ORIGINAL ARTICLE

Retinal Nerve Fibre Layer Thickness in Migraine Patients with or without Aura

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ABSTRACT

The objective of this study was to evaluate the retinal nerve fibre layer (RNFL) thickness using spectral-domain optical coherence tomography (Optos SD-OCT, UK) in migraine patients with or without aura and to search for possible structural effects of migraine on the retina. Eighty eyes of 40 migraine patients and 80 eyes of 40 healthy subjects were included in this study. All four quadrants (temporal, superior, nasal, and inferior) and average peripapillary RNFL measurements were taken with SD-OCT in both groups. The average age of the patients and the control group were 35.7 ± 9.5 and 40.9 ± 12.7 years, respectively. In the migraine group, 45% of patients were with aura, and 55% were without aura. The average frequency of attacks per month and the migraine diagnosis time was 4.6 ± 4.4 and 6.2 ± 5.6 , respectively.

Parameters related to RNFL thickness of right and left eyes' average, superior, inferior, nasal, and temporal quadrant values were found to be similar in migraine and control subjects ($p > 0.05$). Focusing on the RNFL thickness of right and left eyes and the migraine parameters, there were no statistically significant differences between migraineurs with aura and without aura ($p > 0.05$). The correlations between the RNFL thickness parameters and the migraine patient's MIDAS (Migraine Disability Assessment Score) score, frequency of attacks, and diagnosis time of migraine were studied and no correlation was noted ($p > 0.05$). These findings demonstrated that migraine disease with or without aura does not have any effect on the thickness of the RNFL.

Keywords: Migraine, retinal nerve fibre layer thickness, spectral-domain optical coherence tomography

Migraine is a common, chronic, multifactorial neurovascular disorder typically characterised by recurrent attacks of disabling headache and autonomic nervous system dysfunction (migraine without aura); up to one third of patients also have neurological aura symptoms (migraine with aura).¹

Disturbances in the neurovascular system remains one of the most important mechanisms involved in the pathogenesis of migraine, and it is possible that hypoperfusion might affect other areas besides the brain, such as the retina.^{2–13} Although vasoconstriction of cerebral and retinal blood vessels is a transient phenomenon, the chronic nature of the migraine might cause permanent structural abnormalities of the brain and also of the retina. Alterations

of perfusion in the optic nerve head microcirculation or even in the retina may lead to ganglion cell death in migraine patients. On this basis, there are studies that have found differences in retinal nerve fibre layer (RNFL) thickness between migraine patients and healthy subjects.^{3–9}

RNFL thickness measurements can be used as an index to assess ganglion cell and retinal nerve fibre damage. With the introduction of optic coherence tomography (OCT), RNFL thickness measurements with 8–10 μm scale sensitivity have been possible.^{14–16}

The results of the articles addressing RNFL thickness in migraineurs are discrepant. Involved quadrants vary even if statistically significant reduction in RNFL thickness is found. There is no consensus of

opinion about RNFL thickness in migraineurs. The aim of our study is to determine whether there are differences in RNFL thickness between migraine patients (with/without aura) and normal subjects, and to show if there is a correlation between these structural changes and the migraine duration, attack frequency per month, and MIDAS (Migraine Disability Assessment Score) scores.

MATERIALS AND METHODS

This is a prospective, comparative, and descriptive study performed on a group of patients with migraine (study group) and a group of age-matched normal subjects (control group). The study was approved by the institutional ethics committee and conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Eighty eyes of 40 patients with migraine with or without aura according to the criteria of the Headache International Society and 80 eyes of 40 age-matched healthy controls were chosen prospectively. Patients with migraine were recruited from the neurology clinic, and the control group was recruited from the ophthalmology clinic.

All the participants underwent a complete ocular examination, including best-corrected visual acuity (BCVA) testing with Snellen charts, slit-lamp biomicroscopy, dilated fundus examination, pachymetry, and intraocular pressure (IOP) measurement by Goldmann applanation tonometer. Spherical equivalents between +3.00 and -3.00 dioptres were included in the study. Following the clinical examination, patients with glaucomatous damage by increased intraocular pressure or by a secondary mechanism was excluded. Eyes with retinal and optic disc pathology, glaucoma, dense cataract, or corneal opacity, which made OCT imaging impossible, and eyes previously subjected to intraocular surgery or ocular laser treatment were also excluded.

Migraine patients were required to have a clinical diagnosis of migraine, with or without aura, meeting the criteria of the International Headache Society. Migraine severity was assessed by a neurologist using a migraine disability questionnaire: Migraine Disability Assessment Score (MIDAS). Patients were interviewed regarding their type of migraine (with/without aura), number of attacks per month, length of migraine history, and antimigraine medication. MIDAS scores were divided into four grades. Grade I: infrequent disability (0 to 5); grade II: mild disability (6 to 10); grade III: moderate disability (11 to 20); and grade IV: severe disability (>21). Magnetic resonance (MR) scans of all migraine patients were checked for any intracranial pathologies. Patients with diabetes mellitus, hypertension, cardiovascular and renal

diseases, and history of central nervous system disorders including brain tumours, infarction, encephalitis, epilepsy, Alzheimer's disease, head or eye trauma, and any type of headache except for migraine were eliminated from the study.

Control subjects were required to have had less than three headaches in the past year and to never have experienced a migraine attack.

All patients and controls who met the ophthalmological criteria were examined with a spectral-domain (SD)-OCT (Optos SD-OCT, Glasgow, UK). 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 centred on the optic disc.

Parameters including average RNFL thickness in four quadrants were generated automatically in the analysis report. The average, temporal, superior, nasal, and inferior RNFL thickness data were collected and compared in both groups.

The statistical analysis was performed using the Statistical Package for Social Sciences SPSS 20.0 program (IBM, Armonk, NY, USA). The numerical data sets were tested for normal distribution with the Kolmogorov-Smirnov test. The independent *t* test and Mann-Whitney *U* test were used to analyse the quantitative data. The qualitative data were analysed using the chi-square test. Pearson and Spearman correlation analyses were carried out, and *p* values >0.05 were considered as statistically insignificant.

Mean, standard deviation, median, minimum-maximum, rate, and frequency values were used in the descriptive statistics of data. For linear regression analysis, the Pearson correlation coefficient (*r*) was used. The correlations between the OCT results and the migraine variables (MIDAS score, frequency of attacks per month, and migraine diagnosis time) were calculated.

RESULTS

Out of 80 subjects selected for the study, 40 were migraineurs and 40 were controls, all meeting the inclusion criteria. Out of 40 patients in the migraine group, 18 had migraine with aura and 22 had migraine without aura. There were no statistically significant differences between the migraineurs and the control subjects in sex and age (*p* > 0.05).

Comparing average, superior, inferior, and temporal RNFL thickness measurements of right eyes in the two groups, we found no statistically significant difference (*p* > 0.05). The RNFL thickness in the nasal quadrant of migraineurs was significantly higher in the right eyes (*p* < 0.05). The RNFL values of left eyes of both migraineurs and healthy subjects showed no statistically significant difference in all quadrants, including average values (*p* > 0.05) (Table 1).

TABLE 1. Age, sex, retinal nerve fiber layer (RNFL) thickness measurements of right and left eye in the migraine and control group. Intraocular pressure (IOP), migraine parameters and subgroups in migraine patients.

	Migraine group		Control group		<i>p</i>
	Ave. $\pm$ SD/ <i>n</i> , %	Med (Min–Max)	Ave. $\pm$ SD/ <i>n</i> , %	Med (Min–Max)	
Age	35.7 $\pm$ 9.5	36 (16–53)	40.9 $\pm$ 12.7	42 (20–59)	0.051
Sex					
Woman	31 (77.5%)		27 (67.5%)		0.317
Man	9 (22.5%)		13 (32.5%)		
RNFL thickness right eye					
Superior	129.3 $\pm$ 14.7	128 (101–155)	127.0 $\pm$ 13.0	127 (104–152)	0.451
Inferior	141.3 $\pm$ 16.8	137 (117–177)	138.3 $\pm$ 14.3	139 (111–167)	0.388
Nasal	92.7 $\pm$ 15.8	91 (60–125)	85.4 $\pm$ 15.7	81 (59–118)	0.042
Temporal	75.1 $\pm$ 12.4	77 (53–107)	76.1 $\pm$ 11.0	75 (49–103)	0.683
Average	109.6 $\pm$ 8.7	109 (90–126)	106.7 $\pm$ 8.6	106 (90–129)	0.137
RNFL thickness left eye					
Superior	134.3 $\pm$ 18.3	135 (72–172)	128.4 $\pm$ 13.6	129 (101–150)	0.110
Inferior	139.9 $\pm$ 17.7	139 (104–173)	134.1 $\pm$ 16.6	134 (90–170)	0.134
Nasal	85.7 $\pm$ 17.5	81 (62–137)	80.0 $\pm$ 12.1	80 (59–116)	0.094
Temporal	73.8 $\pm$ 10.2	74 (40–98)	74.0 $\pm$ 12.7	73 (50–97)	0.946
Average	108.4 $\pm$ 10.5	107 (83–127)	104.1 $\pm$ 9.3	103 (84–128)	0.057
IOP					
Right	15.0 $\pm$ 3.2	15 (9–23)			
Left	15.5 $\pm$ 3.0	16 (10–20)			
Diagnosis time (years)	6.2 $\pm$ 5.6	5 (0–20)			
Frequency of attacks per month	4.6 $\pm$ 4.4	3 (1–15)			
MIDAS score					
I	24 (60.0%)				
II	7 (17.5%)				
III	7 (17.5%)				
IV	2 (5.0%)				
Migraine type					
With aura	18 (45.0%)				
Without aura	22 (55.0%)				

The independent *t* test/Chi-square test.

We also looked for differences in migraineurs with or without aura. The mean age of migraineurs with aura was significantly lower than the migraineurs without aura ($p < 0.05$). Gender distribution was of no significance between the with aura and without aura groups ($p > 0.05$). We found no statistically significant differences between migraineurs with or without aura in any of the migraine parameters studied: MIDAS score, frequency of attacks, and migraine diagnosis time. Also, we found no statistical difference between the migraineurs with aura and migraineurs without aura in the RNFL thickness parameters of right and left eyes' average, superior, inferior, nasal, and temporal quadrant values ($p > 0.05$). No statistically significant difference was found between the two migraine subgroups in the intraocular pressure measurements ($p > 0.05$).

The correlations between the RNFL thickness of right and left eyes' average, superior, inferior, nasal, and temporal quadrants and the migraine parameters (MIDAS score, frequency of attacks and diagnosis time of migraine) were compared in patients with migraine with aura and without aura, and no significant difference was noted ($p > 0.05$) (Table 2).

TABLE 2. Correlation between the retinal nerve fiber layer (RNFL) thickness of right-left eye and the migraine parameters.

	Superior	Inferior	Nasal	Temporal	Average
RNFL thickness right eye					
MIDAS Score					
<i>r</i>	−0.054	0.059	−0.133	0.285	0.046
<i>p</i>	0.742	0.719	0.415	0.075	0.779
Migraine diagnosis time (years)					
<i>r</i>	0.271	0.206	0.075	−0.119	0.206
<i>p</i>	0.090	0.203	0.647	0.463	0.202
Frequency of attacks per month					
<i>r</i>	0.134	−0.020	−0.239	0.136	−0.013
<i>p</i>	0.408	0.903	0.137	0.403	0.936
RNFL thickness left eye					
MIDAS score					
<i>r</i>	−0.175	0.152	−0.065	−0.041	0.002
<i>p</i>	0.280	0.349	0.689	0.802	0.989
Migraine diagnosis time (years)					
<i>r</i>	−0.131	−0.015	0.071	−0.263	−0.098
<i>p</i>	0.422	0.929	0.663	0.102	0.549
Frequency of attacks per month					
<i>r</i>	0.072	−0.043	−0.100	−0.031	−0.036
<i>p</i>	0.658	0.793	0.537	0.848	0.825

Spearman/Pearson correlation.

DISCUSSION

Migraine is a chronic, progressive neurovascular disorder and can cause several complications, including ischaemic retinal diseases.^{10,11} Retinal alterations described in the literature manifest as acute and chronic retinal damage. Migraine can lead to focal decrease in cerebral blood flow and perhaps in retinal circulation.³⁻⁹ Whether similar changes take place in the retina in migraine with or without aura is a subject of uncertainty and few studies have been conducted on this issue.

In this study, we hypothesised that the measurement of RNFL thickness using OCT in patients with migraine might aid in the search for the ophthalmological complications of migraine.

Retinal infarcts and retinal ischaemic lesions have been reported in migraine patients.¹⁰⁻¹² Using colour Doppler imaging, Kara *et al.*¹³ reported that central retinal artery and posterior ciliary artery vessel resistance was higher in patients with migraine in both headache and headache-free periods compared with the control group. All of these studies support the hypothesis of low perfusion and vascular retinal variations in migraine.

There are studies supporting the ischaemic theory by focusing on the RNFL thickness in migraine patients.³⁻⁹ The use of OCT can demonstrate these changes by obtaining longitudinal cross-sections of the retina and quantifying the thickness of the RNFL.¹⁴⁻¹⁶

In the literature, in 2005 Tan *et al.*³ reported the first study about the measurement of the RNFL thickness in migraine patients with and without aura. Their study group included 39 migraine patients (15 with aura, 24 without aura), and 25 healthy subjects served as a control group. Their results showed no evidence of structural alterations of the RNFL thickness in the study group compared with the control group.

The results of our study corresponds with the results of Tan *et al.*³ The measured RNFL thickness was not significantly different in any of the quadrants in migraineurs with or without aura and healthy controls except for the nasal quadrant of the right eye, which had a significantly higher value. The patient population was small in the study of Tan *et al.*³ It is possible that the migraine group may have included patients with supra-normal RNFL values, which may have affected inter-group comparisons. Recruiting relatively small number of patients is one of the limitations of Tan *et al.*'s study. Similar with the findings of Tan *et al.*'s study, our study shows that RNFL thickness does not correlate with illness duration and frequency.³

In the study of Martinez *et al.*⁴ using scanning laser polarimetry, average RNFL in the migraine subjects was significantly lower than the control group. However, there were no differences between migraine

subjects and controls in mean RNFL thickness in superior and inferior areas. Also, a strong correlation was found between migraine severity and the RNFL thickness parameters.

Another study of Martinez *et al.*⁹ using OCT found that the RNFL was significantly thinner in the temporal region in migraine patients when compared with age-matched healthy subjects. In addition to these findings, a significant correlation was found between migraine severity and RNFL thickness. Moreover, 360° average RNFL was thinner in patients with migraine with aura compared with the migraine patients without aura. In our study, we did not find any correlation between RNFL thickness and MIDAS score or duration of migraine history in migraine patients.

In a similar study, Sorkhabi *et al.*⁷ found that RNFL thickness is significantly lower in the nasal quadrant in the eyes of migraine patients. The correlation between the RNFL thickness and the migraine parameters was studied in patients with migraine with aura and without aura; no significant difference was noted in this study. Sorkhabi *et al.* did not mention MIDAS scores in their study. This may be a causal factor in the discrepancy with our study's results.

In another study, Gipponi *et al.*⁶ concluded that migraine patients have RNFL thickness reduction in the superior retinal quadrant when compared with normal subjects. They did not group patients based on MIDAS score; instead, they divided migraine patients into two subgroups: the first with an illness duration of less than 15 years, and the second one with an illness duration of more than 15 years. They did not find significant differences between these two groups. Classifying patients according to headache frequency also did not reveal statistical differences between RNFL thickness values and headache frequency.

Migraine with aura is an accepted risk factor for subclinic ischaemic lesions of the brain¹⁷ and ischaemic stroke, mostly among women of a young age.^{18,19} For the retinal complications, our study found no significant differences in RNFL thickness between migraine with aura and female patients. In the study of Martinez *et al.*, the average and the temporal quadrant RNFL were thinner in the migraineurs with aura.⁴

The results of the articles addressing RNFL thickness in migraineurs are discrepant. Involved quadrants vary even if statistically significant reduction in RNFL thickness is found. There is no consensus of opinion about RNFL thickness in migraineurs. In our study we also did not find any significant change in RNFL thickness. Larger series with follow-up periods would possibly be more efficacious than cross-sectional studies.

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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