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RESEARCH

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The potential impact of migraine headache on retinal nerve fiber layer thickness

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Abstract

Background: Migraine is a common, chronic, multifactorial neurovascular disorder. It may result in hypoperfusion of other areas other than the brain, as the eye. It may lead to change of the retinal nerve fiber layers (RNFL) thickness and axonal loss even up to severe damage of the eye structures, including the retina with frequent headache attacks. This study aimed to quantify the thickness of RNFL which gives a good idea about the condition of axons and loss of ganglion cells in migraine patients. Also, to detect if there is any correlation between these measurements and clinical characteristics of migraine.

Results: The RNFL thickness was significantly thinner in patients with migraine compared to healthy controls in all quadrants of retina in both sides (p value < 0.05). However, there was no significant difference in RNFL thickness in migraine patients with aura compared to patients without aura in all retinal quadrants in both sides (p value > 0.05). The headache intensity was negatively correlated with RNFL thickness in the inferior ($r = -0.342$, $P = 0.031$) and nasal ($r = -0.349$, $P = 0.027$) quadrants on LT side, also there was a significant positive correlation between RNFL thickness and both of nausea and tolerability in the RT superior quadrant ($r = 0.467$, $P = 0.002$); ($r = 0.322$, $P = 0.043$), respectively, but there was no significant correlation found between the RNFL thickness and disability, attacks duration, disease duration and frequency in all retinal quadrants on both sides ($P > 0.05$).

Conclusion: The main conclusion of our work was that RNFL thickness was significantly affected in migraine patients in comparison to healthy controls, but there were no significant impact of the migraine characteristics including aura, severity, frequency, or duration of headache attacks on RNFL thickness.

Keywords: Migraine, OCT, RNFL thickness

Background

Migraine is one of the commonest chronic, multifactorial neurovascular disorders which is mainly characterized by recurrent attacks of disabling headache with aura presentations in up to one third of the migraine patients [1]. It was classified according to the International Headache classification, 3rd edition (ICHD-3) in 2013, into two main groups of: migraine without aura and migraine with aura [2]. Migraine has been considered as the third most frequent disease worldwide affecting nearly 15% of the overall population [3].

The neurovascular hypothesis was supposed to have important role in migraine pathophysiology, resulting in hypoperfusion of the brain and eye structures, especially the retina with frequent headache attacks due to altering of the retinal nerve fiber layers (RNFL) thickening, leading to axonal injury and even up to permanent massive damage of the eye [4–8].

Also, neuroinflammation, oxidative stress, hypercoagulability status and altered endothelial functions were suggested to be involved in the pathogenesis of migraine previously [9, 10]. Sensitization of the trigeminal vascular system (TGVS), including the intra- and extracranial

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meningeal blood vessels and ocular structures, may also affect the vascular tone and the transmission of pain signals [11–13].

Optical coherence tomography (OCT) represents a simple noninvasive procedure which has been evolved for the assessment of morphological changes in the structure of the optic nerve and the retina. OCT changes can designate the retrograde trans-synaptic neuronal degeneration (RTSD) of the retinal ganglion cells (RGCs) which is a useful measure for the estimation of the neurodegenerative process in different neurological disorders including migraine [14, 15]. The changes in the thickness of RNFL in patients with migraine may be affected by the disease duration, the severity of disease, the involvement of different retinal quadrants and the frequency of the attacks [5, 16–19]. We aimed in this study to quantify the RNFL thickness (which provide information about the loss of ganglion cells and axons) in patients with migraine in comparison to healthy controls, and to clarify the impact of the migraine characteristics including aura, severity, frequency, duration of headache attacks and disease duration on RNFL thickness.

Methods

This case control study was conducted on 40 migraine patients and 40 healthy controls. The patients were recruited from the Neurology Outpatient Clinic, Faculty of Medicine, Fayoum University, in the period between December 2020 and December 2021. We obtained written informed consents from all the included participants in this study. The study was approved by local ethical committee in Faculty of Medicine, Fayoum University.

Patients who fulfilled the diagnostic criteria of migraine headache whether episodic or chronic, based on International Classification of Headache Disorders-III (ICHD-III) diagnostic criteria [20] were included in our study. The age range of the included migraine patients was 18–50 years.

Patients who had any of the following conditions were excluded from the study: secondary headache, optic disc edema, structural brain lesion, ocular disorders such as glaucoma or retinal pathology, medical disorder known to affect the retina. Pregnant patients were also excluded.

Forty healthy controls, with no history of ocular or neurological disease, were recruited from the family members of the patients and never have experienced a migraine attack.

An expert neurologist conducted a semi-structured interview with the included patients for detailed analysis of headache. The patients were asked about the frequency of migraine headache attacks per month, the mean duration of the headache attacks, the aura, the type of abortive medications, and the prophylactic treatment in addition to the response to treatment.

Migraine severity scale (MIGSEV) was used to assess severity of migraine headache attacks. It included the following items: disability in daily activities, tolerability, pain intensity, and nausea. The score of this scale categorizes the patients based on headache severity into 3 categories: mild, moderate, and severe [21].

Assessment of retinal thickness by OCT was done for all included patients and controls using spectral domain OCT (RTVUE XR, Optovue, USA). It has a high axial resolution (10.00 μm). It generates cross-sectional images of the retina. The retinal nerve fiber layer thickness scan protocol was applied (calculates the average of 3 circumferential scans 360° around optic disc, 256 axial scans, 3.4 μm diameter). Tropicamide 1% eye drops were used for dilatation of pupil to allow good OCT imaging. We used internal fixation (blue light) for all OCT scans, and we placed a patch over the other eye to improve fixation. Nasal, temporal, superior, and inferior retinal nerve fiber layer thickness (averaged for prepapillary retina 360 degree around the optic disc) were measured.

Statistical methods: the sample size for this study was calculated using G*Power version 3.1.9.2 Software based on the results of a pilot study conducted before the present study. The probability of type I error (α) was 5%. A total number of eighty participants (40 patients and 40 controls) was required to reach statistical power ($1-\beta$) 80%. The data were analyzed using SPSS (Statistical Package for Social Sciences) version 25 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Quantitative normally distributed data in migraine patients and controls were presented as mean and standard deviation (SD), while quantitative non-normally distributed data were presented as median and interquartile range (IQR). Independent sample *t*-test was used for comparison between migraine patients and control groups in normally distributed quantitative data, while Mann–Whitney test was used for comparison between migraine patients and control groups in non-normally distributed quantitative data. Chi-square test was used for comparison between migraine patients and control groups in categorical variables. The Spearman correlation coefficient (r) was used to correlate between MIGSEV, duration and frequency of migraine attacks and RNFL thickness.

Results

This is a case control study which was conducted on 40 patients with migraine and 40 healthy matched controls, with no significant difference between the two groups regarding the age and sex ($P=0.833$, 0.371), respectively. The clinical characteristics of migraine headache

Table 1 Demographics and clinical characteristics of migraine patients

	Migraine patients ($n=40$)	Controls ($n=40$)	*P*-value
Age in years [mean (SD)]	32.85 (8.76)	33.2750 (9.2)	0.833
Sex			
Males [*n* (%)]	18 (45%)	22 (55%)	0.371
Females [*n* (%)]	22 (55%)	18 (45%)	
Disease duration in years [median (IQR)]	3.5 (2–10)		
Type of migraine			
Episodic [*n* (%)]	12 (30%)		
Chronic [*n* (%)]	28 (70%)		
Frequency of the attacks/month	20 (10–20)		
Attack duration in hours [median (IQR)]	5.5 (4–24)		
MIGSEV scale			
Intensity [median (IQR)]	2.5 (2–3)		
Disability [median (IQR)]	3 (2–3)		
Tolerability [median (IQR)]	2 (2–3)		
Nausea [median (IQR)]	2 (2–3)		
Aura			
Present [*n* (%)]	20 (50%)		
Absent [*n* (%)]	20 (50%)		
Abortive treatment			
Paracetamol [*n* (%)]	16 (40.0%)		
NSAIDS [*n* (%)]	29 (72.5%)		
Triptans [*n* (%)]	13 (32.5%)		
Response to abortive treatment			
Poor [*n* (%)]	22 (55%)		
Moderate [*n* (%)]	14 (35%)		
Excellent [*n* (%)]	4 (10%)		
Prophylactic treatment			
None [*n* (%)]	26 (65.0%)		
Anti-epileptics [*n* (%)]	7 (17.5%)		
Anti-depressants [*n* (%)]	7 (17.5%)		

MIGSEV migraine severity, *NSAIDS* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *n* number

P-value ≤ 0.05 is considered significant

are illustrated in Table 1. The RNFL thickness was significantly thinner in patients with migraine compared to healthy controls in all quadrants of retina in both sides (p value < 0.05; Table 2).

However, there was no significant difference in RNFL thickness in migraine patients with aura compared to patients without aura in all retinal quadrants in both sides (p value > 0.05; Table 3).

Also, there was no significant difference in RNFL thickness in patients with episodic and chronic migraine except in RT temporal quadrant with (p value $= 0.017$; Table 4).

Regarding the comparison of RNFL thickness in migraine patients in relation to response to abortive treatment, there were no statistically significant differences between poor, moderate and excellent responders in RNFL thickness (Table 5).

Regarding the severity of migraine which was assessed by MIGSEV scale, the headache intensity was negatively correlated with RNFL thickness in the inferior ($r=-0.342$, $P=0.031$) and nasal ($r=-0.349$, $P=0.027$) quadrants on LT side. Also there was a significant positive correlation between RNFL thickness and both of nausea and tolerability in the RT superior quadrant ($r=0.467$, $P=0.002$); ($r=0.322$, $P=0.043$), respectively, but there was no significant correlation found between the RNFL thickness and disability in all retinal quadrants on both sides (Table 6). There were no statistically

Table 2 Retinal nerve fiber thickness layer in migraine patients in comparison to controls

RNFL thickness	Migraine patients ($n=40$)	Controls ($n=40$)	*P*-value
Superior retina			
Right [median (IQR)]	133 (122–141)	140 (133–145)	0.013*
Left [median (IQR)]	120 (118–139.75)	135 (122.75–141)	0.047*
Inferior retina			
Right [median (IQR)]	134.5 (125.25–141.25)	136 (135–147.5)	0.027*
Left [median (IQR)]	128 (123–142.75)	136 (126.25–143.5)	0.133
Nasal retina			
Right [median (IQR)]	77.5 (64.25–87.5)	85 (75–95.5)	0.015*
Left [median (IQR)]	73.5 (63.5–81)	81 (72.25–91)	0.013*
Temporal retina			
Right [median (IQR)]	72.5 (66.25–79.75)	78 (72–84.75)	0.011*
Left [median (IQR)]	70 (63–81.5)	75.5 (70–85.5)	0.027*

* : significant

n number, *RNFL* retinal nerve fiber layer

P-value ≤ 0.05 is considered significant

Table 3 Retinal nerve fiber layer thickness in patients with and without aura

RNFL thickness	Patients with aura ($n=20$)	Patients without aura ($n=20$)	*P*-value
Superior retina			
Right [median (IQR)]	136 (127.25–141)	131.5 (118.25–141.5)	0.343
Left [median (IQR)]	121 (118–140.75)	120 (109.75–139)	0.655
Inferior retina			
Right [median (IQR)]	135.5 (125.25–148)	134 (126–138)	0.735
Left [median (IQR)]	128.5 (123–143.25)	127 (118–142.75)	0.766
Nasal retina			
Right [median (IQR)]	72 (64–82)	80.5 (66–90.25)	0.317
Left [median (IQR)]	78 (62–85.75)	73 (63.5–81)	0.336
Temporal retina			
Right [median (IQR)]	72 (66.5–79.75)	73 (65.5–80.5)	0.882
Left [median (IQR)]	67.5 (60.25–79.5)	71 (65.25–84.25)	0.343

n number, *RNFL* retinal nerve fiber layer

P-value ≤ 0.05 is considered significant

significant correlations between RNFL thickness in migraine patients and either frequency, duration of migraine attacks or disease duration ($P>0.05$; Table 7).

Discussion

Our study aimed to quantify the thickness of RNFL and its correlation with the clinical characteristics of migraine. A statistically significant decrease of RNFL thickness of all quadrants bilaterally was detected in the patients of migraine compared to healthy control, these findings were consistent with different previous studies, Abdelatif and his colleague documented a decrease at all quadrants of retinal nerve fiber layer of the eye of migrainous patients [22].

Other studies demonstrated that the nasal peripapillary RNFL (pRNFL) diameter of positive aura patients was less than control group, as thinner nasal pRNFL quadrant was more prone to neurodegeneration [23, 24].

In addition, Yurtoğullari and colleagues found that the thickness of temporal, inferotemporal pRNFL quadrants of the positive aura group, and both of the supero and inferotemporal pRNFL thickness of the negative aura group was thinner than the control group [25]. Similarly, Aksoy and his colleagues reported a remarkable difference in the thickness of temporal pRNFL quadrant compared to healthy control [26].

Although OCT-based measurements of RNFL thickness showed different results, most of the data revealed

Table 4 Retinal nerve fiber layer thickness in patients with episodic migraine in comparison those with chronic migraine

	Patients with episodic migraine ($n=45$)	Patients with chronic migraine ($n=45$)	*P*-value
Superior retina			
Right [median (IQR)]	128.5 (117.5–135.25)	137 (126.25–142)	0.104
Left [median (IQR)]	119.5 (109.75–137.5)	121 (118–140)	0.544
Inferior retina			
Right [median (IQR)]	134.5 (125–137.5)	134.5 (126.75–148.25)	0.416
Left [median (IQR)]	132 (126.25–143.75)	127.5 (120–141)	0.288
Nasal retina			
Right [median (IQR)]	81 (66–91.75)	75 (64–85.5)	0.322
Left [median (IQR)]	80.5 (70.75–86.25)	72.5 (61.5–81)	0.274
Temporal retina			
Right [median (IQR)]	67 (60.75–72.25)	76 (68.5–81.5)	0.017*
Left [median (IQR)]	69 (61.5–74)	71 (63–87)	0.352

* : significant

n number

P-value ≤ 0.05 is considered significant

Table 5 Retinal nerve fiber layer thickness in migraine patients in relation to response to abortive treatment

Response to abortive treatment	Mean	SD	*P*-value
Right superior retina			
Poor ($n=22$)	131.91	12.22	0.576
Moderate ($n=14$)	132.64	16.04	
Excellent ($n=4$)	123.67	8.33	
Right inferior retina			
Poor ($n=22$)	135.59	13.67	0.370
Moderate ($n=14$)	125.29	35.09	

n number, *SD* standard deviation

that there is affection of multiple quadrants based on heterogeneous pathophysiologic mechanism of migraine attributed mainly to the neurovascular theory with the activation of trigeminovascular system release of inflammatory and vasoactive neuropeptides from peripheral nerve endings extracranially at the eye causing inflammatory compromise and vasospasm of ophthalmic, retinal and posterior ciliary arteries with hypoperfusion and axon loss resulting in decreased RNFL diameter [24, 25].

On the contrary, a few studies in the literature did not observe any changes in the diameter of RNFL of migrainous patients when compared to control group. These notifications was explained by using different

Table 6 Correlations between MIGSEV and retinal nerve fiber layer thickness in patients with migraine

RNFL thickness	Intensity		Disability		Tolerability		Nausea	
	(*r*) Coef.	*P*-value	(*r*) Coef.	*P*-value	(*r*) Coef.	*P*-value	(*r*) Coef.	*P*-value
Superior retina								
Right	0.205	0.205	0.302	0.058	0.322	0.043*	0.467	0.002*
Left	−0.073	0.655	0.075	0.645	0.202	0.212	0.111	0.495
Inferior retina								
Right	−0.181	0.265	−0.035	0.829	0.060	0.711	0.237	0.141
Left	−0.342	0.031*	−0.114	0.482	0.016	0.924	0.106	0.516
Nasal retina								
Right	−0.159	0.328	−0.232	0.150	−0.045	0.784	0.091	0.577
Left	−0.349	0.027*	−0.291	0.068	−0.065	0.690	0.243	0.130
Temporal retina								
Right	0.157	0.332	0.271	0.091	0.251	0.119	0.044	0.788
Left	0.042	0.795	0.074	0.650	0.074	0.650	0.005	0.975

* : significant

RNFL retinal nerve fiber layer thickness

P-value ≤ 0.05 is considered significant

Table 7 Correlations between migraine frequency, attacks duration, disease duration and retinal nerve fiber layer thickness

RNFL thickness	Frequency of the attacks		Duration of the attacks		Disease duration	
	(*r*) Coef.	*P*-value	(*r*) Coef.	*P*-value	(*r*) Coef.	*P*-value
Superior retina						
Right	0.275	0.086	0.036	0.827	0.055	0.735
Left	0.168	0.301	− 0.029	0.859	0.136	0.404
Inferior retina						
Right	0.007	0.965	0.07	0.667	0.104	0.525
Left	− 0.206	0.203	− 0.078	0.631	− 0.129	0.426
Nasal retina						
Right	− 0.16	0.326	− 0.132	0.418	− 0.085	0.604
Left	− 0.152	0.350	− 0.158	0.331	− 0.065	0.692
Temporal retina						
Right	0.222	0.168	0.023	0.888	0.170	0.295
Left	0.045	0.781	0.000	0.999	0.072	0.658

RNFL retinal nerve fiber layer thickness, *r* correlation coefficient

P-value $\leq$ 0.05 is considered significant

methodology and the possibility of higher-normal RNFL values of the examined migraine patients, that affect the final data of comparative results [27, 28].

In our presented study there was no significant difference in RNFL thickness in migraine patients with aura compared to patients without aura in all retinal quadrants similarly Simsek et al. found no difference between the two categories of migrainous patients [17].

On the other hand, a study reported a significant decrease in the inferior and nasal quadrants thickness of migraine patients with aura than migraine patients without aura [29].

There is a multifactorial part in migraine patients that can be studied, so we studied (headache intensity, frequency, duration of the attacks and the disease duration) and its correlation to RNFL thickness. We found that thinning of RNFL at left inferior and nasal retinal part was associated with intense headache. Also, thinning of RNFL at right superior quadrant was associated with more nausea and less tolerability through patient assessment with MIGSEV scale.

Similarly, other studies found that thinning of RNFL at inferior, nasal, and temporal retinal quadrants was associated with intense headache [22, 30].

The present study replicates the previous results that found no significant correlation between the RNFL thicknesses of all quadrants bilaterally and any of the disability, frequency and duration of attacks or the disease duration [17, 31, 32].

On contrary, Reggio et al. mentioned that more frequent migrainous attacks were associated with thinning of the RNFL [6]. Another author reported central macular thinning in migraine patient with aura who had frequent attacks [25].

A study led by Martinez et al. found that the thickness of the RNFL at temporal quadrant had a negative correlation with the migraine disability assessment score (MIDAS), frequency of attacks, and the duration of migraine [33]. Also, Feng and colleagues clarified that the finding of marked decrease in the mean value of RNFL thickness was attributed to longer duration of migraine that can exceed 15 years [8].

The discrepancy between the previous studies and our data can be explained by using different scale to assess migraine, small sample size, less frequent attacks and shorter disease duration less than 15 years reported by our patients.

The main limitations of this work were the small sample size, and the lack of vascular assessment of the retina using OCT angiography, and the lack electrophysiological assessment of the retina using electroretinography.

Conclusions

The main conclusion of our work was that RNFL thickness was significantly affected in migraine patients in comparison to healthy controls, but there were no significant impact of the migraine characteristics including aura, severity, frequency, or duration of headache attacks on RNFL thickness.

Abbreviations

ICHD-3: International Headache Classification, 3rd edition; RNFL: Retinal nerve fiber layers; TGVS: Trigeminal vascular system; OCT: Optical coherence tomography; RTSD: Retrograde trans-synaptic neuronal degeneration; RGCs: Retinal ganglion cells; ICHD-III: International Classification of Headache Disorders-III; MRI: Magnetic resonance imaging; MIGSEV: Migraine severity scale; IQR: Interquartile range.

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Author contributions
MA participated in study design, collection of data and helped to draft manuscript. MH participated in study design, analysis of data and helped to draft manuscript. NHT: performed the OCT for the participants. HE: participated in study design, and helped to draft manuscript. LID: manuscript reviewing. SHS: manuscript writing and reviewing. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to the current University regulations and Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

Declarations

Ethics approval and consent to participate
An informed written consent was taken from each patient. All data obtained from every patient were confidential and were not used outside the study. The patients have rights to withdraw from the study at any time without giving any reason. All the cost of the investigations was afforded by the researcher. Our study was approved by ethical committee of the Department of Neurology, Faculty of Medicine, Fayoum University on 4/2/2021.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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