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RESEARCH LETTER

# Neuropathic changes in corneal nerve endings—A potential objective biomarker for migraine frequency and response to treatment

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The cornea is one of the most densely innervated structures in the body, mainly supplied by sensory fibers from the ophthalmic division of the trigeminal nerve—a key player in migraine pathophysiology.[1] Previous studies have demonstrated variable differences in the corneal nerve morphology of patients with migraine[2–4]; therefore, the cornea could represent a potential window into migraine pathophysiology.

We hypothesized that migraine frequency and/or progression are associated with changes in corneal nerve morphology. A cross-sectional study was conducted where eligible patients who were aged ≥18 years and had an International Classification of Headache Disorders, 3rd edition diagnosis of migraine were recruited from a neurology/headache clinic. Patients with diabetes, multiple sclerosis, current or previous history of B12 deficiency, other medical conditions known to cause neuropathy, previous history of chemotherapy, refractive ocular surgery, corneal ulceration, or ocular infection with herpes viruses, those who were pregnant/lactating, using topical medicated eye drops, and habitual contact lens wearers, were excluded. Slit lamp biomicroscopy was conducted to exclude these eye conditions. The study adhered to the tenets of the Declaration of Helsinki, was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee and all participants provided written informed consent.

A total of 25 patients with migraine and 25 age- and sex-matched healthy controls participated in the study. In vivo corneal confocal microscopic images (Heidelberg Retinal Tomograph III with Rostock Corneal module; Heidelberg Engineering GmbH, Heidelberg Germany) were taken of both eyes at the central and inferior whorl regions of the cornea.[5] The images were analyzed with automated image analysis software (ACCMetrics, The University of Manchester, Manchester, UK). Statistical analyses were performed using the IBM® SPSS® Statistics, version 27 (IBM Corp., Armonk, NY, USA).

For the analysis, the patients were categorized into three groups: those with episodic migraine (EM); chronic migraine (CM); and previously chronic-now-episodic migraine (CM → EM). All data are presented as mean ± standard deviation. Paired *t*-tests showed no difference in corneal nerve parameters between eyes; hence, only right eye data were used. Data normality and equal variance were confirmed with the Shapiro–Wilk normality and the Levene tests. Differences between migraine groups and controls were identified

**Abbreviations:** CM, chronic migraine; CM → EM, previously chronic-now-episodic migraine; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; EM, episodic migraine.

**TABLE 1** Distribution of age, sex, migraine diagnosis, disability score and corneal nerve morphology.

| Variable | Control ($n=25$) | Migraine group ($n=25$) | | | ANOVA |
|---|---|---|---|---|---|
| Age, years, mean (SD) | 48.6 (15.2) | 43.3 (15.8) | | | |
| | | EM ($n=11$) | CM ($n=6$) | CM → EM ($n=8$) | |
| | | 37.2 (13.9) | 44.8 (16.2) | 48.7 (18.1) | $p=0.228$ |
| Sex, *n* | | | | | N/A |
| Female | 21 | 10 | 4 | 7 | |
| Male | 4 | 1 | 2 | 1 | |
| Migraine diagnosis, *n* | N/A | | | | N/A |
| Without aura | | 5 | 5 | 6 | |
| With aura | | 5 | – | 1 | |
| Both | | 1 | 1 | 1 | |
| HIT-6 score, mean (SD) | N/A | 66 (7.7) | 70.2 (6.3) | 62.8 (7.5) | $p=0.207$ |
| MIDAS score, mean (SD) | N/A | 33.5 (21.0) | 92.3 (99.5) | 26.9 (16.6) | $p=0.051$ |
| Central morphology, mean (SD) | | | | | |
| CNFD, number/mm$^2$ | 27.20 (6.14) | 30.83 (7.16) | 24.65 (9.76) | 25.36 (5.55) | $p=0.223$ |
| CNFL, mm/mm$^2$ | 16.23 (3.52) | 16.89 (3.01) | 13.84 (4.43) | 15.13 (2.76) | $p=0.308$ |
| Inferior whorl morphology, mean (SD) | | | | | |
| CNFD, number/mm$^2$ | 23.60 (6.94) | 21.44 (7.00) | 10.10 (8.26) | 16.87 (5.13) | $p=0.001$*, $\eta^2=0.31$ |
| CNFL, mm/mm$^2$ | 18.07 (4.51) | 17.47 (4.80) | 9.73 (4.67) | 14.63 (2.25) | $p=0.001$*, $\eta^2=0.30$ |

Abbreviations: ANOVA, analysis of variance; CM, chronic migraine, CM → EM; previously chronic-now-episodic migraine; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; EM, episodic migraine; HIT-6, six-item Headache Impact Test; MIDAS, Migraine Disability Assessment; N/A, not applicable; $\eta^2$, eta-squared.

*$p<0.05$.

using one-way analysis of variance (post hoc Tukey's Honest Significant Difference). All analyses were two-tailed and $p<0.05$ was considered statistically significant.

The distribution of age, sex, migraine diagnosis and disability, of the participants are described in Table 1. There were significant differences between the groups in corneal nerve fiber density (CNFD) and corneal nerve fiber length (CNFL), in the inferior whorl region (described in Table 1). Furthermore, post hoc analysis showed significant reduction of CNFD and CNFL in those with CM compared to EM (CNFD: $p=0.011$; CNFL: $p=0.005$) and to controls (CNFD: $p=0.0004$; CNFL: $p=0.001$). There was no significant difference observed between EM and CM → EM group in CNFD and CNFL.

Our study corroborates previous findings that there are significant differences in corneal nerve morphology in migraine and that the extent of the neuropathic changes could be related to the frequency of attacks.[2–4] Specifically, we have shown that the inferior whorl region of the cornea, where distal nerve endings are located,[6] appears to be more sensitive in reflecting the nerve changes compared to the central region; a similar observation that was also found in other neuropathic disorders.[7,8] It is particularly interesting to note that the non-significant difference shown in CNFD and CNFL between the EM and CM → EM group may suggest the regeneration of corneal nerves after receiving effective migraine treatment, such as observed in other conditions.[9] Future longitudinal studies should be carried out to further investigate this possibility. Our findings suggest that corneal nerve morphology may be an objective biomarker for migraine frequency and response to treatment. More details on the study design are available in Supporting Information.

## AUTHOR CONTRIBUTIONS

*Study concept and design*: Katherine Spira, Maria Markoulli, Eric B. Papas, Arun V. Krishnan, Alessandro S. Zagami, Nur Amalina Md Isa. *Acquisition of data*: Nur Amalina Md Isa, Shyam S. Tummanapalli, Jeremy Chung Bo Chiang, Alessandro S. Zagami, Katherine Spira. *Analysis and interpretation of data*: Nur Amalina Md Isa, Arun V. Krishnan, Alessandro S. Zagami, Eric B. Papas, Maria Markoulli, Katherine Spira. *Drafting of the manuscript*: Nur Amalina Md Isa, Katherine Spira. *Revising it for intellectual content*: Arun V. Krishnan, Alessandro S. Zagami, Eric B. Papas, Maria Markoulli, Jeremy Chung Bo Chiang, Shyam S. Tummanapalli. *Final approval of the completed manuscript*:

Nur Amalina Md Isa, Shyam S. Tummanapalli, Jeremy Chung Bo Chiang, Arun V. Krishnan, Alessandro S. Zagami, Eric B. Papas, Maria Markoulli, Katherine Spira.

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## CONFLICT OF INTEREST STATEMENT

**Nur Amalina Md Isa, Shyam S. Tummanapalli, Jeremy Chung Bo Chiang, Arun V. Krishnan, Alessandro S. Zagami, Eric B. Papas, Maria Markoulli,** and **Katherine Spira** declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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