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ORIGINAL ARTICLE

Decreased Ocular Pulse Amplitude and Retinal Nerve Fibre Layer in Multiple Sclerosis

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ABSTRACT

This study was conducted to assess ocular pulse amplitude and retinal nerve fibre layer in patients with multiple sclerosis and their correlation with disease duration and with severity. Retinal nerve fibre layer thickness was measured by Heidelberg Retinal Tomography II (HRT-II; Heidelberg Engineering, Dossenheim, Germany) and ocular pulse amplitude was measured by dynamic contour tonometry (Ziemer Ophthalmic Systems, Port, Switzerland) in 37 multiple sclerosis patients and 72 age- and gender-matched controls. Ocular pulse amplitude was significantly reduced and retinal nerve fibre layer was significantly thinner in temporal, superotemporal, and nasal sectors in patients with multiple sclerosis regardless of having an optic neuritis attack. The retinal nerve fibre layer was thinner in eyes with a previous optic neuritis attack compared with the eyes without an attack, but the difference was not significant. Ocular pulse amplitude showed a positive correlation with visual evoked potential amplitude and a negative correlation with visual evoked potential latency. Retinal nerve fibre layer thickness showed a significant negative correlation with the disease duration but not with visually evoked potential, disease severity, nor previous optic neuritis. These findings indicate that the process of degeneration starts in the early period of the disease, as our study group is composed of early–middle-stage multiple sclerosis patients, and is independent of relapses.

Keywords: Multiple sclerosis, ocular pulse amplitude, optic neuritis, retinal nerve fibre layer, visual evoked potential

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease characterized by axonal injury in the central nervous system.[1] Among various ophthalmic abnormalities, optic neuritis is the most widely described visual disturbance in MS, but less common manifestations such as uveitis and ophthalmoplegia secondary to cranial nerve palsy may also occur.[2,3] Recently, it was reported that retinal nerve fibre layer (RNFL), which comprises non-myelinated axons of retinal ganglion cells, reflects the disease activity in MS.[1,4]

The underlying pathophysiology is unknown, but some recent models support the presence of three mechanisms including inflammation, demyelination, and neurodegeneration in MS.[4] A secondary vascular dysfunction has also been proposed, which might cause a reduction in optic disc and choroidal perfusion.[5]

Ocular pulse amplitude (OPA) is the difference between the systolic and diastolic intraocular pressure (IOP).[6–8] OPA is accepted as an indirect indicator of choroidal perfusion that reflects the ocular blood flow corresponding to the heart pulse.[7] OPA can be measured by dynamic contour tonometry, which is a slit lamp mounted contact tonometer that uses a transcorneal method to measure IOP. The tonometry gathers 100 IOP readings per second, records dynamic IOP, and therefore measures not only IOP but also the OPA.

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Since its introduction as an indicator of choroidal blood flow, OPA has been investigated and evaluated in different clinical settings such as glaucoma, Behçet disease, thyroid ophthalmopathy, and carotid artery stenosis.[9–12] In MS, a reduction of ocular blood flow in retro-orbital vessels had been shown by Doppler ultrasonography (USG); however, until now OPA in MS patients has not been reported.[13–15] In this study, we aimed to measure OPA and to determine any changes in choroidal perfusion in patients with MS. Another objective of this study was to evaluate RNFL changes in MS patients and to find out whether a past history of optic neuritis (ON) attack affects OPA and RNFL.

METHODS

Patients with a diagnosis of MS were included in this prospective study after institutional board approval. The control group consisted of healthy subjects who were recruited from the hospital staff. All participants provided informed consent to participate in the study.

Both eyes from each participant were included in the study. Exclusion criteria were a history of intraocular surgery; ON episode within 2 months prior to the beginning of the study; coexistent ocular disease (glaucoma, uveitis, etc.); significant refractive error (more than 4 dioptres of spherical equivalent refraction or 3 dioptres of astigmatism); any vascular or autoimmune diseases (diabetes mellitus, hypertension, Buerger, vasculitis etc.); or any media opacity that could prevent optimum imaging by retinal tomography.

The study group consisted of patients who were diagnosed as definite relapsing remitting MS according to modified McDonald criteria.[16] All patients were relatively in the early–middle phases of the disease. All patients had two or more attacks and those with the diagnosis of clinical isolated syndrome were excluded from the study. The time elapsed from the last attack was at least 1 month for all patients included in the study. The duration of MS was 4.97 ± 3.47 (1–15) years and the mean time period since last attack was 11.2 ± 5.1 months (Table 1). Disease duration, the Expanded Disability Status Scale (EDSS), and treatments were documented by the neurologist. EDSS was designed for defining the neurological disability of patients with MS and ranged from 0 to 10 (0 reveals normal neurological examination while 10 means death). The diagnosis of ON was based on clinical findings, which included the presence of decreased visual acuity and colour vision, visual field defect, relative afferent pupil defect, and a compatible fundus examination.

Each eye was considered separately in the study. Participants had detailed ophthalmic evaluation including best-corrected visual acuity and intraocular pressure measurement, biomicroscopic anterior segment, and dilated posterior segment examination. Additionally, OPA, visually evoked potential (VEP), and RNFL analyses were performed in all participants.

Ocular pulse amplitude was measured by dynamic contour tonometry (Ziemer Ophthalmic Systems, Port, Switzerland). Topical proparacaine 0.5% was applied before each measurement. OPA measurement was performed according to the methods that had been described previously and the measurements of acceptable quality (Q1 to Q3) were recorded.[7,17]

RNFL thickness measurements were performed by Heidelberg Retinal Tomograph II (HRT-II; Heidelberg Engineering, Dossenheim, Germany). HRT is a confocal laser scanning system that creates a three-dimensional (3D) image of the optic nerve and gives information about optic nerve and peripapillary RNFL. Stereometric parameters were calculated automatically by the software. The values obtained from the HRT-II scan for the study included RNFL thickness in temporal, superotemporal, inferotemporal, nasal, superonasal, and inferonasal sectors.

Visually evoked potentials (VEPs) were examined in a quiet room with dimmed light (30 lux). For VEP recordings subjects were seated 1 m away from a television monitor. Tests were performed by a computerized electromyography (EMG) device (Medelec Premiere Plus, Vickers Medical - Medelec Ltd, Woking, UK). Stimuli were given as a checkerboard pattern of black and white squares while subjects were instructed to look to a point in the middle of the screen with one eye closed. Needle electrodes were inserted into the scalp in the midline

TABLE 1 Clinical characteristics of patients with multiple sclerosis (MS).

MS duration (years)	
Mean ± SD	4.97 ± 3.47
Range	1–15
EDSS	
Mean ± SD	1.37 ± 1.08
Range	0–4.5
Time period since last MS attack (months)	
Mean ± SD	11.2 ± 5.1
Treatment *n* (%)	
Interferon	23 (62.1)
Glatiramer	11 (29.7)
None	3 (8.1)
Number of eyes with ON attack *n* (%)	19 (27.5)
VEP amplitude (μv)	
Mean ± SD	10.1 ± 15.5
Range	2.6–135
VEP latency (ms)	
Mean ± SD	118.5 ± 18.4
Range	13–153

N = 37 for MS patients.
EDSS = Expanded Disability Status Scale; ON = optic neuritis; VEP = visual evoked potentials.

over the occipital region 2.5 cm above the inion (Oz: active electrode) and over the frontal region (Fz: reference). The ground electrode was placed on the forearm. During the test 256 responses were averaged for both eyes and were analysed in terms of peak latencies and peak-to-peak amplitudes of the maximal negative and positive deflections determined by visual inspection: the N75 peak was defined as the most negative point, P100 as the most positive point following N75, and N145 as the second most negative point. P100 latency and amplitudes were recorded for each subject.

Statistical analysis was performed by SPSS statistical software (SPSS 17.0.0 for MS Windows; SPSS, Chicago, IL, USA). Descriptive statistics were expressed as mean ± SD. Student's *t* test was used to compare means of the study and the control groups for each variable.

RESULTS

A total of 37 MS patients (69 eyes) and 42 controls (84 eyes) were included in the study. The mean age was 38.78 ± 11.22 years in MS group and 35.97 ± 6.82 years in the control group. There were 32 females (86.5%) and 5 males (13.5%) in MS group, whereas there were 28 females (66.7%) and 14 males (33.3%) in the control group. The groups were not significantly different in terms of age and gender ($p = 0.192$ and $p = 0.064$, respectively). In MS group, 19 eyes (27.5%) had previous ON attack. Table 1 shows the clinical characteristics of patients with MS.

Ocular Pulse Amplitude

OPA was significantly lower in MS group (2.16 ± 0.93) than the control group (2.57 ± 1.08; $p = 0.014$). When MS group was divided into two groups based on having an ON attack or not, OPA did not significantly differ between the groups (2.12 ± 0.81 in eyes with an ON attack versus 2.18 ± 0.97 in eyes without an ON attack; $p = 0.820$). OPA showed a significant positive correlation with VEP amplitude and a negative correlation with VEP latency but not with disease duration and severity (Table 2).

Retinal Nerve Fibre Layer

RNFL was significantly thinner in temporal, superotemporal and nasal sectors in MS group compared with the control group ($p = 0.017$, $p = 0.049$, and $p = 0.039$, respectively; Table 3). In MS group, RNFL thickness was not significantly different in any of the sectors based on having a previous ON attack or not.

In MS group, RNFL thickness in temporal sector significantly and negatively correlated with the disease duration ($r = -0.244$, $p = 0.043$) but not with disease severity, VEP amplitude, and latency (Table 4).

DISCUSSION

The novel finding in our study was that OPA, an indirect indicator of choroidal perfusion, was significantly reduced in patients with MS, regardless of a past history of ON, when compared with healthy controls. RNFL was significantly thinner in temporal, superotemporal, and nasal sectors in patients with MS compared with controls. RNFL was thinner in eyes with previous ON attack compared with the eyes without an attack, but the difference was not statistically significant.

TABLE 2 The correlation between ocular pulse amplitude (OPA) and the disease duration, disease severity (EDSS), and visual evoked potential (VEP) amplitude and latency in patients with multiple sclerosis.

	n	*r*	*p*
Duration	69	0.118	0.332
EDSS	69	0.039	0.749
VEP amplitude	66	0.269	**0.029**
VEP latency	66	−0.294	**0.017**

r = correlation coefficient.
p values significant at < 0.05 are shown in bold.

TABLE 3 The comparison of retinal nerve fibre layer (RNFL) thickness in patients with multiple sclerosis (MS) and the control group.

	MS group					
	ON attack (+) (*n* = 19)	ON attack (−) (*n* = 50)	*p* Value	Total MS (*n* = 69)	Control group (*n* = 84)	*p* Value
Mean RNFL (mm)	0.24 ± 0.05	0.26 ± 0.06	0.231	0.25 ± 0.05	0.27 ± 0.06	0.120
Temporal RNFL (mm)	0.08 ± 0.02	0.09 ± 0.02	0.340	0.08 ± 0.02	0.09 ± 0.02	**0.017**
Superotemporal RNFL (mm)	0.28 ± 0.08	0.30 ± 0.06	0.210	0.29 ± 0.07	0.32 ± 0.07	**0.049**
Inferotemporal RNFL (mm)	0.25 ± 0.08	0.29 ± 0.08	0.101	0.28 ± 0.08	0.29 ± 0.08	0.639
Nasal RNFL	0.28 ± 0.08	0.29 ± 0.07	0.414	0.29 ± 0.08	0.32 ± 0.1	**0.039**
Superonasal RNFL (mm)	0.35 ± 0.08	0.35 ± 0.09	0.891	0.35 ± 0.08	0.36 ± 0.09	0.517
Inferonasal RNFL (mm)	0.34 ± 0.08	0.37 ± 0.11	0.314	0.36 ± 0.1	0.38 ± 0.09	0.220

The table also shows the comparison of RNFL thickness in MS patients with or without previous optic neuritis (ON) attack.
p values significant at < 0.05 are shown in bold.

TABLE 4 The correlation between retinal nerve fibre layer (RNFL) thickness and the disease duration, disease severity (EDSS), and visual evoked potential (VEP) amplitude and latency in patients with multiple sclerosis (MS).

	MS Duration ($n = 69$)		EDSS ($n = 69$)		VEP amplitude ($n = 66$)		VEP latency ($n = 66$)	
	r	p	r	p	r	p	r	p
Mean RNFL	−0.114	0.351	0.060	0.627	0.039	0.754	−0.030	0.814
Temporal RNFL	−0.244	**0.043**	−0.043	0.725	−0.129	0.304	0.061	0.626
Superotemporal RNFL	−0.137	0.266	−0.050	0.687	−0.147	0.243	0.022	0.861
Inferotemporal RNFL	−0.173	0.155	0.127	0.298	0.011	0.931	0.047	0.706
Nasal RNFL	−0.020	0.873	0.055	0.653	0.067	0.591	−0.076	0.546
Superonasal RNFL	−0.045	0.716	0.026	0.830	0.158	0.204	−0.107	0.391
Inferonasal RNFL	−0.046	0.707	0.125	0.307	0.077	0.538	−0.007	0.954

r = correlation coefficient.
p values significant at < 0.05 are shown in bold.

A reduction in ocular blood flow was shown by Doppler USG in patients with MS. Hradilek et al.[15] noticed a short-term effect in ocular blood flow following ON attack, which was lost in the chronic phase. Modrzejewska et al.[14] showed decreased blood flow parameters both in eyes with previous ON attack and in fellow, unaffected eyes of MS patients. Similarly, Pache et al.[13] reported significantly reduced blood flow velocity in ocular vessels in MS patients regardless of a previous ON attack, indicating a general reduction of retrobulbar blood flow in these patients. In our study, OPA was significantly reduced in patients with MS regardless of having an ON attack compared with healthy controls. The suggested mechanism for this reduction of perfusion is vasoconstriction secondary to increased levels of serum endothelin-1 (ET-1), which is a potent vasoconstrictor.[5,13] Matrix metalloprotease-2, which is expressed in and around MS plaques, is identical to the endothelin-converting enzyme, which changes the precursor protein big endothelin-1 to its active form ET-1 and might be responsible from the increased levels of ET-1 in MS patients.[13,18,19] It was proposed that high ET-1 level affects choroidal and optic nerve head circulation and causes a reduction in the blood flow of retroocular vessels and a slight paleness in the optic nerve head.[5] More evidence is needed to claim that there is an association between OPA and ET-1 levels, and it is unclear whether ocular hypoperfusion is a secondary pathology in addition to demyelination and degeneration process in MS.

Recent studies have revealed that RNFL was significantly affected in MS and this reduction of RNFL thickness was not limited to eyes with a previous ON attack. Oberwahrenbrock et al.[20] reported that eyes of MS patients without a previous ON showed a significant reduction of RNFL thickness compared with healthy controls. Fernandes et al.[21] showed that RNFL thickness was significantly reduced in patients with MS, either with or without ON. Similarly, in our study, RNFL was significantly thinner in MS patients than controls and in MS group, the difference in RNFL between eyes with or without ON was not significant. Although RNFL thinning occurred in eyes of patients with MS in general, some investigators found that the thinning could be greater in eyes with ON attack.[4,22] However, having ON attack was not associated with further progressive thinning compared with fellow eyes and was not a risk factor for increased chronic damage in MS patients without ophthalmic relapses.[4] This loss of RNFL was believed to reflect the progressive degeneration associated with the disease and it was more prominent in more advanced stages of the disease.[4,22] However, we found significant thinning in an early–middle stage MS group. This finding indicates that degeneration starts earlier, long before the disease becomes advanced. Briefly, the measurement of RNFL appears to be a valuable tool for monitoring the progression of axonal degeneration in MS disease.[1]

MS primarily affects young women, which can explain the relative predominance of female patients in our study.[23] This predominance may bring the question of possible effect of gender on our findings. However, our study and control groups were well balanced in terms of gender. Additionally, the previous studies did not reveal an association between gender and RNFL.[24] Therefore, we believe that our findings were not significantly affected by the predominancy of females in our study group.

Our findings revealed that OPA and RNFL thickness were significantly reduced in MS patients regardless of having an ON attack. OPA significantly correlated with VEP amplitude, which reflects the axonal damage, and VEP latency, which reflects the demyelination. However, the lack of correlation between RNFL, VEP, disease severity, and ON attacks suggests that this degeneration process is independent from attacks. The newly emerging concept is that the course of MS disease is defined by the appearance of neurological symptoms during attacks and by ongoing progressive subclinical axonal degeneration.[25] Our findings also indicate that degeneration starts in the early period of the disease, since our study group is composed of early–middle-stage MS patients. However, since this topic remains

controversial in the scientific literature, further studies with larger sample sizes are needed.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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