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Choroidal vascularity index and retinal nerve fiber layer reflectivity in newly diagnosed migraine patients

Emine Temel [a,*], Nazife Aşikgarip [a], Yusuf Koçak [b], Cevdet Şahin [b], Gökçen Özcan [a], Özkan Kocamiş [c], Kemal Örnek [c]

[a] Kırşehir Ahi Evran Training and Research Hospital, Department of Opthalmology, Kırşehir, Turkey
[b] Kırşehir Ahi Evran University School of Medicine, Department of Neurology, Kırşehir, Turkey
[c] Kırşehir Ahi Evran University School of Medicine, Department of Opthalmology, Kırşehir, Turkey

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ABSTRACT

Purpose: To evaluate the choroidal structural parameters, peripapillary retinal nerve fiber layer (RNFL) thickness, and optic density index (ODI) and their correlations in patients with migraine.
Methods: Twenty-eight newly diagnosed migraine patients and 28 age-matched healthy controls were included in this prospective cross-sectional study. The enhanced depth-optical coherence tomography images were evaluated. The choroidal area (CA) was binarized to the luminal area (LA) and stromal area (SA) using Image J. The choroidal vascularity index (CVI), the mean peripapillary RNFL thickness, superior-inferior-nasal-temporal quadrant RNFL thicknesses, and the ODI were compared statistically.
Results: The difference in the mean CVI between the patient group and controls reached a statistical significance (p=0.035). The mean RNFL thickness was significantly decreased in patients with migraine compared with the controls (p=0.040). The mean RNFL thickness in the superior, temporal, and inferior quadrants was significantly decreased in the patient group in comparison to the control subjects (p=0.030, p=0.001, and p=0.022, respectively). There were no significant differences between the migraine group and the controls for the mean ODI of RNFL (p=0.399).
Conclusion: The CVI and the RNFL thickness except for the nasal quadrant were significantly decreased in newly diagnosed migraine patients.

1. Introduction

Migraine is characterized by moderate to severe headache, nausea, vomiting, nervousness and light and sound sensitivity.[1] According to the Global Burden of Disease Study 2016, with more than one billion people, migraine is a leading cause of disability worldwide and contributes to the social-economic burden.[2]

The pathogenesis of the disease is very complex and has not been fully understood yet. Cortical spreading depression activates the trigeminal vascular system and triggers the associated neurological and vascular responses and the neurovascular responses lead to the spasm of the cerebral and retrobulbar vessels.[3,4] The chronic nature of the disease can be a risk factor for the structural damage to the brain and possibly to the retina or optic nerve due to the decreased blood flow.[5] The perfusion changes in the optic nerve head circulation may contribute to the retinal ganglion cell death and retinal nerve fiber layer (RNFL) thinning.[6,7]

Optical coherence tomography (OCT) is a reliable, non-invasive imaging technique that provides cross-sectional imaging of the retina.[8] In the recent years, studies have evaluated the RNFL thickness changes in patients with migraine.[9,10] The optic density index (ODI) of the RNFL is a promising measure that may indicate optic nerve damage in the preperimetric stage.[11] The choroidal vascularity index (CVI) is also a new quantitative parameter described by Agrawal et al. as a novel OCT parameter for measuring the vasculature status of the choroid.[12]

Therefore, in this study, we evaluated, for the first time in the literature, the binarized choroidal structural parameters, the RNFL thickness, and the ODI in a group of patients with migraine.

* Corresponding author at: Department of Ophthalmology, Kırşehir Ahi Evran Training and Research Hospital.
E-mail address: emine912@hotmail.com (E. Temel).

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2. Materials and methods

This prospective cross-sectional study included 28 participants who were newly (in the last 3 months) diagnosed with migraine and 28 age-matched healthy volunteers. The study was approved by the Institutional Review Board Committee of the Ahi Evran University and was performed according to the ethical principles of the Declaration of Helsinki. After explaining the nature of the study, informed consent was obtained from all participants.

The patients were recruited from the headache outpatient clinic of the Neurology Department between January 2021 and May 2021. All patients had migraines without aura and with a frequency of migraine attacks less than five times per month. The mean blood pressure was within the normal range for both groups. All subjects underwent a comprehensive ophthalmologic evaluation, including measurement of best-corrected visual acuity with the Snellen chart (BCVA), pupillary responses, slit-lamp examination, and Goldmann applanation tonometry.

Exclusion criteria were as follows; eyes with BCVA less than 20/25, spherical equivalent refractive error more than ±2.0 diopters and intraocular pressure more than 21 mmHg, systemic (diabetes mellitus, hypertension, cardiac diseases, other central nervous system diseases) or ocular diseases (glaucoma, uveitis, high myopia, optic neuropathy, age-related macular degeneration), media opacities preventing adequate imaging, previous intraocular intervention, history of smoking. None of the participants consumed caffeine and/or alcohol or received analgesic medications, triptans, or ergot alkaloids for 24 hours prior to the examination.

After pupillary dilatation, enhanced depth imaging (EDI) OCT (Spectralis®, SD-OCT; software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany) was performed. All examinations were done within the same time interval (between 1:00 pm and 3:00 pm) under dim light conditions. A single, experienced staff technician captured the EDI-OCT images. EDI-OCT was conducted using the technique described by Spaide et al.[13] The participants with a maximum image quality score of less than 15 were excluded. Only the eyes with the highest scan score index were selected. All OCT scans were reviewed by the first author (ET) who is experienced at evaluating OCT images of the optic nerve and retina.

The OCT device contained a superluminescent diode with a wavelength of 870 nm and could obtain 40.000 A-scans per second. The axial and transverse resolutions were 7 and 14 μm, respectively. Two high-quality horizontal line scans were obtained through the fovea using a1 × 30-degree areas. One hundred scans were averaged for each section. The automatic real-time averaging mode that maximizes the signal-to-noise ratio was used to ensure high-quality images.

The choroidal area (CA) was binarized to the luminal area (LA) and stromal area (SA) using Image-J, an open-code Java-based image processing software (version 1.50a; National Institutes of Health). The CA was measured manually at a 3000 micrometers area, with a margin of 1500 micrometers nasal and temporal to the foveal center horizontally and from the retina pigment epithelium (RPE) to the choroidoscleral border vertically. Binarization was performed using the Niblack auto local threshold method (Fig. 1). The white pixels were accepted as the SA, and the dark pixels were accepted as the LA.[14] The CVI was calculated as the proportion of the LA to the total CA.

The Heidelberg OCT automatically measured RNFL thickness in each B-scan provided by HRA software version 5.4.8.0. We assessed the mean RNFL thickness (360̊ measured), temporal, superior, nasal, and inferior quadrant thicknesses (Fig. 2). The ODI measurements were obtained using ImageJ.[15] The "region of interest (ROI) selection method" was used as, two quadrangular shaped ROIs of identical shape and size were chosen at the same vertical line one for the RNFL and the other for the RPE located inferiorly, ODs of the RNFL and RPE calculated (Fig. 3). For all four quadrants of the papilla, the same measurements were taken and the average was given in the results. ODI was the measured ODs of the

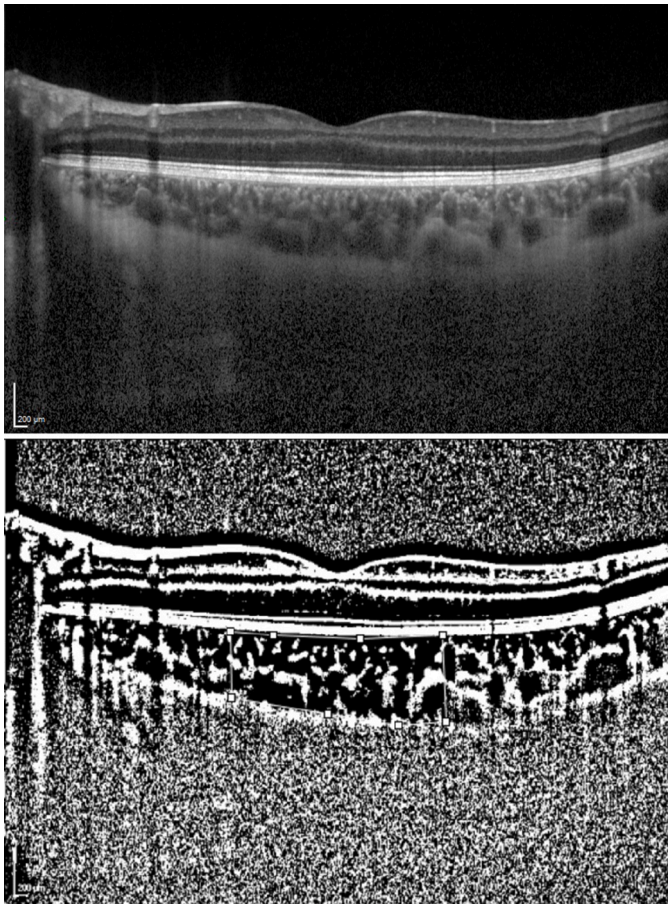

Fig. 1.. Representative CVI measurement: A converted binary image using Image-J with the area of interest in the choroid was demarcated with a white line. The white pixels were accepted as the SA, and the dark pixels were accepted as the LA. The CVI was defined as the proportion of the LA to the total CA.

RNFL and RPE calculated according to the formula:

$$\mathbf{ODI} = \mathbf{OD}(\mathbf{RNFL_{ROI}})/(\mathbf{RPE_{ROI}})$$

Statistical analysis was done using SPSS (Statistical Package for Social Sciences version 15. A Shapiro–Wilk test was performed for all variables to detect departures from a normal distribution. Spearman correlation coefficients for measurement results were calculated. The data adjusted for age and corrected means were estimated with standard error and 95% confidence interval. Statistically significance was considered at a p-value of $\leq$0.05.

3. Results

In all, there were 28 patients with migraine and 28 healthy control subjects. The mean age of the participants was 38.4 ± 4.8 years (range: 35-45) for the migraine group and 38.9 ± 5.2 years (range: 35-45) for the control group (p=0.644). Of the migraine patients, 15 (53.6%) were female and 13 (46.4%) were male. There were 14 (50.0%) females and 14 (50.0%) males in the control group. There were no significant differences between the groups in terms of gender distribution (p=0.564).

The BCVA of all participants was 0.0 logMAR. The mean intraocular pressure was 12.6 ± 1.8 mmHg (range: 11-14) for the migraine group and 12.3 ± 2.0 mmHg (range: 11-14) for the controls. The mean refractive error was –0.84 ± 0.54 D (range –1.25 to 1.0 D) in the migraine group, and –0.82 ± 0.56 D (range –1.25 to 1.0 D) in healthy subjects. There were no significant differences with respect to the refractive error and intraocular pressure between groups (p=0.498 and

Fig. 2.. Representative RNFL thickness measurement: Automatically measurement of mean RNFL thickness (360̊ measured), temporal quadrant thickness, superior quadrant thickness, nasal quadrant thickness, and inferior quadrant thickness.

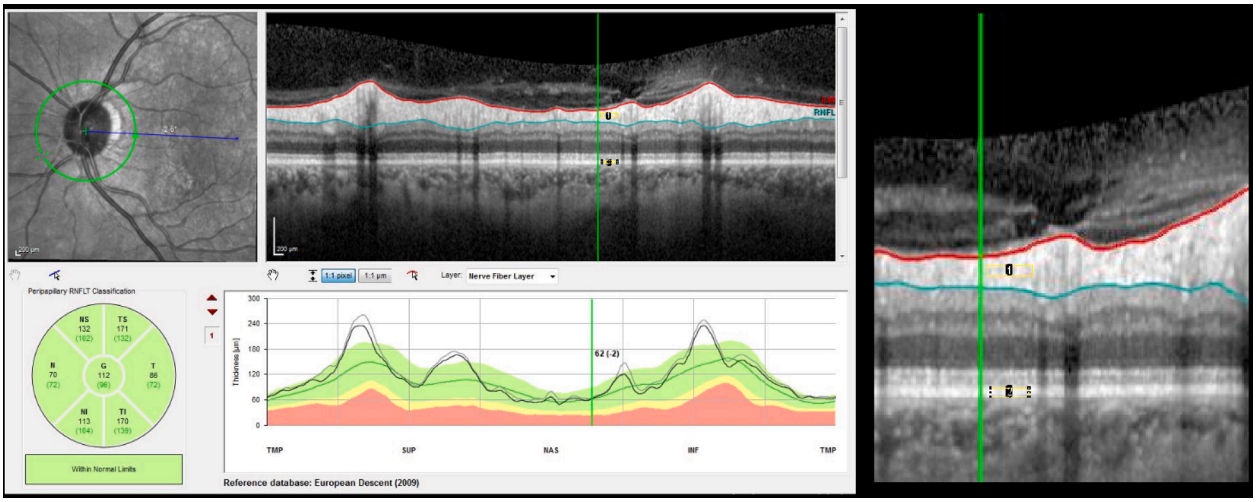

Fig. 3.. Representative ODI measurement: Original OCT image and ROI selection of RNFL and RPE layers. The ODI was calculated as the proportion of the OD of RNFL to the OD RPE.

p=0.845, respectively). The demographic and clinical characteristics of participants are shown in Table 1.

The mean RNFL thickness was 102.23 ± 9.09 µm (range: 89-118) in patients with migraine and 107.19 ± 6.93 µm (range: 99-126) in the control group (p=0.040).

The mean RNFL thickness in the superior quadrant was 112.4 ± 15.4 µm (range: 82-142) in the migraine group and 119.4 ± 16.5 µm (range: 84-138) in the control group (p=0.030). The mean RNFL thickness in the inferior quadrant was 129.4 ± 17.4 µm (range: 95-178) in the migraine group and 136.4 ± 19.5 µm (range: 92-185) in the control group (p=0.022). The mean RNFL thickness in the nasal quadrant was 92.4 ± 15.2 µm (range: 58-146) in the migraine group and 93.5 ± 16.4 µm (range: 62-148) in the control group (p=0.082). The mean RNFL thickness in the temporal quadrant was 61.4 ± 16.3 µm (range: 42-92) in the migraine group and 70.5 ± 14.4 µm (range: 46-108) in the control group (p=0.001).

The mean ODI of RNFL was 0.934 ± 0.064 (range: 0.810-1.120) in patients with migraine and 0.949 ± 0.057 (range: 0.768-1.022) in the control group (p=0.399) (Table 2).

The mean CA was 0.834 ± 0.108 mm^2 (range: 0.602-1.040), 0.986 ± 0.248 mm^2 (range: 0.611-1576) (p = 0.012), the mean LA was 0.579 ± 0.112 mm^2 (range: 0.315-0.826), 0.725 ± 0.191 mm^2 (range: 0.426-1.174) (p = 0.003), the mean SA was 0.254 ± 0.081 mm^2 (range: 0.122-0.398), 0.261 ± 0.064 mm^2 (range: 0.165-0.402) (p = 0.756) for the migraine group and the controls, respectively. The mean CVI was measured as 69.43% ± 8.99 (range: 53.33-76.73) in the patient group

Table 1.
Demographic and clinical characteristics of participants.

	Migraine (n=28)	Control (n=28)	p-value
Gender (n)			
Male	13	14	0.564
Female	15	14	
Age (years)			
Mean ± SD	38.4 ± 4.8	38.9 ± 5.2	0.644
Range	(35-45)	(35-45)	
Mean BCVA (logMAR)	0.0	0.0	1.000
Intraocular pressure			
Mean ± SD	12.6 ± 1.8	12.3 ± 2.0	0.845
Range	(11-14)	(11-14)	
Refractive error			
Mean ± SD	–0.84 ± 0.54 D	–0.82 ± 0.56 D	0.498
Range	(–1.25 to 1.0)	(–1.25 to 1.0)	

SD: Standard deviation; BCVA: Best-corrected visual acuity.

Table 2.
Structural OCT parameters in the study groups.

Variables (Mean±SD) (Range)	Migraine (n=28)	Controls (n=28)	p-value
Mean RNFL thickness (μm)	102.23 ± 9.09 (89-118)	107.19 ± 6.93 (99-126)	0.040 *
RNFL thickness at superior quadrant	112.4 ± 15.4 (82-142)	119.4 ± 16.5 (84-138)	0.030 *
RNFL thickness at inferior quadrant	129.4 ± 17.4 (95-178)	136.4 ± 19.5 (92-185)	0.022 *
RNFL thickness at nasal quadrant	92.4 ± 15.2 (58-146)	93.5 ± 16.4 (62-148)	0.082
RNFL thickness at temporal quadrant	61.4 ± 16.3 (42-92)	70.5 ± 14.4 (46-108)	0.001 *
ODI	0.934 ± 0.064 (0.810-1.120)	0.949 ± 0.057 (0.768-1.022)	0.399
CA (mm^2)	0.836 ± 0.108 (0.602-1.040)	0.986 ± 0.248 (0.611-1576)	0.012 *
LA (mm^2)	0.581 ± 0.107 (0.315-0.826)	0.725 ± 0.191 (0.426-1.174)	0.003 *
SA (mm^2)	0.256 ± 0.081 (0.122-0.398)	0.261 ± 0.064 (0.165-0.402)	0.756
CVI (%)	69.43 ± 8.99 (53.33-76.73)	73.38 ± 3.08 (66.77-79.71)	0.035 *

OCT: Optical coherence tomography; RNFL: Retinal nerve fiber layer; ODI: Optic density index; CA: Choroidal area; LA: Luminal area; SA: Stromal area; CVI: Choroidal vascularity index.
* Statistically significant p-value

Table 3.
Correlation between mean RNFL thickness and choroidal parameters.

Correlation*	Mean RNFL Thickness	ODI
CA	p=0.001* (r_s=0.617)	p=0.001* (r_s=0.474)
LA	p=0.001* (r_s=0.552)	p=0.001* (r_s=0.481)
SA	p=0.001* (rs=0.451)	p=0.195 (rs=0.193)
CVI	p=0.986 (r_s=-0.003)	p=0.232 (r_s=0.178)

r_s: Spearman's correlation coefficient
CA: Choroidal area; LA: Luminal area; SA: Stromal area; CVI: Choroidal vascularity index; RNFL: Retinal nerve fiber layer; ODI: Optic density index
* Spearman's rank-order correlation

and 73.38% ± 3.08 (range: 66.77-79.71) in the control group. (p=0.035) (Table 2).

4. Discussion

In the current study, the RNFL thickness and CVI were significantly decreased in patients with migraine. Although the ODI was also decreased in patients with migraine, the difference did not reach statistical significance. To the best of our knowledge, this is the first study demonstrating the choroidal structure and CVI, ODI of RNFL in patients with migraine.

The RNFL thickness in migraine patients, measured by OCT, has been evaluated by many studies. While some studies found thinner mean RNFL, others reported thinner RNFL only at a specific quadrant. Such distinct results might be caused by different imaging techniques, inadequate sample size, racial differences, and lack of standardization in terms of inclusion and exclusion criteria for the participants.

In 2005, Tan et al. reported the first study that evaluated the RNFL thickness in migraine patients with and without aura.[16] The study group included 39 migraine patients (15 with aura, 24 without aura), and 25 healthy subjects as the control group. The results did not find any evidence of RNFL thickness changes in the patient group compared with the control group. However, in the current study, we found a statistically significant decrease in the mean RNFL thickness in migraine patients when compared with the healthy controls. The disparity between the results could be attributable to the different imaging techniques, whereby Tan et al. used scanning laser polarimetry for the measurement.

The result of a study by Simsek et al.[17] is in agreement with the result of Tan et al. The RNFL thickness was not significantly different between the migraine patients with or without aura and healthy controls, except for the nasal quadrant of the right eye, which had a significantly higher value. A meta-analysis concluded that the RNFL thickness of migraine patients is lower than that of healthy controls.[18] Similarly, in another meta-analysis, the RNFL thickness was found to be decreased in migraine patients compared with healthy controls.[19]

As the vasogenic theory is one of the competing theories dominating the discussion of migraine pathogenesis, the choroid -being the most vascularized tissue of the eye- has become the center of interest. Zengin et al. evaluated the choroidal thickness (CT) using SD-OCT in patients with migraine and healthy controls.[20] According to the results, there was a significant difference between the patients and the controls. The decrease in mean CT could be related to the vascular pathology observed in the pathogenesis of migraine.

Optical coherence tomography angiography (OCT-A), still a rapidly evolving technology, has proven to be a valuable tool for the depth-resolved evaluation of the retinal and choroidal circulation without the need for dye injection. Since this imaging technique has overcome several significant limitations of previous dye-based techniques for the evaluation of the choroid, OCT-A is assuming the role of a key technological tool for the evaluation of the choroid, offering new and important insights into the pathogenesis of many retinal and choroidal disorders. There are few studies assessing the retinal and choroidal microvasculature in patients with migraine using OCT-A.[21-23] Chang et al. used OCT-A to assess the perfusion of the macula and optic nerve in migraine patients, with and without aura. According to their results, migraine with aura was associated with foveal and peripapillary vascular decrements.[21] Ulusoy et al. evaluated the retinal vessel densities of migraine patients with and without aura. On macular OCT-A, superficial and deeper retinal foveal vessel density were significantly lesser in migraine patients with or without aura than in controls.[22] Kızıltunc et al. evaluated choriocapillaris flow in migraine patients with and without aura, and they found a borderline significant decrease in choriocapillaris flow in migraine patients with aura.[23]

We propose that the CT can not fully represent the vasogenic effects on the choroidal tissue as a clinical biomarker. Evaluating the vascular parameters with the help of the binarization method gives further information about the vascular and stromal components of the choroid. Unlike the CT measurements, the CVI is relatively unaffected by physiologic parameters.[12] It has already been validated as a biomarker of ocular and systemic conditions, like central serous retinopathy, neovascular age-related macular degeneration or diabetes mellitus without retinopathy.[24-26]

It has been previously reported that the choroidal parameters can be a potential biomarker for neurodegenerative conditions, including

Alzheimer's disease.[27] The TCA, LA, and CVI differed among the individuals with Alzheimer's disease, mild cognitive impairment, and healthy cognition.[27] The CVI changes were also investigated in multiple sclerosis, a degenerative disease of the central nervous system.[28] Compared with the healthy subjects, the CVI values were decreased in the affected and unaffected eyes of the patients who had previous optic neuritis in relation to the multiple sclerosis.[28] In the current study, the difference in the mean CVI between the migraine group and the controls reached statistical significance. In addition, the CA and LA were statistically significantly decreased in the migraine group in comparison to the healthy controls.

The current study has some limitations; the sample size was relatively small, which may have limited the strength of the statistical analysis. The cross-sectional nature of the study did not allow us to evaluate the longitudinal changes. The CVI is not an actual measure of the blood flow velocity, so it can not provide sufficient knowledge about the dynamic blood flow. The strength of our study is the comparison of the choroidal structural parameters, CVI, and ODI in a group of patients with newly diagnosed migraine.

5. Conclusion

We demonstrated a significant decrement of the RNFL thickness, choroidal and luminal areas in patients with migraine when compared with the healthy subjects. In the future, prospective population-based clinical trials are needed to reveal the longitudinal impact of migraine on the choroidal structure.

6. Funding

There are no sources of funding.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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