June 2013
Received in revised form 26 August 2013
Accepted 19 September 2013
Available online 1 October 2013

Keywords:
Multiple sclerosis
Optic coherence tomography
OCT
Visual evoked potentials
VEP
RNFL

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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http://dx.doi.org/10.1016/j.jns.2013.09.027

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.