Neurology Asia 2022; 27(1) : 153 – 160

Evaluation of iris epithelial and stromal thickness in patients with migraine by using optical coherence tomography

[1]Mustafa Cam, [2]Sedat Arikan

[1]Department of Neurology and [2]Opthalmology, Canakkale Onsekiz Mart University, Çanakkale, Turkey

Abstract

Objective: The amount of light reaching to the retina is an important factor for photophobia formation. Therefore, investigation of iris thickness in patients with migraine can be valuable for revealing their susceptibility to photophobia. In this study, it was aimed to evaluate the iris epithelial and stromal thickness, retinal ganglion cell layer (RGCL) thickness, and retinal nerve fibre layer (RNFL) thickness of patients with migraine. *Methods:* Forty-nine migraine patients (Group 1) and 50 control participants (Group 2) were included into this study. For obtaining standard measure in all participants, the epithelial and stromal thickness of dilatory and sphincter iris muscle was measured from the equal distance to the pupillary margin by using anterior segment mode of optical coherence tomography (AS-OCT). Additionally, RNFL and RGCL thicknesses were measured by using posterior segment mode of OCT (PS-OCT). *Results:* The epithelial thickness of iris sphincter muscle and the epithelial thickness of iris dilatory muscle was found to be significantly higher in patients with migraine compared to control subjects ($p<0.001$, $p=0.001$ respectively). Additionally the stromal thickness of both iris sphincter and iris dilatory muscle ($p<0.001$, $p<0.001$ respectively) as well as the total thickness of iris sphincter and iris dilatory muscle was significantly higher in patients with migraine than control subjects ($p<0.001$, $p=0.02$ respectively). However, no significant difference was found between patients with migraine and control subjects in terms of RNFL and RGCL thicknesses ($p=0.1$ and $p=0.7$ respectively). *Conclusion:* The finding of high epithelial and stromal iris thickness in patients with migraine may support the possible role of increased pupillary dynamic in photophobia formation.

Keywords: Migraine, choroid thickness, retinal nerve fibre layers

INTRODUCTION

Migraine is a common neurological condition, of which symptoms include chronic, episodic, and disabling headache that can have a significant impact on daily functioning, and occur in conjunction with gastrointestinal, neurological, and autonomic changes.[1] Although migraine is the most common neurological disorder and considerable research has been conducted in the field of migraine, the mechanisms that give rise to headache, aura, and photophobia in migraine have not yet to be fully determined. Among the demonstrated mechanisms of action, vascular dysregulation is the foremost mechanism in migraine pathogenesis, with the neurovascular system that is most affected in this pathology.[2-4]

Aura and photophobia are two disorders which are common in migraine patients. Aura is characterised by transient ocular and neurological disturbances like sensing periorbital pain and perceiving flying objects particularly in zigzag configuration. The photophobia occurs in approximately 25% of patients in normally just prior to, but frequently in the aftermath of the headache, with clinical data indicating ocular involvement.[5]

Photophobia is a disorder caused by light reaching to the retina; it is thought that retinal photoreceptors and light-perceiving pathways have an important effect on the occurrence of this symptom. It has been demonstrated that there are different sensory systems that respond to the different quality of light.[6] Retinal nerve fibre layer (RNFL) changes seen in migraine patients may be due to the transneuronal retrograde degeneration of the primary visual cortex. Choroid

Address correspondence to: Dr. Mustafa CAM, Assistant Prof Dr., Canakkale Onsekiz Mart University Department of Neurology. Çanakkale, Turkey. Tel: +900286 263 5950, e-mail: mustafacam20@hotmail.com

Date of Submission: 8 May 2021; Date of Acceptance: 14 December 2021

https://doi.org/10.54029/2022kpy

thickness changes may be indicative of the TVS mechanism present in migraine with aura. RNFL may be utilised as a novel biomarker of neuronal degeneration in nervous system diseases.[7] RNFL thickness decrement has been found in several neurological disorders.[8-10] Retinal ganglion cell layer (RGCL) thickness could be used as a morphological biomarker in relation to axonal damage in specific optic neuropathies.[11,12] The advantages of optical coherence tomography (OCT) (a non-invasive, transpupillary diagnostic technique) are that it is reliable, results are replicable, and objective, and it allows for a quantitative in vivo high-resolution measurement of peripapillary RNFL, GCL, and choroid layer thickness.[13-15] In recent years, a number of investigators have employed OCT to determine through an analysis of RNFL whether patients with migraine have evidence of macular and choroidal changes. IpRGHs, which have an effective role in the formation of photophobia, have been detected in the iris besides the retina, which would suggest that changes in iris thickness and morphology may accompany patients diagnosed with migraine.

The objective of this particular study was to investigate whether the thickness and structure of the iris were affected in addition to retinal ganglion cell thickness (RGCC), retinal nerve fibre layer (RNFL) and choroidal thickness in patients with migraine.

METHODS

This prospective case-control study was conducted between 01.12.2019 and 01.06.2020. Forty-nine migraine patients (Group 1) and 50 control participants (Group 2) were included into the study. Group 2 was consisted of patients who were diagnosed with migraine according to the 2004 criteria of the International Headache Society (IHS).[16]

Participants with any corneal diseases, iris disorders, vitreous opacity, pterygium, participants with a history of previous corneal refractive surgery or any intraocular surgery, participants with a diagnosis of glaucoma or keratoconjunctivitis sicca, and those which could effect retinal morphology such as diabetes mellitus, nephropathy, macular degeneration, and a previous history of eye trauma, hypertensive retinopathy and any retinal disorder such as central serous chorioretinopathy and solar retinopathy, were excluded from the study.

In the ophthalmology outpatient clinic, all participants who met the inclusion criteria, underwent a routine ophthalmological examination with autorefractometer and air-blast tonometer. After biomicroscopic evaluation, cornea, lens, optic nerve and retina were determined. The posterior segment mode of optical coherence tomography (OCT) (Cirrus 4000 HD, Carl Zeiss) device was employed to measure the average and sectorial (temporal, nasal, superior and inferior) thickness of RNFL, in addition to the measurement of average thickness and minimum thickness of RGCL evaluate the retinal morphology, such as measuring thicknesses of RNFL and RGCL. The anterior segment mode of OCT (AS-OCT) was used to measure the epithelial, stromal and total thickness of iris sphincter and dilatory muscles. Figure 1 and 2 displays examples of the measurement of total and epithelial thickness of the iris by using AS-OCT respectively. Informed consent, which was obtained from all individuals, accorded with the principles of the Declaration of Helsinki, with approval granted by the local ethics committee.

Statistical analysis

SPSS 27.0 (IBM Corporation, Armonk, New York, United States) and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were utilised in the analysis of variables. The compliance of the data to normal distribution was determined by the Kolmogorov-Smirnov and Shapiro-Wilk Francia tests. The Independent-Samples *t* test was employed in conjunction with the Bootstrap results, while the Mann-Whitney U test was used with Monte Carlo results for a comparison of two independent groups with each other according to the quantitative data. In comparing categorical variables, the Pearson Chi-Square test was tested with the Monte Carlo Simulation technique. The Odds ratio was used, with confidence intervals set at 95%. The sensitivity and specificity ratios with respect to the relationship between the classification separated by the cut-off value calculated in accordance with the variables of the groups and the actual classification were evaluated and expressed by ROC (Receiver Operating Curve) curve analysis. The logistic regression test was utilised in conjunction with the Enter method to ascertain the cause - effect relationship of the categorical response variable with the explanatory variables. The power and sample analyses of thicknesses of iris dilatory and sphincter muscles was performed by using G*Power 3.1.9.2 test. While the calculated effect size value for total thickness of iris dilatory muscle

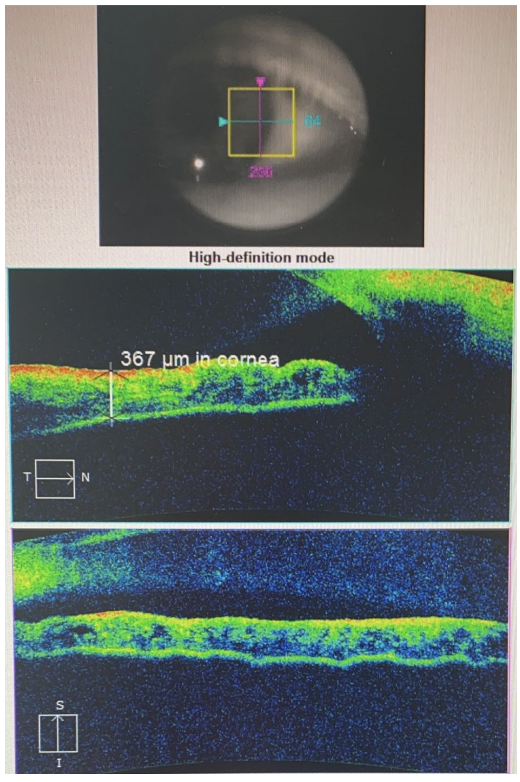

Figure 1. The measurement of total iris thickness by using anterior segment optical coherence tomography (AS-OCT).

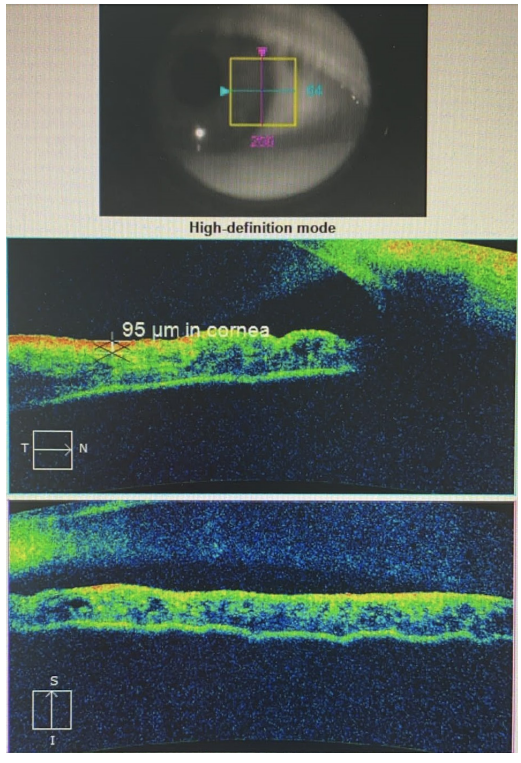

Figure 2. The measurement of epithelial thickness of iris by using anterior segment optical coherence tomography (AS-OCT).

was 1.171, the post power value was 99.9%. The calculated effect size value for total thickness of sphincter muscle was 0.51, and post power value was 71.3. The power level for total thickness of iris dilatory muscle was high whereas the power level for total thickness of iris sphincter muscle was within the acceptable range. The post power value for in the tables, quantitative variables were set out as mean (standard deviation) and median (percentile 25 / percentile 75), while categorical variables were depicted as n (%). Variables were analysed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

RESULTS

A total of 49 (64%, n=32 female) consecutive patients with migraine (Group 1) and 50 (68%, n=34 female) control subjects (Group 2) were included into this study. The mean age of Group 1 and Group 2 was 38.68 ± 10.00 years, and 35.02±9.27 years respectively. No statistically significant difference was seen between patient and control groups with respect to age and gender (p>0.05). The mean epithelial thickness of iris dilatory muscle was 60.72±7.98 mm and 81.39±13.07 mm in patients with migraine (Group 1) and in control subjects (Group 2) respectively, and there was a statistically significant difference between two groups regarding this parameter (p=0.001).The epithelial thickness of iris sphincter muscle was also found to be statistically significantly higher in patients with migraine (Group 1) when compared to control subjects (Group 2) as 97 mm and 78.5 mm in Group 1 and Group 2 respectively (p<0.001). Besides that, either the stromal thickness of iris dilatory muscle [292 mm in patients with migraine (Group 1) vs. 255 mm in control subjects (Group 2), p<0.001], or the stromal thickness of iris sphincter muscle [331 mm in patients with migraine (Group 1) vs. 316.5 mm in control subjects (Group 2), p<0.001] was statistically significantly higher in patients with migraine (Group 1), in comparison to control subjects (Group 2). The total thicknesses of iris dilatory muscle [358 mm in patients with migraine (Group 1) vs. 311 mm in control subjects (Group 2), p<0.001], and sphincter muscle [422 mm in patients with migraine (Group 1) vs. 400 mm in control subjects (Group 2), p=0.02] were statistically significantly higher in patients with migraine (Group 1) than the control subjects (Group 2).

However, there were no significant difference between the patients with migraine (Group 1) and control subjects (Group 2) in terms of average (RGC) thickness, minimum (RGC) thickness, average (RNFL) thickness, temporal RNFL thickness, nasal RNFL thickness, and superior RNFL thickness (p>0.05). The OCT findings were summarized in Table 1. According to ROC curve analysis, new variables were found with cut-off values (Table 2). The multiple logistic regression analysis covered age, iris sphincter epithelium diameter, and choroid thickness, while iris dilator total diameter showed independent factors in patients with migraine (p=0.046, p= 0.027, p=0.004, p=0.025) (Table 3).

DISCUSSION

Some 80% of the global population are impacted by primary headache, with the most common migraine.[17] Vasospasm and local blood flow decrease, which were identified in one hemisphere, were also detected in migraine patients[18] and very occasionally, hypoperfusion begins even in the retina. In addition, temporary reccurent migraine attacks can develop due to structural damage after cerebral vasospasm.[19]

In migraine patients, ganglion cell damage may occur as a result of changes in perfusion quality in optic nerve head microcirculation or in the retina. RNFL thickness measurements can be employed as a suitable index for the assessment of ganglion cell and retinal nerve fibres.[20]

In our study, RNFL, GCL and choroidal thickness in migraine patients was assessed with OCT and results compared with those from the control group. No significant difference in RNFL thickness was identified between migraine patients and those in the control group; although, in the control group, choroid thickness was significantly lower. The multiple logistic regression analysis covered age, iris sphincter epithelium diameter, and choroid thickness, and iris dilator total diameter showed independent factors in patients with migraine.

In a study conducted by Uludag *et al*., a statistically significant difference was noted in RNFL and GCC thicknesses between migraine and control groups.[21] In contrast, Gunes *et al*. and Tan *et al*. reported no significant difference in RNFL thickness in their identified patient groups.[22,23] Martinez *et al*., however, noted that there was a significant reduction in RNFL thickness in those with migraine in comparison with healthy subjects, although these differences in the superior and inferior areas were not observed between

Table 1: The comparison of OCT findings between the patients with migraine and the control group

	Control Group (n=50)	Patient Group (n=49)	P value
	n (%)	**n (%)**	
Gender			
Female	29 (58.0)	35 (71.4)	0.208 [c]
Male	21 (42.0)	14 (28.6)	
	median (Q1 / Q3)	**median (Q1 / Q3)**	
Age	37.5 (28 / 41)	40 (35 / 43)	**0.044** [u]
Average ganglion	83 (78 / 86)	82 (78 / 85)	0.731 [u]
Minimum ganglion	79 (72 / 83)	78 (73 / 81)	0.641 [u]
Iris sphincter epithelium	78.5 (74 / 85)	97 (89 / 110)	**<0.001** [u]
	mean (SD.)	**mean (SD.)**	
Iris dilator Epithelium	60.72 (7.98)	81.39 (13.07)	**0.001** [t]
Average RNFL	93.08 (7.63)	90.73 (8.68)	0.181 [t]
Temporal RNFL	67.18 (11.45)	64.10 (10.21)	0.200 [t]
Nasal RNFL	69.62 (10.07)	68.69 (8.21)	0.614 [t]
Superior RNFL	114.10 (16.90)	108.69 (14.19)	0.089 [t]
	median (Q1 / Q3)	**median (Q1 / Q3)**	
Inferior RNFL	124.5 (114 / 131)	119 (113 / 127)	0.222 [u]
Iris Dilator Stroma	255 (242 / 262)	292 (280 / 312)	**<0.001** [u]
Iris Sphincter Stroma	316.5 (308 / 322)	331 (314 / 350)	**<0.001** [u]
Iris Dilator Total	311 (302 / 318)	358 (343 / 371)	**<0.001** [u]
Iris Sphincter Total	400 (395 / 409)	422 (397 / 450)	**0.020** [u]

[c] Pearson Chi-Square Test (Monte Carlo), [t] Independent Samples T test (Bootstrap), [u] Mann Whitney u test (Monte Carlo), SD.:Standard deviation, q1: Percentile 25, q3: Percentile 75 RNFL:Retinal Nerve Fibre Layer

Table 2: According to ROC curve analysis, new variables were found with cut-off values

	Cut-off	Sensitivity	Specificity	AUC (SE.)	p	Odds Ratio (95% C.I. for Odds ratio)
Age	42.5	30.6%	90.0%	0.617 (0.057)	**0.045**	4.0 (1.3 - 12.0)
Iris sphincter epithelium	86.5	81.6%	78.0%	0.838 (0.041)	**<0.001**	15.8 (5.9 - 42.2)
Iris dilator epithelium	68.5	81.6%	88.0%	0.899 (0.031)	**<0.001**	23.3 (8.2 - 66.4)
Iris dilator stroma	279	75.5%	90.0%	0.838 (0.043)	**<0.001**	27.8 (9.0 - 85.9)
Iris sphincter stroma	327.5	61.2%	86.0%	0.705 (0.056)	**<0.001**	9.7 (3.6 - 25.9)
Iris dilator total	340	75.5%	94.0%	0.813 (0.048)	**<0.001**	48.3 (12.7 - 183.8)
Iris sphincter total	413.5	69.4%	80.0%	0.688 (0.056)	**0.001**	9.1 (3.6 - 22.8)

Table 3: Multiple logistic regression analysis results according to independent variables

Dependent variable: Groups	B	S.E.	p	Odds ratio	95% C.I.for Odds ratio	
					Lower	Upper
Age (>42.5)	-3.115	1.603	**0.046**	22.537	1.063	430.556
Iris sphincter epithelium (>86.5)	-2.322	1.050	**0.027**	**10.198**	**1.303**	**79.808**
Iris dilator epithelium (>68.5)	-1.874	1.157	0.105	6.513	0.674	62.940
İris dilator stroma (>279.0)	-0.057	1.435	0.968	1.059	0.064	17.625
İris sphincter stroma (>327.5)	-0.934	1.425	0.512	2.545	0.156	41.534
İris dilator total (>340.0)	-3.995	1.781	**0.025**	**54.353**	**1.658**	**1781.933**
İris sphincter total (>413.5)	0.079	1.316	0.952	1.082	0.082	14.273
Constant	10.267	2.897	<0.001			
Predicted; Migraine = 95.9	**Control=90**	**Total: 92.9**	**P Model<0.001**			

Multiple Logistic Regression (Method = Enter), C.I.:Confidence interval, B: regression coefficients, SE: Standard error

the two groups.[24] In another study by Martinez *et al*., findings showed that RNFL thickness in patients with migraine was similar to that in healthy subjects, although the temporal quadrant was seen to be thinner.[20]

The pathogenesis of migraine is still unclear and several hypotheses have been suggested.[25] In this study, the fact that a significant difference in RNFL thickness is not observed in migraineurs when compared to that in the control group may be attributable to the variable nature of migraine. Differences in frequency, and severity of seizures, whether they occur with or without aura, the disease duration, and whether other co-morbidities are present may account for the differences among studies. Although no neurologic sign may be present, as white matter lesions are currently held to be of ischemic origin, nonetheless, there was some expectation that retinal nerves would be affected.[26]

Choroid thickness was also evaluated in our study. A significant difference was seen between the choroidal layers in migraine patient group and those in the control group. The choroidal layer was found to be thicker in migraine patients in our study group. The vascular pathogenesis of the disease can serve to explain increased choroidal thickness during acute migraine attack. During migraine attack some findings would indicate that mean choroidal thickness was significantly higher than the healthy control participants.[22,27] The choroidal layer is the most vascular area in the retina, and nourishes retina in medical condition, which affects circulation of blood, may also affect it.[28] In migraine patients, it has been seen that choroid thickness may decrease due to a decrease in both posterior ciliary artery and central retinal vessels blood stream.[29] In a study undertaken by Colak *et al*., the choroid layers were found to be thinner in migraine patients.[30] Additional caffeine, smoking, medications, systemic disease, age, and gender can all also affect the choroid layer.[31,32] As such, differences in choroidal measurements may be detected on a daily basis or more frequently. Given that changes in the migraine patient's condition may occur during imaging (whether they are in a seizure phase or not, taking other medication, caffeine usage, smoking habits, etc.) changes in the choroidal layer texture may also be observed, accordingly, no specific findings may be obtained.

To best our knowledge, there are no studies about ganglion cell changes with migraine patients in the literature. The ganglion cells in the retina are responsible for transmitting the signals which receive from the outer segments of the retina to the brain via the optic nerve and are located in the innermost layer of the retina. Continuous and spontaneous action potentials occur in ganglion cells. The pineal gland, which is a neuroendocrine organ that converts light-related signals into endocrine signals, provides the biological rhythm mostly with the effect of the hormone melatonin.[33] Melatonin receptors in the retinal ganglion cells stimulate dopamine release, and the circadian rhythm is kept under control.[34] It is known that mobile phones, electromagnetic waves, excessive smoking and alcohol use, working with the shift system, and sleep disorders reduce the secretion of melatonin. Studies have reported that patients with neurodegenerative diseases, autism, and depression have an abnormality in

melatonin secretion, and an increased risk of cancer in individuals working in shifts.[33-35] We think these factors might also trigger migraine and photophobia.

Our study has a number of limitations. OCT measurements could not be obtained during migraine attacks, as the majority of patients were unable to be present during attacks. In addition, evaluation of the choroidal doppler via ultrasound would be better and this then correlated with OCT findings. Finally, consideration should be given to a number of additional factors including patient disease duration, other medical treatments, alcohol and caffeine consumption, smoking, blood pressure, and environmental status, the menstrual and pregnancy status of female participants all of which can affect OCT prominently.

In conclusion, the prolonged migraine and a greater frequency of attacks would result in damage and in changes in thickness measurements; however, the results of recent studies do not concur. Further research is required with respect to the correlation between disease progress, RNFL, GCL, and choroid thickness values.

REFERENCES

1. La Pira F, Zappala' G, Giuffrida S, Lo Bartolo ML, Reggio E, Morana R, Lanaia F. Memory disturbances in migraine with and without aura: a strategy problem? *Cephalalgia* 2000;20:475-8. doi:10.1046/j.1468-2982.2000.00074.x.
2. Sacco S, Ripa P, Grassi D, Pistoia F, Ornello R, Carolei A, Kurth T. Peripheral vascular dysfunction in migraine: a review. *J Headache Pain* 2013;14:80. doi:10.1186/1129-2377-14-80.
3. Perko D, Pretnar-Oblak J, Šabovič M, Zaletel M, Žvan B. Associations between cerebral and systemic endothelial function in migraine patients: a post-hoc study. *BMC Neurol* 2011;11:146. doi:10.1186/1471-2377-11-146.
4. Vanmolkot FH, Van Bortel LM, de Hoon JN. Altered arterial function in migraine of recent onset. *Neurology* 2007;68:1563-70. doi:10.1212/01.wnl.0000260964.28393.ed.
5. Charles A, Hansen JM. Migraine-aura: new ideas about cause, classification and clinical significance. *Curr Opin Neurol* 2015; 28:255-60. doi:10.1097/WCO.0000000000000193.
6. Kawasaki A, Kardon RH. Intrinsically photosensitive retinal ganglion cells. *J NeuroOphthalmol* 2007;27(3):195-204. doi:10.1097/WNO.0b013e31814b1df9.
7. Ao R, Wang R, Yang M, Wei S, Shi X, Yu S. Altered retinal nerve fiber layer thickness and choroid thickness in patients with migraine. *Eur Neurol* 2018;80(3-4):130-7. doi:10.1159/000494671.
8. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical coherence tomography (OCT): imaging the visual pathway as a model for neurodegeneration. *Neurotherapeutics* 2011; 8:117-32. doi:10.1007/s13311-010-0005-1.
9. Kirbas S, Turkyilmaz K, Anlar O, Tufekci A, Durmus M. Retinal nerve fiber layer thickness in Alzheimer disease. *J Neuroophthalmol* 2013; 33:58-61. doi:10.1016/j.arr.2021.101361.
10. Monterio ML, Fermandes DB, Apóstolos-Pereira SL, Callegaro D. Quantification of retinal neural loss in patients with neuromyelitis optica and multiple sclerosis with or without optic neuritis using Fourier-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012; 53:3959-66. doi:10.1167/iovs.11-9324
11. Colak HN, Kantarcı FA, Tatar MG, *et al*. Retinal nerve fiber layer, ganglion cell complex, and choroidal thicknesses in migraine. *Arq Bras Oftalmol* 2016; 79:78-81. doi:10.5935/0004-2749.20160024.
12. Kardon RH. Role of the macular optical coherence tomography scan in neuro-ophthalmology. *J Neuroophthalmol* 2011; 31:353-61. doi:10.1097/WNO.0b013e318238b9cb.
13. Huang D, Swanson EA, Lin CP, *et al*. Optical coherence tomography. *Science* 1991; 254:1178-81. doi:10.1126/ science.1957169.
14. Drexler W, Sattmann H, Hermann B, *et al*. Enhanced visualization of macular pathology with the use of ultrahighresolution optical coherence tomography. *Arch Ophthalmol* 2003; 121:695-706. doi:10.1001/archopht.121.5.695
15. Fercher AF. Optical coherence tomography – development, principles, applications. *Z Med Phys* 2010; 20:251-76. doi:10.1016/j.zemedi.2009.11.002
16. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache* 2013;53(3):427-36. doi:10.1111/head.12074
17. Stovner Lj, Hagen K, Jensen R, *et al*. The global burden of headache: a documentation of headache prevalence and disability. Cephalalgia 2007; 27(3):193-210. doi:10.1111/j.1468-2982.2007.01288.x
18. Olesen J, Friberg L. Xenon-133 SPECT studies in migraine without aura. In: Olesen J, ed. Migraine and other headaches: The vascular mechanisms. Philadelphia, PA: Lippincott Williams & Wilkins, 1991; 237-243.
19. Abdul-Rahman AM, Gilhotra JS, Selva D. Dynamic focal retinal arteriolar vasospasm in migraine. *Indian J Ophthalmol* 2011; 59: 51-3. doi:10.4103/0301-4738.73717
20. Martinez A, Proupim N, Sanchez M. Retinal nerve fibre layer thickness measurements using optical coherence tomography in migraine patients. *Br J Ophthalmol* 2008; 92: 1069-75. doi:10.1136/bjo.2008.137471
21. Uludag G, Ozer D, Tanyildiz B, Ceylan E, Cinici E. Evaluation of retinal nerve fiber layer and ganglion cell complex thicknesses by optical coherence tomography in chronic migrain patients. *J Glaucoma-Cataract* 2014; 9: 263-6. doi:10.5935/0004-2749.20160024
22. Gunes A, Karadag AS, Yazgan S, Celik HU, Simsek A. Evaluation of retinal nerve fibre layer, ganglion

cell layer and choroidal thickness with optical coherence tomography in migraine patients: a case-control study. *Clin Exp Optom* 2018; 101: 109-15. doi:10.1111/cxo.12585
23. Tan FU, Akarsu C, Gullu R. Retinal nerve fiber layer thickness is unaffected in migraine patients. *Acta Neurol Scand* 2005;112(1):19-23. doi:10.1111/j.1600-0404.2005.00423.x
24. Martinez A, Proupim N, Sanchez M. Scanning laser polarimetry with variable corneal compensation in migraine patients. *Acta Ophthalmol* 2009; 87(7):746-53. doi:10.1111/j.1755-3768.2008.01356.x
25. Colombo B, Dalla Libera D and Comi G. Brain white matter lesions in migraine: What's the meaning? *Neurol Sci* 2011; 32: S37–40. doi:10.1007/s10072-011-0530-7
26. Kurth T, Mohamed S, Maillard P, *et al*. Headache, migraine, and structural brain lesions and function: Population based epidemiology of vascular ageing-MRI study. *BMJ* 2011;18(342):c7357. doi:10.1136/bmj.c7357
27. Sorkhabi R, Mostafaei S, Ahoor M, Talebi M. Evaluation of retinal nerve fiber layer thickness in migraine. *Iran J Neurol* 2013; 2: 51-5. PMCID: PMC3829288
28. Tuncer I, Karahan E, Zengin MO. Subfoveal choroidal thickness in normal eyes measurement using optical coherence tomography. *Ret-Vit* 2014; 22(2):137-9.
29. Parver LM. Temperature modulating action of choroidal blood flow. *Eye* (Lond) 1991;5(2):181-5. doi:10.1038/eye.1991.32
30. Colak HN, Kantarci FA, Tatar MG, *et al*. Retinal nerve fiber layer, ganglion cell complex, and choroidal thicknesses in migraine. *Arq Bras Oftalmol* 2016;79(2):78-81. doi:10.5935/0004-2749.20160024
31. Linsenmeier RA, Braun RD. Oxygen distribution and consumption in the cat retina during normoxia and hypoxia. *J Gen Physiol* 1992; 99(2):177-97. doi:10.1085/jgp.99.2.177.
32. Lee SW, SY Y, Seo KH, Kim ES, Kwak HW. Diurnal variation in choroidal thickness in relation to sex, axial length, and baseline choroidal thickness in healthy Korean subjects. *Retina* 2014; 34(2):385-93. doi:10.1097/IAE.0b013e3182993f29
33. Sapède D, Cau E. The pineal gland from development to function. *Curr Top Dev Biol* 2013;106:171-215. doi: 10.1016/B978-0-12-416021-7.00005-5
34. Ostrin LA. Ocular and systemic melatonin and the influence of light exposure. *Clin Exp Optom* 2019;102(2):99-108. doi:10.1111/cxo.12824
35. Reiter RJ, Tan DX, Erren Tc, Fuentes-broto L, Paredes SD. Light-mediated perturbations of circadian timing and cancer risk: a mechanistic analysis. *Integr Cancer Ther* 2009;8(4):354-60. doi:10.1177/1534735409352026