Leiden Headache Center

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Corneal Confocal Microscopy Reveals Nerve Fiber Alterations in Migraine Irrespective of Subtype or Visual Hypersensitivity

Objective

- This dense, dynamic plexus contains small nerve fibers from the ophthalmic branch of the trigeminal nerve.
- This study aimed to evaluate corneal nerve alterations in individuals with migraine, including its subtypes and visual hypersensitivity (measured with L-VISS).

Methods

- Corneal confocal microscopy (CCM) is a noninvasive ophthalmic imaging technique for evaluating the corneal microstructure, particularly the subepithelial nerve plexus.
- Participants were individuals with episodic (EM) or chronic (CM) migraine, and controls.
- All subjects underwent CCM, and automated corneal nerve fiber density (ACNFD), length (ACNFL), and branch density (ACNBD) were assessed using the Rostock Cornea Module (Heidelberg Retina Tomograph III).
- Data were compared with age- and sex-matched healthy volunteers.[1]

Table 1. Baseline characteristics of the included subjects.

	EM (n = 26)	CM (n = 29)	Total (n = 55)	p-value
Age (years), mean ± SD*	44.0 ± 10.9*	37.3 ± 13.4*	40.5 ± 12.6	0.048
Sex (female), n (%)	26 (100%)	28 (96.6%)	54 (98.2%)	n.s.
Migraine with aura, n (%)	10 (38.5%)	17 (58.6%)	28 (49,1%)	n.s.
MMD, mean ± SD	3.7 ± 1.9	13.9 ± 4.3	9.1 ± 6.1	<.001
MHD, mean ± SD	5.2 ± 2.8	17.8 ± 4.2	11.8 ± 7.3	<.001
MAMD, mean ± SD	4.1 ± 1.9	12.7 ± 3.8	8.6 ± 5.3	<.001
Simple analgesics, mean ± SD	2.1 ± 2.0	8.7 ± 5.6	5.6 ± 5.4	<.001
Triptans, mean ± SD	2.5 ± 1.9	6.0 ± 5.0	4.3 ± 4.2	0.002
Medication overuse, yes (%)	0 (0%)	26 (89.7%)	26 (47.3%)	<.001
Prophylactic prescription, yes (%)	16 (61.5%)	7 (24.1%)	23 (41.8%)	0.004
L-VISS score, median±IQR	23.3 ± 19.8	30 ± 20	25 ± 20.5	n.s.
L-VISS: interictal, median±IQR	9.5 ± 10	10 ± 12	9 ± 10	n.s.
L-VISS: ictal, median±IQR	16 ± 11.3	21 ± 12	17 ± 12	n.s.

EM = Episodic migraine; CM = Chronic Migraine;
MMD = Monthly Migraine Days;
MHD = Monthly Headache Days; MAMD = Monthly Acute Medication Days;
Medication overuse = defined as ≥15 days of simple analgesics/NSAIDS or ≥10 days of triptans or combination of analgesics/NSAIDS/triptans.
L-VISS = Leiden Visual Sensitivity Scale (range 0-36); IQR = interquartile range. n.s. = non-significant

Figure 1. A. Representative CCM images from the subbasal plexus, illustrative case of migraine patient. B. Fully automated corneal nerve quantification. Green indicates the nodes. Blue and red represent identified fibers, with red indicating the main branches and blue the side branches.

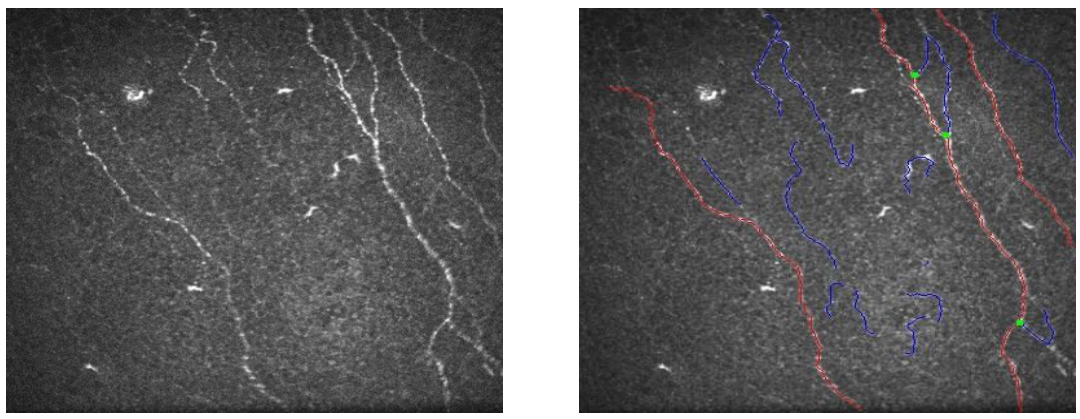

Table 2. Results of Corneal confocal microscopy (CCM). Linear regression models were used to compare migraine to controls and ANOVA with Tukey HSD post hoc tests were used to compare EM, CM and controls. Age and sex were added as covariates. P-value <0.05 was considered significant. *indicates significantly different compared to controls.

	ACNFD (median±IQR) number/mm²	ACNFL (median±IQR) mm/mm²	ACNBD (median±IQR) number/mm²
Controls (n=60)	33.3 ± 8.3	18.9 ± 3.2	44.9 ± 23.1
Migraine patients (n=55)	22.3 ± 7.1*	13.7 ± 4.0*	27.5 ± 18.5*
EM (n=26)	23.6 ± 6.7*	14.5 ± 4.2*	30.9 ± 16.3*
CM (n=29)	20.5 ± 7.8*	13.1 ± 4.3*	25.6 ± 17.5*

EM = Episodic migraine; CM = Chronic Migraine; ACNFD = Automated Corneal Nerve Fiber Density; ACNFL = Automated Corneal Nerve Fiber Length; ACNBD = Automated Corneal Nerve Branch Density; IQR = interquartile range.

Results

- Reduced ACNFD, ACNFL, and ACNBD were found in migraine participants compared to controls (all p <.001).
- No difference was found between EM and CM, and regression analysis showed no significant effect for (inter)ictal visual

Conclusions

- These findings support the utility of CCM as a sensitive tool for detecting nerve fiber pathology in migraine and highlight its potential in further understanding migraine pathophysiology.
- The observed nerve changes, present irrespective of migraine frequency status or visual hypersensitivity, suggest a broader role for peripheral nerve dysfunction in migraine beyond sensory hypersensitivity symptoms.

References

1. Tavakoli M, et al. Diabetes Care. 2015 May;38(5):838-43. doi: 10.2337/dc14-2311

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