# Ocular microvascular and neurodegenerative changes in episodic migraine

Ph.D. thesis

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# 1. Introduction: migraine and its ophthalmological relevance

Migraine is the most common primary headache disorder, accounting for about 20 percent of all headaches [1]. It typically presents with throbbing pain and is often associated with nausea, vomiting; photophobia and phonophobia. According to the current International Classification of Headache Disorders (ICHD III), unilateral presentation of the headache is one of the major diagnostic criteria for migraine [2]. Migraine is the leading cause of disability among people under 50, affecting more than 1 billion people worldwide [3].

One of the widely accepted theories in migraine pathophysiology is associated with the sensitization and activation of the trigeminovascular system [4], whose repeated stimulation leads to structural and functional changes in both the central and peripheral nervous systems [5]. The trigeminal nerve supplies the basal plexus of the cornea, which is accountable for the sensation of pain and the characteristics of the tear film. In vivo confocal microscopy (IVCM) is a non-invasive imaging tool to study the structure of the cornea, allowing high-resolution assessment and quantitative analysis of the ocular surface at the cellular level. Structural changes in the subbasal nerve plexus of the cornea and an increase in the number of Langerhans cells (dendritic cells, DC) in patients with episodic or chronic migraine have been described in the literature. [6,7].

Among the vascular complications of migraine, an increase in white matter hyperintensities (WMH) is well recognized [8]. Based on the vasospastic aetiology of migraine, several authors have recently described abnormalities in the circulation of the retina, choroid and optic nerve and their potential neurodegenerative consequences [9]. For this reason, we applied optical coherence tomography (OCT) and OCT angiography (OCTA) to analyse the structure and circulation of the retina and optic nerve.

# 2. Aims

The transparency of the cornea and the ability to examine the blood vessels in the fundus make the human eye a unique model to study neurovascular and immune system changes in vivo. With the development of non-invasive imaging techniques, our aim is to describe early biomarkers that can help to identify high-risk patients and detect complications in a timely manner in order to prevent further morbidity.

Our aim was to evaluate ultrastructural changes in the cornea of episodic migraine patients, including the morphology of the subbasal nerve fibres and the density and area of dendritic cells by in vivo confocal microscopy. Furthermore, we wished to correlate the changes found with tear film parameters using a new imaging tool (LacryDiag). In the light of the known neurovascular abnormalities of the central nervous system in migraine patients, we aimed to quantify structural changes in macular circulation and optic nerve head morphology, taking into account the lateralization of migraine headache and the WMHs described on magnetic resonance imaging (MRI).

### Main hypotheses:

1. In vivo confocal microscopic changes in the subbasal plexus and cellular components of the cornea are associated with the severity and duration of episodic migraine.
2. Tear film parameters differ in episodic migraine patients from the normal population as a function of changes in innervation, even after eliminating the confounding effect of dry eye disease.
3. Neurodegeneration identified by OCT and capillary plexus abnormalities uncovered by OCT angiography can be detected in the early phases of the disease and the severity of the lesions correlates with the lateralization and stage of migraine.
4. Neurovascular abnormalities detected by OCT and OCTA may be an early indicator of potential migraine complications and serve as new biomarkers.

# 3. Patients and methods

## 3.1. Patients

All patients included in the study were admitted to the Outpatient Headache Division of the Department of Neurology, Medical School, University of Pécs, Hungary between July 2022 and April 2023 and met the criteria of episodic migraine (International Headache Society, 3rd edition (ICHD III).

For the retrospective analysis of ophthalmological findings, patients were selected from the electronic medical patient register who did not have any serious co-morbidities that could have affected corneal status, retinal circulation and optic nerve parameters.

Patients were divided into 3 categories based on disease duration (0-10 years, 11-20 years, >20 years). A comprehensive ophthalmological examination was performed interictally; including visual acuity, intraocular pressure, examination of the anterior segment and fundus, and imaging studies of the ocular surface and fundus (in vivo corneal confocal microscopy, OCT, OCTA). Control individuals had no history of systemic or ophthalmological disease or surgery.

Analysing our results, patient data were anonymised and, after coding, stored in a database accessible only to research staff. The methodology of these studies is in accordance with the literature, and the research design was drawn up in accordance with the legislation in force and the Declaration of Helsinki. The protocol was approved by the University of Pécs Institutional Ethical Review Board (Number: 9535-PTE 2023).

In our study "Analysis of the ocular surface functional unit in episodic migraine", 87 eyes of 44 migraine patients were enrolled and compared to 25 randomly selected eyes of 25 healthy age-matched volunteers. Our study "Neurovascular changes of the retina and optic nerve head in episodic migraine" included 65 subjects, 40 patients with episodic migraine and 25 age-matched controls. Thirty patients having a dominant side of the headache were included in the further statistical analysis. Data from the dominantly affected side were compared with contralateral data and healthy controls. A total of 31 migraine patients underwent brain MRI (Siemens Trio Tim 3T MRI, 12-channel head coil).

## 3.2. Methods

Analysis of corneal nerve fibres and dendritic cells involved in immunogenicity was performed by in vivo confocal microscopy. IVCM is a high-resolution, non-invasive imaging and diagnostic tool for studying the microstructure of the cornea, allowing depiction at the cellular level [10].

Optical coherence tomography (OCT) and OCT angiography (OCTA) are non-invasive imaging techniques as well; they allow the evaluation of the structure and circulation of the retina and optic nerve without the need for a contrast medium.

The innovative LacryDiag® is a new, non-invasive instrument capable of performing complex tear film diagnostics [11]. In our study we determined the height of the lower tear meniscus, the characteristics of the lipid layer and Meibomian glands, and the non-invasive tear film break-up time (NIBUT) using this device.

## 3.3. Statistical analyses

Data were analysed and plotted using SPSS Statistics 25.0 (IBM Corp., Armonk, NY). The mean, standard deviation (SD) and 95% confidence interval (95% CI) of the mean were determined. Kolmogorov-Smirnov test was performed to test whether the data was normally distributed. As the distribution of data did not follow the Gaussian distribution, the non-parametric Mann-Whitney U test was performed to compare data between migraine patients and controls. Analysis of variance (ANOVA) was used for subgroup analysis and Spearman's rank correlation for bivariate correlation analysis. The dominantly affected side of the migraine patient was compared with the contralateral side using Wilcoxon test. Multiple logistic regression was applied to eliminate the confounding effect of dry eye on corneal parameters. Results were considered statistically significant if the p value was less than 0.05.

# 4. Results

## 4.1. Analysis of the ocular surface functional unit in episodic migraine

We included 87 eyes of 44 migraine patients (7 men and 37 women) (mean age 33.23 ± 11.41 years, range 18 to 59 years) in our study and compared them to 25 randomly selected eyes of 25 healthy volunteers (6 men and 19 women) (mean age 30.16 ± 12.59 years, range 22 to 79 years, p = 0.190). All patients suffered from episodic migraine, with a mean duration of 16.02 ± 11.17 years and a monthly attack frequency of 4.37 ± 0.86.

In vivo confocal microscopy of corneal subbasal nerve fibres revealed no significant difference in nerve fibre parameters (nerve fibre density, -length, -area, -width, -branching density, fractal dimension) in the migraine group compared to controls. However, we found a significant increase in corneal dendritic cell density ($p<0.0001$) and area ($p<0.0001$) in migraine patients compared to healthy volunteers. Furthermore, dendritic cell density was positively correlated with monthly attack frequency ($r=0.307$; $p=0.005$).

Analysing tear film parameters, we found a significantly greater loss of Meibomian gland area in the upper eyelid in migraine patients ($p=0.005$). After eliminating the possible confounding effect of dry eye on the differences in corneal parameters between the migraine and control groups by multiple linear regression, none of the covariates had a statistically significant effect on the results.

## 4.2. Neurovascular changes of the retina and optic nerve head in episodic migraine

A total of 80 eyes of 40 patients diagnosed with episodic migraine (6 males and 34 females) were enrolled in our study, with a mean age of 31.75 ± 10.74 years (range: 18–59 years). The predominant side of migraine involvement was the right side in 22 patients, the left side in 8 patients, while 10 patients exhibited bilateral involvement. For statistical analysis, 30 patients with unilateral migraine (5 males and 25 females; mean age: 31.67 ± 9.54 years, range: 18–49 years) were compared to 25 randomly selected eyes of 25 healthy control subjects (5 males and 20 females) with a

mean age of 34.4 ± 12.11 years (range: 18–59 years) (p = 0.361). All 30 migraine patients suffered from episodic migraine with an average disease duration of 14.45 ± 10.93 years and a monthly attack frequency of 4.21 ± 3.70 episodes. Twelve patients experienced a visual aura on a regular basis and 6 patients demonstrated with WMHs on MRI scans.

Comparative OCTA analysis of the dominant side of migraine patients and healthy controls revealed alterations in macular microvasculature. Notably, vessel density was significantly reduced in the central zone of both the superficial capillary plexus (SCP) (p = 0.01) and the deep capillary plexus (DCP) (p = 0.004). However, no significant differences were found in the superior, nasal, inferior, or temporal quadrants. Additionally, the foveal avascular zone (FAZ) was significantly enlarged in migraine patients compared to controls (p = 0.04). The ganglion cell layer (GCL) thickness was also markedly reduced in the central ring, with significant thinning observed in both GCL + (p = 0.042) and GCL ++ layers (p = 0.029). An inverse correlation was identified between migraine duration and SCP vessel density in the nasal quadrant (p = 0.016, r = -0.445), as well as with vessel density across all DCP regions: superior (p = 0.004, r = -0.519), inferior (p = 0.004, r = -0.519), nasal (p = 0.006, r = -0.496), temporal (p = 0.005, r = -0.508), and the central field (p < 0.001, r = -0.634). Conversely, neither patient age nor migraine attack frequency showed significant correlations with any of the evaluated parameters.

Evaluation of optic nerve head (ONH) parameters revealed a significant decrease in the retinal nerve fibre layer (RNFL) thickness in the temporal quadrant (p=0.021) and in border tissue of Elschnig (BTE) diameter (p=0.035) on the dominant side of migraine patients compared to controls, while no difference was found in the RNFL thickness in the other 3 quadrants or among further ONH parameters.

Investigating the difference between the dominant and non-dominant side of migraine patients an impairment of several parameters could be detected on the dominant side. The vessel density was significantly diminished on the dominant side in the inferior (p=0.04) and temporal quadrants (p=0.023) of the DCP and showed a tendency to decrease in the temporal quadrant of the SCP (p=0.064). Additionally, the thickness of GCL++ inner ring showed a significant reduction (p=0.046). Regarding the optic nerve head parameters, no significant alteration was observed. Similarly, no significant difference was found between the dominant and non-dominant sides of migraine patients in the presence of aura or white matter hyperintensities, or when

assessing the 3 subgroups defined based on the frequency of migraine attacks or the duration of migraine.

# 5. Discussion

### 5.1. Analysis of the ocular surface functional unit in episodic migraine

The trigeminal nerve is integral to the physiological function of the ocular surface unit. It provides among others the sensory innervation of the cornea and conjunctiva [12]. In vivo corneal confocal microscopy allows detailed structural imaging of the cornea and it is highly consistent with immunohistochemistry in determining dendritic cell density in the human cornea, as previously described [10]. Recent studies have revealed significantly increased dendritic cell densities in a number of settings, including dry eye disease [13], infectious keratitis [14], systemic autoimmune diseases [15,16] and following infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [17]. According to a recent meta-analysis, the average DC density of the central cornea in healthy subjects was 26.4 ± 13.6 cells/mm² [18], which corresponds well to the results of our study. Compared to healthy controls, DC density in migraine patients increased more than threefold. Previously, dendritic cell aggregation in the immediate vicinity of the subbasal nerves of the cornea has been published in 10 migraine patients [7]. Our study confirmed this result in a larger cohort. In addition, we found a significant increase in DC area, indicating dendritic cell activation. These changes point to a general activation of inflammatory processes in the peripheral trigeminal system. Previous studies have demonstrated that dendritic cells are involved in the modulation of nociception and pain through their effects on T cells [19]. Dendritic cell-mediated inflammation of trigeminal nerve fibres may play a role in the positive feedback cycle of nociception and inflammation in migraine. Since dendritic cell area correlated with monthly attack frequency, it would be worth following patients longitudinally or even to monitor changes of neuroinflammation in the cornea during a specific therapy. CGRP-inhibitor drugs are widely used in migraine prevention. CGRP levels have been shown to be elevated in the tear film of migraine patients even interictally compared to healthy controls. Given that dendritic cells express CGRP [20], their increased density and activated state align closely with

the previously reported elevated CGRP levels in the tear film.

The comprehensive tear film imaging tool used in our study showed a significantly greater reduction in Meibomian gland area in the upper eyelid. The altered meibography score may be characteristic of Meibomian gland dysfunction. A recent meta-analysis concluded that migraine headache is associated with a higher risk of dry eye disease, thus headache can be considered an independent risk factor for dry eye disease [21].

In conclusion, our results suggest that the presence of neuroinflammation in the cornea of migraine patients affects the peripheral trigeminal system. The dendritic cells surrounding the subbasal plexus may be involved in pain induction and modulation in migraine. Changes reflected in the pathology of the cornea may offer valuable insights into the underlying mechanisms of migraine pathogenesis.

### 5.2. Neurovascular changes of the retina and optic nerve head in episodic migraine

Recent advances in OCT technology enable rapid, non-invasive and detailed imaging of the posterior segment, including quantitative analysis of changes in ocular circulation in migraine patients. Previous studies have implicated that altered retrobulbar circulation plays a crucial role in the aetiology of migraine; presumably due to increased resistance in the branch systems of the arteria centralis retinae and arteriae ciliares posteriores interictally as well as during a migraine attack [22]. A case report of a patient experiencing a migraine attack with visual aura revealed constriction of the retinal vessels and a reduction in radial peripapillary capillary density ictally, as well as decreased superficial and deep foveal vascular density [23]. Consequently, a temporary, but recurrent decrease in the blood supply to the optic nerve head can lead to ischaemic ganglion cell death [24]. In accordance, in our patients with episodic migraine, we found significantly reduced vascular density in the central zone of both the superficial and the deep capillary plexus. As a structural consequence, a significant reduction of the ganglion cell layer (GCL+, GCL++) thickness was documented in the central zone. Our results also confirm the presence of significantly enlarged FAZ described in migraine with aura patients [25]. Romozzi et al. proposed that retinal microangiopathy could result from ongoing microvascular damage accumulated over time. [25]. Our finding—that migraine duration was

inversely correlated with the vascular density (VD) of the deep capillary plexus across all quadrants and with the VD of the superficial capillary plexus (SCP) in the nasal quadrant—supports this concept. Similarly to our findongs, Altunisik et al. also reported no significant difference in OCT parameters between migraine patients with and without white matter hyperintensities (WMH) or aura. [26].

In migraine patients, we found a significant reduction of RNFL thickness in the temporal quadrant both on the dominant and the contralateral side. Changes in RNFL thickness in migraine patients have been extensively studied using spectral domain OCT; however, data from different studies are not homogeneous. Martinez and colleagues described a significant reduction of RNFL thickness in the temporal quadrant consistent with our findings [27].

The intraocular segment of the optic nerve measures 1.0 mm in length, extending from the optic nerve's surface to the posterior margin of the sclera. Recent advances in swept-source OCT technology have enabled precise quantification of the morphological parameters of the optic nerve head. In our study, we assessed the parameters of the pre-scleral neural canal and observed significantly smaller border tissue of Elschnig diameters on the dominant side in migraine patients compared to healthy controls. Similarly, Sahan et al. demonstrated increased optic nerve rigidity in migraine patients, potentially due to fibrosis, by using the quantitative elastic modulus of the optic nerve. They also reported a reduced mean diameter of the optic nerve sheath in individuals with migraines compared to controls [28].

Literature data suggests the importance of the lateralization of migraine headache in relation to pathological changes in the visual system. Gunes et al. described a significant thinning of the nerve fibre layer on the dominantly affected side compared to the contralateral side [29]. Additionally, interhemispheric differences of fMRI responses to visual stimuli in patients with side-fixed migraine aura have been observed even during the interictal phase [30].

# 6. Summary of novel findings and future plans

To the best of our knowledge, our study analysing ocular surface functional integrity is the largest cohort of patients with episodic migraine in the literature to date. Significant increases in corneal dendritic cell density and dendritic cell area were detected in migraine patients compared to healthy volunteers, suggesting the presence of neuroinflammation in the cornea. Timely detection of changes in the peripheral nervous system reflected in corneal pathology is essential for understanding the pathogenesis of migraine and for development of future therapies.

Studying microvascular abnormalities of the retina and the configuration of the optic nerve head, we were the first to describe certain circulatory and structural changes associated with the lateralisation of migraine headache. Further longitudinal studies may help to identify retinal parameters that are objective indicators of episodic migraine.

In the future, we plan to develop biomarkers for early recognition of migraineurs with late severe cardiovascular or cerebrovascular complications based on ocular surface or fundus findings. This will allow prompt treatment optimization and reduction of morbidity.

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# 8. Publications and conference abstracts

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Patzkó Á, Csutak A, Tóth N, Kölkedi Z, Pfund Z, Kis-Jakab G, Bosnyák E, Rozgonyi R, Szalai E. Neurovascular changes of the retina and optic nerve head in episodic migraine. Sci. Rep. 2024 Aug 30;14(1):20243

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