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Retinal and Choroidal Alterations in Migraine Patients Compared to Normal Healthy Controls

Miriam L. Conway*, Irene Ctori

Department of Optometry and Visual Science, City, University of London, London, UK
Email: *miriam.conway.1@city.ac.uk

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Abstract

Purpose: Migraine is an incapacitating neurovascular disorder that primarily affects the working-age population. Researchers have postulated that the transient vascular alterations during each migraine attack lead to ischemic damage in the eye which can be measured via optical coherence tomography. **Methods**: We recruited 29 volunteers: 13 migraineurs (mean age 28 ± 8.8 years; 12 female and 1 male) and 16 age-matched controls (mean age 26.6 ± 6.9; 9 female and 7 male). All individuals underwent a detailed ophthalmic examination by a qualified optometrist and a Migraine Disability Assessment. The investigators were blind to the migraine diagnosis. Retinal Nerve Fiber Layer (RNFL) thickness, Retinal Thickness (RT), Ganglion Cell Complex (GCL), ranging from the inner-limiting membrane to the inner plexiform layer, and Choroidal Thickness (CT) were measured using the 3*D OCT*-1*Maestro*, Topcon, a Spectral Domain OCT (SD-OCT) device. **Results:** In the migraine population average RNFL was lower for several parameters. However, results did not reach statistical significance. A significant decrease in the right eye inferior parafoveal ganglion cell layer in the migraine group of patients (mean = 25.15, SD = 4.08) compared to normal healthy controls (mean = 28.81, SD = 4.85; t = (27) = 2.17, p = 0.039) was documented. No other ganglion cell layer or choroidal thickness reached significance. No significant relationship between ocular thickness parameters and MIDAS score, parameters and either MIDAS score or frequency of headaches was found. **Conclusion:** A significant decrease in the right inferior parafoveal ganglion cell layer for migraine patients was reported. All other parameters did not reach significance.

Keywords

Retinal, Choroidal, Migraine

1. Introduction

Migraine is the second leading cause of worldwide disability in the under fifties

[1]. Eleven percent of the general population has frequent attacks [2] which are known to last anywhere between a few hours and several days. Women are three times more likely to be diagnosed with the condition [3], with some research suggesting that it might be related to the normal hormonal variation over a woman's lifetime [4]. In the UK, migraine is estimated to result in a loss of approximately 25 million days from work or school [5] at an estimated conservative cost of £3.42 billion per year (headache disorders-not respected, not resourced). The exact aetiology behind migraine is not understood. However, most clinicians consider it to be a neurovascular disorder involving the trigeminal-vascular pathway with associated autonomic nervous system dysfunction [6]. Researchers have postulated that stimulation of the sensory neurones originating in the trigeminal ganglion innervates blood vessels from the meninges and cerebral arteries via the release of vasoactive neuropeptides [7]. The transient vasodilation of these structures activates the mechanical and chemical stimulation of the adjacent nociceptors, triggering migraine pain. The perception of pain, however, is known to vary significantly between individuals [8]. Treatments such as triptans are used to treat migraine through the vasoconstriction of meningeal vessels, decreased neurogenic inflammation, and reduced central nociception [9]. Researchers have documented an increased association between vascular disease and migraineurs [10] [11] [12] [13]. Additionally, there is some suggestion that migraine is linked to endothelial dysfunction which is required to regulate vasomotor tone [14].

Because the retina is an embryological extension of the brain, it is likely that repetitive episodes of cerebral vascular fluctuations have ocular implications which can be measured in the optic nerve, retina and choroid. In normal-tension glaucoma (NTG), the vascular theory suggests that is the haemodynamic alterations and not an increase intraocular pressure that leads to glaucomatous progression [15] [16]. In migraineurs, there are also reports of retinal ischemia, secondary to retinal artery occlusions [17] [18] [19] [20]. An important area of research is therefore to investigate any potential relationship between recurrent migraine attacks and structural changes in the eye linked to transient episodes of ischemia. Evaluating the thickness of ocular structures in individuals experiencing migraines is important because it can aid in the timely identification of physical changes in the eye before symptoms and irreversible visual loss occurs. Such alterations can serve as indicators of anomalies that are commonly associated with conditions such as glaucomatous optic neuropathy [15] [16] [17] and retinal vascular abnormalities [18] [19]. The collection of data from individuals with migraines in research studies can therefore enhance our comprehension of the connection between migraines and ocular well-being.

A meta-analysis has already analyzed the retinal nerve fiber layer (RNFL) thickness in migraine patients compared to normal healthy controls [21]. The study included 1530 migraine patients and 1105 healthy controls and documented thinner RNFL in the migraine population when measurements were taken during their interictal (between headaches) period via Optical Coherence Tomography

(OCT). The impact of the severity or duration of migraine on the RNFL was not assessed due to a limited sample size, and the authors concluded that more studies were needed to assess the value of OCT measurement in migraine patients. Elsewhere, there is some suggestion that choroidal thickness and ganglion cell layer are thinner in a proportion of migraineurs [22]-[27]. Findings, however, are inconsistent [28] [29] [30]. The aim of the present study was therefore to determine if RNFL, ganglion cell layer or choroidal thickness varies in migraine patients compared to normal healthy controls and to examine if there is any relationship between severity and or frequency of migraine.

2. Materials and Methods

Participants aged between 18 and 45 years old, were recruited from the staff and students attending City, University of London between 2018 & 2019, via a poster outlining the research study. The study received ethical approval from City, University of London's Optometry Proportionate Review Ethics Committee. Volunteers diagnosed with any ocular disease, amblyopia, previous eye surgery, neurological disorders, systemic diseases (such as diabetes, hypertension or heart disease), pregnancy or anti-epileptics treatments were excluded from the study.

Prior to enrolment in the study written informed consent was obtained for all volunteers, following the tenets of the Declaration of Helsinki. An anonymous questionnaire was completed by all volunteers. The questionnaire was developed according to the Headache International Society (HIS) criteria [31] and included a Migraine Disability Assessment Score (MIDAS). Volunteers were assigned to the control group if they reported less than 3 headaches in the past year and they had never experienced a migraine. In accordance with the (ICHD-3rd) [32] patients diagnosed with migraine were classified into those with and without aura. All volunteers were asked not to intake alcohol or caffeine 24 hours before their data collection visit. Migraineurs were additionally asked to confirm that they had not experienced a migraine attack in the last 24 hours to ensure that they were examined during the interictal period. All data was collected at City, University of London. Patients from both groups were randomly assigned to either the morning or afternoon sessions to minimize the effect of choroidal thickness variation due to diurnal rhythm [33].

The following tests were carried out monocularly by all patients. Best-corrected visual acuity was recorded using a logMAR chart (Thomson Software Solutions). Ocular axial length was recorded using the Topcon Aladdin Optical Biometer and Corneal Topographer HW 3.0, visual fields were examined using the Humphrey Field Analyzer (HFA-3). Objective refraction, central corneal thickness (CCT) and intraocular pressure (IOP) measurements were taken via the Topcon Auto Kerato-Refracto Tonometer (TRK-2P). Fundus photograph, peripapillary Retinal Nerve Fiber Layer (RNFL) thickness, Retinal Thickness (RT), Ganglion Cell Complex (GCL), ranging from the inner-limiting membrane to the inner plexiform layer, and Choroidal Thickness (CT) were measured using the 3*D OCT*-1*Maestro*,

Topcon, a Spectral Domain OCT (SD-OCT) device. The OCT measurements were performed following the protocol described by [34]. For each eye, the radial scan and 3D Disc analysis functionalities within the 3*D OCT*-1*Maestro* software were used. Only scans with a signal of strength of at least 5 or above were included in the analysis. The OCT 3D Disc analysis automatically calculated the foveal retinal thickness, the average RNFL thickness and the foveal ganglion cell complex. Choroidal thickness was determined using the software's *Caliper* function, which allows one to take linear measurements of the image. The thickness was measured perpendicular from the outer edge of the hyperreflective retinal pigmented epithelium to the inner sclera. Measurements were taken at the central fovea and at approximately 750 μm temporal and nasal to the fovea.

3. Results

Out of the 31 volunteers aged between 18 to 45 years old that were identified, 29 met the inclusion criteria. One participant was excluded because of a history of heart disease the other participant had an incomplete data set. The population therefore consisted of 13 migraine-suffering volunteers (mean age 28 ± 8.79, 12 female and 1 male) and 16 normal healthy controls (mean age 26.6 ± 6.89, 9 female and 7 male). Among the 13 participants suffering from migraines: 61.5% (8/13) had migraines with aura; 38.5% (5/13) had migraines with no aura.

A Kolmogorov Smirnoff test was initially carried out to determine which data sets were normally distributed. Based on these results, either an independent T-test or a Mann Whitney U was then used to determine any significant differences between the normal healthy controls and the migraine group during their interictal period. Analysis revealed that neither age, gender, systolic and diastolic blood pressure (SBP and DBP), visual acuity, IOP, and axial length were significantly different between the two groups (Table 1). Unsurprisingly, a significant difference between the control and migraine group MIDAS score and headache frequency (Table 2) was documented ($p \leq 0.0001$).

Table 1. Baseline demographic characteristics. Values are presented as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; MIDAS, migraine disability assessment score. For the Mann-Whitney * non-parametric analysis, mean rank was used.

	Migraine (n = 13)	Control Group (n = 16)	p Value
Age (Years)	Mean Rank = 15.38	Mean Rank 14.69	0.846*
Gender	Mean Rank = 17.88	Mean Rank 12.66	0.101*
SBP (mm Hg)	116.39 ± 12.01	122.75 ± 16.27	0.251
DBP (mm Hg)	79.15 ± 10.74	77.31 ± 8.58	0.612
MIDAS Score	**Mean Rank 22.96**	**Mean Rank 8.53**	**<0.0001***
Headache Frequency	**Mean Rank 22.00**	**Mean Rank 9.31**	**<0.0001***

Table 2. Comparison of ocular characteristics. Values are presented as mean ± standard deviation. IOP, intraocular pressure; CCT, central corneal thickness. For the Mann-Whitney * non-parametric analysis, mean rank was used.

	Migraine (n = 13)	Control Group (n = 16)	p Value
Visual Acuity Right Eye (logMAR)	−0.02 ± 0.07	−0.07 ± 0.09	0.125
Visual Acuity Left Eye (logMAR)	−0.04 ± 0.08	−0.07 ± 0.12	0.577
IOP Right Eye (mm Hg)	Mean Rank = 16.42	Mean Rank = 13.84	0.423*
IOP Left Eye (mm Hg)	Mean Rank = 16.00	Mean Rank = 14.19	0.589*
CCT Right Eye (μm)	505.62 ± 27.53	512.50 ± 39.22	0.598
CCT Left Eye (μm)	501.31 ± 26.41)	510.38 ± 37.90	0.472
Axial Length Right Eye (mm)	23.69 ± 1.22	24.09 ± 1.34	0.418
Axial Length Left Eye (mm)	23.60 ± 1.23	23.96 ± 1.32	0.451

Independent sample T-tests were carried out to determine if there were any significant differences between various OCT thickness parameters (RNFL, GCL, Choroidal) in migraine patients on a non-attack day compared to normal healthy controls. Table 3 indicates that although the average RNFL was lower in the migraine population for several parameters, all RNFL variables did not reach statistical significance. A significant decrease in the right eye inferior parafoveal ganglion cell layer in the migraine group of patients (mean = 25.15, SD = 4.08) compared to normal healthy controls (mean = 28.81, SD = 4.85; $t = (27) = 2.17$, $p = 0.039$) was documented (Table 4). The magnitude of the differences in the means was also large, with eta squared equal to 0.15 (Figure 1). No other ganglion cell layer or choroidal thickness (Table 5) reached significance. An independent sample T-test was then carried out to determine if there was a significant difference between any of the thickness parameters in the right and left eyes for migraine patients with aura versus those without. Again, all variables were found to be insignificant. Finally, a correlation was used to investigate any potential relationship between any OCT thickness parameters and either MIDAS score or frequency of headaches. No significant relationship was documented ($p > 0.05$).

4. Discussion

The aim of the present study was to investigate variations in RNFL, ganglion cell layer or choroidal thickness in migraine patients compared to normal healthy controls. We report that although the RNFL was thinner in the migraineurs for several parameters, current results did not reach statistical significance. Nonetheless, these findings are in line with a recent quantitative meta-analysis, consisting of 26 separate studies, that reported thinner RNFL in migraineurs when

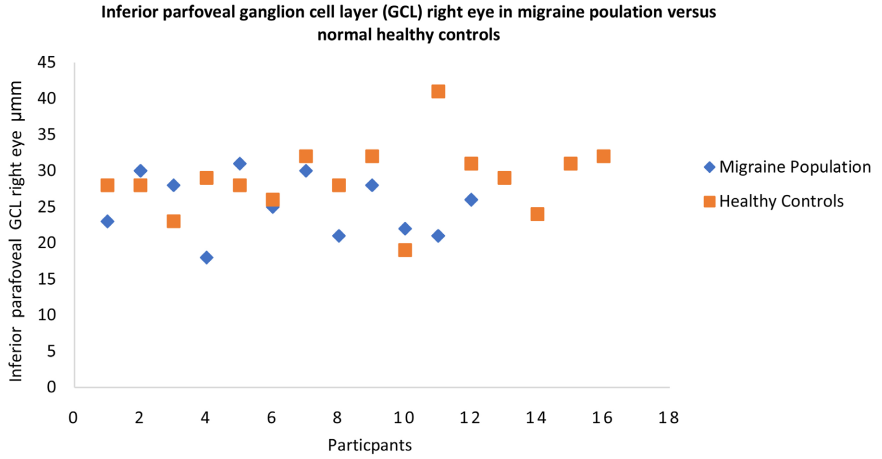

Figure 1. Showing the difference in parafoveal GCL thickness in the right eyes between the migraineurs and normal healthy controls.

Table 3. Comparison of RNFL thickness between migraineurs and normal healthy controls (Right Eye = RE; Left Eye = LE). *Non-parametric analysis carried out.

	Migraine (n = 13)	Control Group (n = 16)	p Value
Average RNFL µm RE	*Mean Rank = 13.92*	*Mean Rank = 15.88*	0.559*
Average RNF µm L LE	*Mean Rank = 13.85*	*Mean Rank = 15.94*	0.531*
Temporal RNFL µm RE	76.46 ± 12.45	76.94 ± 10.67	0.913
Temporal RNFL µm LE	73 ± 10.58	72.56 ± 9.81	0.909
Superior RNFL µm RE	*126.23 ± 27.40*	*128.63 ± 21.10*	0.792
Superior RNFL µm LE	*127.46 ± 26.76*	*129.69 ± 21.25*	0.805
Inferior RNFL µm RE	135.38 ± 24.11	135.25 ± 16.97	0.986
Inferior RNFL µm LE	138.69 ± 23.67	137.56 ± 18.38	0.886
Nasal RNFL µm RE	*76.00 ± 17.73*	*81.94 ± 15.23*	0.340
Nasal RNFL µm LE	*75.38 ± 14.28*	*81.31 ± 16.67*	0.319

Table 4. Comparison of GCL thickness between the migraineurs and normal healthy controls (Right Eye = RE; Left Eye = LE). *Non-parametric analysis carried out.

	Migraine (n = 13)	Control Group (n = 16)	p Value
Central Fovea GCL µm RE	4.31 ± 1.38	4.31 ± 1.66	0.948
Central Fovea GCL µm LE	Mean Rank = 13.23	Mean Rank = 16.44	0.329*
Parafovea Temporal GCL µm RE	20.54 ± 1.76	21.13 ± 1.63	0.360
Parafovea Temporal GCL µm LE	Mean Rank = 18.00	Mean Rank = 12.56	0.092*
Parafovea Superior GCL µm RE	Mean Rank = 16.81	Mean Rank = 13.53	0.308*
Parafovea Superior GCL µm LE	29.85 ± 2.82	28.38 ± 2.09	0.119
Parafovea Inferior GCL µm RE	***25.15 ± 4.08***	*28.81 ± 4.85*	***0.039***
Parafovea Inferior GCL µm LE	*26.85 ± 3.18*	*27.19 ± 3.25*	0.341
Parafovea Nasal GCL µm RE	Mean Rank = 14.54	Mean Rank = 15.38	0.812*
Parafovea Nasal GCL µm LE	Mean Rank = 15.35	Mean Rank = 14.72	0.846*

Table 5. Comparison of choroidal thickness between migraineurs and normal healthy controls (Right Eye = RE; Left Eye = LE).

	Migraine (n = 13)	Control Group (n = 16)	p Value
Temporal Choroid µm RE	339.46 ± 76.80	328.75 ± 70.35	0.699
Temporal Choroid µm LE	323.69 ± 71.12	314.63 ± 67.67	0.728
Superior Choroid µm RE	334.92 ± 62.19	333.19 ± 57.18	0.938
Superior Choroid µm LE	333.62 ± 62.22	312.63 ± 66.28	0.391
Inferior Choroid µm RE	325.23 ± 50.60	320.69 ± 67.48	0.842
Inferior Choroid µm LE	320.38 ± 67.09	312.81 ± 67.12	0.765
Nasal Choroid µm RE	319.15 ± 77.43	313.25 ± 73.23	0.835
Nasal Choroid µm LE	312.38 ± 49.72	324.56 ± 82.75	0.645

compared against normal healthy controls [21]. Results from Table 3 indicate that although the RNFL was thinner in the migraineurs for several parameters, current results did not reach significance. A likely explanation for this difference is that our study did not have a sufficient sample size to detect these differences. This study highlights the importance of combining single trials like this one, into a meta-analysis to provide a more precise estimate. Our data is therefore presented in full to enable researchers to include this in their future analysis. Other potential reasons for the differences not becoming statistically significant include methodological disparities between studies such as varying devices to measure ocular parameters, heterogeneity within the migraine population or different approaches to analysis. Current findings add further support to the hypothesis that repetitive ocular haemodynamic alterations, either during a migraine attack or systemically, lead to hypoxic injury and cell death. The role of oxidative stress in migraine and its effect on treatment has already been documented [35] [36]. Both cerebral [37] [38] and retinal [17] vasospasm in migraine have also been highlighted. Researchers have postulated that hypoxia caused by intermittent vasospasm is a risk factor for the progression of visual field loss in normal tension glaucoma [39]. Migraine [40] and NTG [39] have a known female predominance. The increased number of females in the current migraine cohort therefore reflects the known preponderance of migraine in this specific population. However, it must be acknowledged that the gender imbalance between the two groups might have confounded results further. The exact aetiology behind the gender difference in migraine is unknown. However, some have postulated that the higher frequency of vasospasm [41] [42] and vascular disease [13] found in females, contributes towards the higher prevalence of normal tension glaucoma and migraine.

The impacts of recurring episodes of haemodynamic alterations in migraineurs are probably not limited to the RNFL. This study also investigated any differences between either the GCL or CT in migraineurs versus normal healthy

controls. Our results suggest that migraineurs have significantly reduced inferior parafoveal ganglion cell layer in their right eye, during the interictal period ($p = 0.039$). The large effect size suggests that 15% of the variance in the para foveal inferior GCL is explained by a migraine diagnosis. Similar findings have been documented elsewhere [24] [25] [26] [27] [43] and it is of particular interest to note that several authors have recorded thinning, specifically within the inferior hemisphere [25] [26] [27]. Nevertheless, it is important to acknowledge that these findings have not been replicated consistently across the literature [28] [29] [30]. This highly explorative study was developed with multiple comparisons and a small sample size. When small group sizes are employed it has been suggested that it might be necessary to adjust the alpha upwards to either 0.10 or 0.15 in order to account for insufficient numbers [44]. When a large number of comparisons are used it is conventional to adjust the alpha level down by dividing the alpha level by the number of comparisons used. In this case, the alpha would be divided by a minimum of two (for each eye examined) or a maximum of 10, if all the examined parameters were included (**Table 4**). When both factors are considered together, this would leave a significant alpha to lie anywhere between 0.075 and 0.015. With this in mind, it suggests that current results are at best borderline and that the study would definitely benefit from repetition. Alternatively, the data could be included in a systematic review and meta-analysis investigating the GCL and CT in migraineurs, as to date none has been carried out. For this reason, all findings, including negative results have been presented to ensure that that a positive bias is not introduced into future meta-analysis. The average inferior parafoveal GCL measurements were also reduced in the left eye for the migraine population, however, the figures again did not reach statistical significance. One possible explanation for this slight disparity between eyes is that the thickness is primarily reduced on the side where the headache was localized to. Unfortunately, when we reviewed the questionnaire most participants failed to fill in this section and we must therefore conclude that further research is necessary to investigate this hypothesis. Indeed, a more comprehensive questionnaire that consistently identifies the side of the brain where the migraine is localized, whilst also addressing other potential confounding variables such as lifestyle questions will therefore benefit future research.

Twenty percent of people living with migraines report a visual illusion known as an aura preceding their headache [45]. Typical symptoms include scintillating shapes, adjacent to the central vision, expanding peripherally over a 5 to 20-minute period [46]. It has been suggested that decreased visual sensitivity might be caused by localized vascular events [47]. Temporary alterations in ocular perfusion during a migraine attack could result in focal hypoxia to both the optic nerve head and the retina, resulting in transient changes to vision. We did not find any relationship between migraine with aura and migraine without aura and any of the thickness parameters, however again we must concede to our small sample size.

A further aim was to examine if there is any relationship between severity

and/or frequency of migraine and ocular thickness. In the present study, we did not find any relationship between the two. A significant relationship between the severity and duration of migraine and the thickness of posterior ocular structures has been documented however, this study employed a significantly larger sample size [27]. Negative findings, therefore suggest that either there is no relationship between the two or that the small sample size was insufficient to detect a positive relationship. Presenting future results in full even when negative will allow future researchers to reliably investigate this variable as part of a meta-analysis.

It is important for clinicians to possess a comprehensive understanding of how migraine can impact both normal ocular health and ocular diseases like glaucomatous optic neuropathy [15] [16] [17] and retinal vascular abnormalities [18] [19]. Such knowledge equips them with the tools necessary for assessing the likelihood of disease and its progression in their patients. Furthermore, it is important for clinicians to establish baseline measurements of ocular structures in individuals affected with migraines. This serves the crucial purpose of discerning any longitudinal alterations on an individualized basis. Existing research has already attempted to investigate the potential associations between structural changes and variables such as the frequency, severity, or duration of migraine diagnosis [27]. It is vital to note that these alterations may not follow a consistent pattern of accumulation over time. Instead, they may be triggered by acute incidents without subsequent progression. Consequently, researchers have postulated that findings derived from cross-sectional studies fail to provide definitive insights into whether the observed disparities result from recurrent migraine-induced ischemia or stem from systemic factors predisposing individuals to retinal microvascular alterations [48]. They encourage documentation of migraine frequency and proximity to the most recent migraine episode, particularly in individuals at risk of developing glaucoma. They also advocate longitudinal research to help determine whether retinal vascular dysregulation is a predictor or indicator of cortical vascular damage [48].

5. Conclusion

The outcomes from this study suggest that conducting a systematic review and meta-analysis would be highly advantageous. Such analysis should attempt to utilize longitudinal designs wherever possible and should not be limited to the RNFL. Instead, it should encompass a broader evaluation that includes the GCL and the choroidal thickness in individuals with migraines compared to normal healthy controls. This methodology would also allow the researchers to control for bias introduced by utilizing various devices to measure ocular structures. Finally, researchers should determine the impact of migraine type (with or without aura) MIDAS score and the frequency of headaches. There is some suggestion from the literature that these parameters have ocular implications which can be measured *in vivo*.

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Conflicts of Interest

I can confirm that there is no conflict of interests to report.

Author Contribution

Miriam L Conway-designed the study, collected the date, analysed the data, study write up Irene Ctori-designed the study, contributed to the write up.

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