Aus dem NeuroCure Clinical Research Center
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Veränderungen der Cornea bei neurodegenerativen Erkrankungen

zur Erlangung des akademischen Grades
Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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aus Köthen/ Anhalt

Datum der Promotion: 08.12.2017

Inhaltsverzeichnis

Reduzierte corneale subbasale Nervenfaserdichte bei Patienten mit Multipler Sklerose

Abstrakt

Hintergrund

Viele Studien über Multiple Sklerose (MS) haben bisher die Retina untersucht. Allerdings ist wenig über den Einfluss der MS auf die Cornea, welche durch den Nervus trigeminus innerviert wird, bekannt. Die Cornea ist diejenige Stelle im Körper, an welcher die neuronale Immunreaktion lokaler dendritischer Zellen auf Umwelteinflüsse stattfindet.

Zielstellung

Ziel dieser Studie ist es, die Wirkung der MS auf die kornealen Nervenfasern und die dendritischen Zellen des subbasalen Nervenplexus mittels in vivo Konfokalmikroskopie (IVCM) zu untersuchen.

Methodika

Mit dem Heidelberg Retina Tomographen® mit Rostock Cornea Modul wurden bei 26 MS-Patienten und dazu hinsichtlich Alter und Geschlecht gematchten gesunden Kontrollen die Dichte der kornealen Nervenfasern und die der dendritischen Zellen gemessen. Zusätzlich wurde die Schwere der MS-Erkrankung mit dem Multiple Sclerosis Functional Composite (MSFC) und der Expanded Disability Status Scale (EDSS) ermittelt. Des Weiteren wurde die Sehschärfe und retinalen Parameter mittels Optischen Kohärenztomographie (OCT) erhoben.

Ergebnisse

Es konnte eine signifikante Reduktion der kornealen Nervenfaserdichte der MS-Patienten im Vergleich zu den gesunden Kontrollen festgestellt werden. Hingegen war

die Dichte der dendritischen Zellen bei beiden Gruppen ähnlich. Des Weiteren wurde ein Zusammenhang zwischen reduzierter kornealer Nervenfaserdichte und einem erhöhten Behinderungsgrad infolge der MS, ermittelt mit dem EDSS festgestellt. Kein Zusammenhang bestand hingegen zwischen reduzierter kornealer Nervenfaserdichte und dem früheren Auftreten von klinischen Symptomen am N. trigeminus, einer mittels OCT gemessenen neuroaxonaler Schädigung der Netzhaut, einer veränderter Sehschärfe oder der Krankheitsdauer.

Schlussfolgerung

Die korneale Nervenfaserdichte könnte eine vielversprechende neue bildgebende Methode für die Bewertung der Krankheitsschwere der MS sein und sollte weiter untersucht werden.

Patients with multiple sclerosis demonstrate reduced subbasal corneal nerve fibre density

Abstract

Background

Many studies in multiple sclerosis (MS) have investigated the retina. Little, however, is known about the effect of MS on the cornea, which is innervated by the trigeminal nerve. It is the site of neural-immune interaction with local dendritic cells reacting in response to environmental stimuli.

Objective

This study aims to investigate the effect of MS on corneal nerve fibres and dendritic cells in the subbasal nerve plexus using in vivo confocal microscopy (IVCM).

Methods

We measured the corneal nerve fibre and dendritic cell density in 26 MS patients and age and gender matched healthy controls using a Heidelberg Retina Tomograph® with cornea module. Disease severity was assessed with the Multiple Sclerosis Functional Composite, Expanded Disability Status Scale, visual acuity and retinal optical coherence tomography.

Results

We observed significant reduction in total corneal nerve fibre density in MS patients compared to controls. Dendritic cell density was similar in both groups. Reduced total nerve fibre density was associated with worse clinical severity but not with previous clinical trigeminal symptoms, retinal neuroaxonal damage, visual acuity or disease duration.

Conclusion

Corneal nerve fibre density is a promising new imaging marker for the assessment of disease severity in MS and should be investigated further.

Eidesstattliche Versicherung

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Publikation: **Mikolajczak J**, Zimmermann H, Kheirkhah A, Kadas EM, Oberwahrenbrock T, Muller R, Ren A, Kuchling J, Dietze H, Prüss H, Paul F, Hamrah P, Brandt AU, Patients with multiple sclerosis demonstrate reduced subbasal corneal nerve fibre density, Multiple Sclerosis Journal, 2016, Impact Factor 4.671, Eigenfactor® Score 0.02148

Im Rahmen der o.g. Publikation war ich maßgeblich an mind. 70% beteiligt.
Diese teilten sich auf in:

- Rekrutierung der Studienteilnehmer mit Multipler Sklerose nach vorheriger Sichtung der Patientenakten
- Rekrutierung der gesunden Studienteilnehmer (gesunde Kontrollen)
- Terminierung und Koordination der Untersuchungszeitpunkte
- Durchführung des Multiple Sclerosis Functional Composite (MSFC) und des Symbol Digit Modality Tests (SDMT)
- Erfassung der Sehschärfe (Visual Acuity, VA)
- Durchführung der Messungen mittels Optischer Kohärenztomographie (OCT)
- Durchführung der Messungen der cornealen Parameter mittels in vivo Mikroskopie mit dem Heidelberg Retina Tomograph mit Rostock Cornea Modul (HRT3/RCM)
- Erstellung und dem Ausfüllen der Untersuchungsbögen vor, während und nach den Untersuchungen
- statistische Voranalyse und
- Schreiben des Manuskriptes.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

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Original Research Paper

Patients with multiple sclerosis demonstrate reduced subbasal corneal nerve fibre density

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Multiple Sclerosis Journal

1–7

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Abstract

Background: Many studies in multiple sclerosis (MS) have investigated the retina. Little, however, is known about the effect of MS on the cornea, which is innervated by the trigeminal nerve. It is the site of neural-immune interaction with local dendritic cells reacting in response to environmental stimuli.

Objective: This study aims to investigate the effect of MS on corneal nerve fibres and dendritic cells in the subbasal nerve plexus using in vivo confocal microscopy (IVCM).

Methods: We measured the corneal nerve fibre and dendritic cell density in 26 MS patients and matched healthy controls using a Heidelberg Retina Tomograph with cornea module. Disease severity was assessed with the Multiple Sclerosis Functional Composite, Expanded Disability Status Scale, visual acuity and retinal optical coherence tomography.

Results: We observed significant reduction in total corneal nerve fibre density in MS patients compared to controls. Dendritic cell density was similar in both groups. Reduced total nerve fibre density was associated with worse clinical severity but not with previous clinical trigeminal symptoms, retinal neuroaxonal damage, visual acuity or disease duration.

Conclusion: Corneal nerve fibre density is a promising new imaging marker for the assessment of disease severity in MS and should be investigated further.

Keywords: Multiple sclerosis, cornea, subbasal nerve plexus, trigeminal neuralgia, peripheral nerves, retina

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Introduction

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system (CNS). The cause of MS is unknown, but suggested factor in accruing clinical disability in MS are the myelin and axonal damage as well as neurodegeneration caused by an autoimmune reaction against CNS-specific myelin and myelin-forming oligodendrocytes.[1]

Changes in the eye's retina have been intensely studied in MS (for a recent review, see Balcer et al.[2]). The retina is affected by retrograde damage from acute optic neuritis[3] and shows chronic axonal and ganglion cell degeneration also without clinically overt optic neuritis.[4–6] Imaging the retina using optical coherence tomography (OCT) has, therefore, been suggested as potential surrogate marker of disease severity in clinical trials.[7]

In contrast to the retina, the cornea has not been investigated in MS. Axons of the trigeminal nerve's third terminal branch, the ophthalmic nerve, form the subbasal nerve plexus (SNP) in the human cornea. Imaging of nerve fibres in the SNP is possible with corneal in vivo confocal microscopy (IVCM), a non-invasive imaging technique providing high-resolution real-time images of corneal tissue at cellular resolution.[8]

Next to nerve fibres, dendritic cells (DCs) can be analysed using IVCM. These cells usually respond to external stimuli, for example, from contact lenses or dirt and maintain a healthy immune state of the cornea on the outer surface to the environment. IVCM, thus, provides a unique opportunity for analysing immune and peripheral nerve system interactions with microscopic resolution in vivo.[9–14]

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Our study explored the potential of IVCM imaging of the SNP as a tool in the assessment of MS-related clinical parameters. First and foremost, we aimed to assess nerve fibre and DC differences in the corneal SNP in patients with MS compared to healthy controls (HC). We also investigated the association between corneal SNP differences and measures of clinical disability, as well as neuro-axonal damage in the retina assessed by OCT.

Material and methods

Patients and controls

In total, 26 MS patients and 26 HC were initially enrolled. Patients with relapsing-remitting MS (RRMS) were recruited from the neuroimmunology outpatient clinic of the Charité – Universitätsmedizin Berlin. Inclusion criteria were age between 18 and 65 years, diagnosis of MS according to the 2010 revised McDonald criteria[15] and stable immunomodulatory therapy for at least 6 months. Exclusion criteria were disease attacks and administration of intravenous corticosteroids within 6 months prior to study recruitment, any known neurologic or ophthalmologic disorder unrelated to MS, diabetes mellitus, previous refractive surgery, pathological cornea changes due to corneal dystrophy or keratoconus, history of corneal transplantation and any other form of ocular surgery. HC were recruited from volunteers. All participants were surveyed regarding eye dryness, specifically epiphora or burning and aching, and usage of artificial tears and contact lenses to account for exogenous factors influencing SNP.[16] Exclusion criteria for HC were corneal DC density exceeding 137.1 cells/mm^2 corresponding to two standard deviations of published reference data.[17] All MS patients were clinically scored using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) with its components Timed 25-foot Walk Test (T25FW), Nine-Hole Peg Test (9-HPT) and paced auditory serial addition test (PASAT).[18] Multiple sclerosis severity scores (MSSS) were calculated from disease duration and EDSS.[19]

Single eyes of two patients and two controls were excluded after IVCM measurement due to insufficient image quality. Both eyes of three HC and single eyes of four further HC were excluded because DC density exceeded 137.1 cells/mm^2 in each eye, leaving 23 subjects in the HC cohort and the initial 26 subjects in the patient cohort. A demographic and clinical overview of the cohort after application of exclusion criteria is given in Table 1.

The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin and was conducted in conformity with the 1954 Declaration of Helsinki in its currently applicable version and applicable German laws. All study participants gave written informed consent.

Corneal IVCM

Corneal laser IVCM to analyse SNP nerve density and immune DCs was performed using the Rostock Cornea Module as add-on to the Heidelberg Retina Tomograph 3 (Heidelberg Engineering, Germany). Prior to examination, topical anaesthesia with oxybuprocaine hydrochloride 4.0 g (Conjuncain® EDO®; Dr. Gerhard Mann, Chem.-pharm. Fabrik GmbH, Germany) as active ingredient was applied to both eyes, followed by a drop of lubricant 2 mg/g carbomer-containing gel (Vidisic gel®; Bausch & Lomb, Heidelberg, Germany). The IVCM imaging using 'composite' mode was then performed as previously described in detail.[9,10,20] The maximum possible corneal scan area in composite mode (3.2 mm × 3.2 mm) was acquired wherever possible (Figure 1). DCs were identified by the morphology of cell bodies surrounded by dendriform structures, which were clearly distinguishable from the linear structures of corneal nerve fibres. To calculate the density of DCs, ImageJ (National Institutes of Health, USA) was used. For the composite IVCM images, the surface area of the image was first measured using ImageJ in mm^2. The cell number of DCs in the entire image was counted using ImageJ's Cell Counter plug-in. The DC density was then expressed as cells/mm^2. To measure subbasal nerve fibre density, nerves were traced using NeuronJ software (http://www.imagescience.org/meijering/software/neuronj/), which is a semi-automated nerve analysis plug-in of ImageJ that traces all visible nerve fibres in the image and calculates their total length in millimetres. Nerve fibre density was then expressed in µm/mm^2 in relation to the composite image's surface area. All nerve measurements were performed by two independent blinded observers.

OCT

Retinal examination of all patients was performed using spectral domain OCT (Spectralis, Heidelberg Engineering, Germany). Peripapillary retinal nerve fibre layer thickness (pRNFL) was determined from a ring scan around the optic nerve head using the OCT device's standard protocol with a 12° circular scan, resulting in 3.4 mm diameter, and with activated eye tracker. Whenever possible, the maximum 100 averaging frames in the automatic real-time

Table 1. Cohort description.

		MS	HC	*p*
Subjects	*N*	26	23	
Sex	Male/female (*N*)	7/19	7/16	>0.999 (χ^2)
Age/years	Mean ± SD (range)	42.8 ± 9.5 (28–62)	38.2 ± 13.7 (21–63)	0.135 (MWU)
Use of contact lenses	Yes	5	4	>0.999 (χ^2)
	No	21	19	
Eyes with previous ON	Yes/no (*N*)	23/27		
Time since diagnosis in months	Mean ± SD (range)	121 ± 64 (33–286)		
EDSS	Median (range)	2.5 (1–6.5)		
MSSS	Median (range)	3.1 (0.64–7.14)		
9-HPT (seconds)	Mean ± SD (range)	20.1 ± 3.6 (15.0–31.1)		
T25FW (seconds)	Mean ± SD (range)	7.2 ± 11.4 (3.5–62.9)		
PASAT	Mean ± SD (range)	49.5 ± 11.1 (19–60)		

MS: multiple sclerosis patients; HC: healthy controls; SD: standard deviation; ON: optic neuritis; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Scale; 9-HPT: Nine-Hole Peg Test (component of the multiple sclerosis functional composite); T25FW: Timed 25-foot Walk (component of the multiple sclerosis functional composite); PASAT: paced auditory serial addition test (component of the multiple sclerosis functional composite); SD: standard deviation; MWU: Mann–Whitney *U* test.

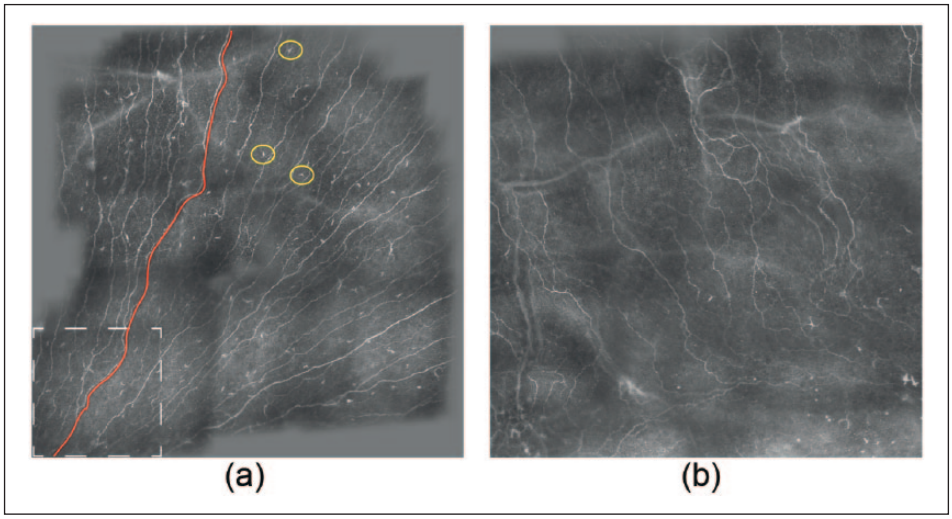

Figure 1. Composite image of the corneal subbasal nerve plexus. The device's software automatically fuses repeated section measurements in a composite image: (a) sample image of a healthy control subject. The dashed white box depicts the size of one section image. A sample corneal nerve segment is delineated in red, sample dendritic cells shown by a yellow circle; (b) sample image of a multiple sclerosis patient.

mode (ART) were used. Macular scans were acquired using a custom protocol generating 61 vertical slices (B-scans) focusing on the fovea at 30° × 25° scanning angle with resolution of 768 A-scans per B-scan and ART 13. All scans were evaluated for sufficient signal strength, correct centring and segmentation. Intraretinal segmentation was performed using the above OCT manufacturer's semi-automatic beta software (Heidelberg Eye Explorer V1.8.6.0 with Spectralis Viewing Module V6.0.0.2). The latter software detects and verifies boundaries between retinal layers automatically but necessitates manual error correction by an experienced grader. Based on the intraretinal segmentation, ganglion cell and inner plexiform (GCIP) layer thickness and inner nuclear layer (INL) thickness were determined as volume within the standard 6-mm early treatment diabetic retinopathy study (ETDRS) ring around the fovea. Whereas pRNFL and GCIP are established parameters of neuroaxonal degeneration in MS, INL has been suggested as a correlate of neuroinflammation.[21]

Statistical analysis

Statistical analysis was performed with R version 3.1.2 and geepack 1.2-0. To account for within-subject inter-eye effects, generalized estimating equation (GEE) models with working correlation matrix 'exchangeable' were used for all group comparisons and correlations involving corneal, retinal and visual function measurements. GEE results are given with regression coefficient (B) and standard error (SE). In HC, higher corneal nerve fibre density and DC density showed a trend to an association with higher age ($B=107.9$, SE$=57.2$, $p=0.059$ and $B=0.8$, SE$=0.4$, $p=0.052$, respectively), which is why we included age as a covariate in all analyses. Demographic group differences between patients and HC were analysed using a non-parametric Mann–Whitney U test (MWU) for age and Pearson's χ^2 test for sex. Trigeminal neuralgia (TN)-related symptom frequency comparisons between patients with and without history of such symptoms were calculated with Pearson's χ^2 statistics. Statistical significance was established at $p<0.05$. No a priori sample size calculation was performed, and significance levels were not corrected for multiple comparisons. The study should, therefore, be considered exploratory.

Results

Corneal nerve fibre density was significantly lower in MS patients than in HC (16,531.7±4426.6 vs 19,399.1±4546.1 µm/mm^2, $B=3227.1$, SE$=1192.0$, $p=0.007$). The density of 13 of 50 MS eyes (26%) in 12 of 26 patients (46%) was below that of the fifth percentile of HC. In contrast, DC density was not significantly different between MS patients and HC (28.6±24.5 vs 37.0±28.3 cells/mm^2, $B=12.2$, SE$=7.6$, $p=0.11$) (Figure 2). As expected, pRNFL and ganglion cell and inner plexiform layer (GCIPL) were reduced in MS patients in comparison to HC, but INL was similar (Table 2).

In MS patients, lower corneal total nerve fibre density was associated with worse MSFC ($B=1.810.4$, SE$=431.8$, $p<0.001$) and worse EDSS ($B=-822.9$, SE$=366.2$, $p=0.025$) scores. Corneal nerve density was not associated with time since diagnosis ($B=-1.29$, SE$=10.67$, $p=0.90$) but with MSSS ($B=-855.6$, SE$=406.2$, $p=0.035$). Analysing the individual MSFC tests, reduced corneal nerve fibre density correlated with worse T25FW times ($B=-77.0$, SE$=15.9$, $p<0.001$) and reduced PASAT performance ($B=123.1$, SE$=55.1$, $p=0.026$), but not with 9-HPT results ($B=-0.538$, SE$=0.714$, $p=0.451$). None of the OCT and visual function parameters correlated significantly with corneal nerve fibre density or DC density (Table 2). Likewise, there was no association with a previous optic neuritis (not shown).

We then assessed if corneal nerve fibre density was associated with a history of trigeminal symptoms. None of the MS patients had a history of diagnosed TN; however, 11 out of 25 patients (for one patient this information was not available) had other TN-related symptoms in their medical record, that is, facial hypaesthesia, dysaesthesia or paraesthesia. Patients with a history of TN-related symptoms had similar corneal nerve density compared to patients without TN-related symptoms (15,731.0±4546.0 vs 17,177.0±4391.0 µm/mm^2, $B=1676.0$, SE$=1561.0$, $p=0.28$). Moreover, these patients did not show corneal nerve fibre densities below the fifth percentile of HC more frequently ($p=0.74$) than patients without TN-related symptoms.

Discussion

In this study, we show that (a) corneal nerve fibre density is reduced in MS patients, (b) this reduction is associated with disease severity, (c) the reduction is not associated with retinal damage and (d) the reduction is independent of a history of clinical trigeminal-related symptoms.

Corneal nerve fibre density is an interesting new biomarker in MS as suggested by the consistent correlations with clinical severity. The marker was not affected by mild trigeminal symptoms, which suggests little dependency on focal symptoms or lesions. This is in contrast to OCT derived parameters, where optic neuritis causes additional damage and thus frequently interferes with the use of OCT parameters as surrogates for disease progression.[22] Recent applications of OCT as disease progression biomarker have, therefore, focused on eyes without previous optic neuritis.[23,24] The high frequency of optic neuritis in MS patients (confirmed in our random sample) thus limits these novel OCT applications. In contrast, no patient reported a history of TN, which is in line with its low prevalence.

The corneal SNP comprises terminal nerve endings from pseudo-unipolar sensory neurons originating in the trigeminal ganglion. Cell bodies from these neurons reside in the ganglion, connecting the cornea with peripheral axonal branches and the thalamic trigeminal nuclei with central axonal branches. Comparable to dorsal root ganglia in structure and function, these neurons are part of the peripheral nervous system (PNS) and are void of CNS-specific myelin from oligodendrocytes. Instead, Schwann cells ensheath both the peripheral and central axonal branches with peripheral myelin, which is composed of disparate cellular components and does not incorporate antigen targets thought to be relevant in MS.[25]

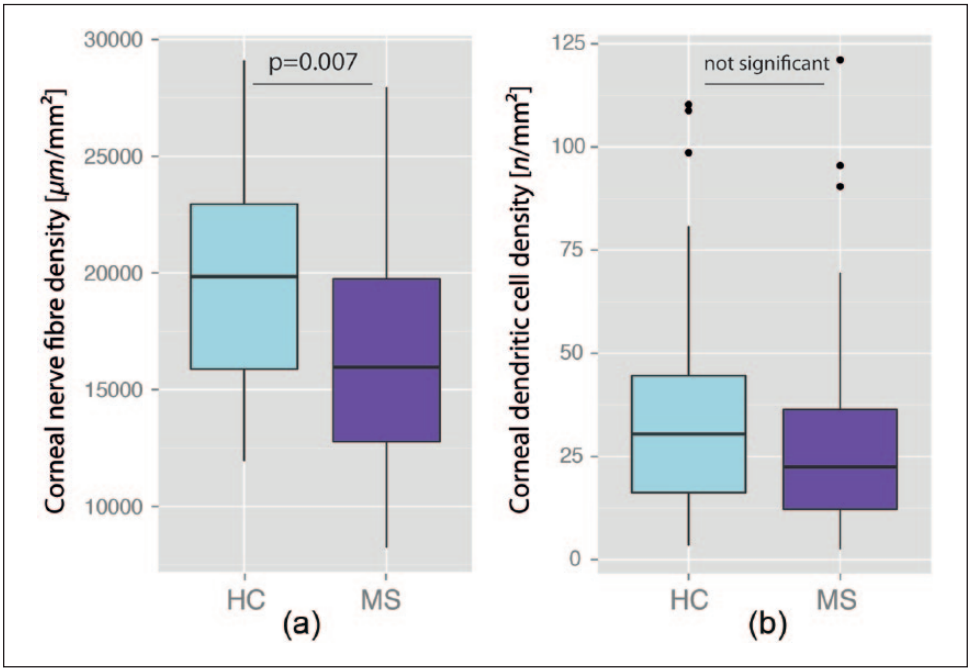

Figure 2. Corneal microscopy measurements. Comparison of corneal measurements between RRMS patients and healthy controls (HC): (a) corneal nerve fibre density expressed as total nerve length in µm per mm^2 and (b) dendritic cell density expressed as *n* per mm^2.

Table 2. Retinal measurements.

	MS	HC	MS/HC group comparison			Correlation with corneal nerve fibre density in MS			Correlation with corneal DC density in MS		
	Mean ± SD	Mean ± SD	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
pRNFL (µm)	83.7 ± 13.7	96.6 ± 7.4	12.7	2.8	<0.001	11.2	35.7	0.75	0.2	0.3	0.45
GCIP (mm^3)	1.74 ± 0.20	1.97 ± 0.13	0.23	0.04	<0.001	1766	2468	0.47	2.3	15.1	0.88
INL (mm^3)	0.96 ± 0.07	0.95 ± 0.07	0.02	0.02	0.37	1960	8864	0.83	−9.3	54.6	0.87

MS: multiple sclerosis; HC: healthy controls; DC: dendritic cells; SD: standard deviation; *B*: coefficient; SE: standard error; pRNFL: peripapillary retinal nerve fibre layer thickness; GCIP: ganglion cell and inner plexiform layer volume; INL: inner nuclear layer volume.

However, the trigeminal nerve is the fifth cranial/brain nerve, and the trigeminal ganglion receives direct input from brainstem nuclei. As such the nerve is anatomically considered to be part of the CNS, despite belonging to the PNS from its cellular composition. The trigeminal ganglion and nerve thus represent an interesting target at the interface between central and PNS. The trigeminal nerve is myelinated outside the cornea, but the terminal nerve endings in the corneal SNP are unmyelinated. The corneal SNP is highly dynamic and changes its fibre layout over a 6-week period.[26] The neuronal regulators of this dynamic turnover are enigmatic in humans. Trigeminal, sympathetic or parasympathetic modulators have been shown in animal studies.

In our study, almost half of all investigated MS patients (42%) and 26% of all analysed eyes from these patients exhibited a corneal nerve fibre density below the fifth percentile of that of HC corneas. Few previous studies have suggested that the PNS might be affected in up to 5% of MS patients.[27–31] However, the mechanisms underlying this MS-related PNS involvement and the contribution to overall clinical disability in MS are yet to be determined. Transsynaptic neurodegeneration after CNS nerve cell damage is most likely, but also primary neurodegeneration of peripheral neurons, have been discussed in studies of PNS impairment.[31]

TN, a painful affection of the trigeminal nerve, affects 2%–6% of MS patients, which is a 20-fold increased

risk of developing TN compared to the general population.[32–34] Our study shows that the trigeminal nerve can be affected in MS without a history of clinically diagnosed TN. However, such impairment might render the nerve susceptible to further damage and eventually trigger TN. Our random sample of MS patients did not include any patients with previous TN, thus a follow-up study of patients with diagnosed TN is needed to investigate this notion.

MS patients had similar DC density in the corneal SNP as that of the study's HC and that of previously published controls.[35] Local corneal inflammation, usually caused by exogenous influences like microbes, pollen or desiccating stress, leads to DCs migrating into the central part of the cornea, where they can be found up to 6 weeks after an inflammatory response.[36] Previous studies have suggested that resident corneal DCs are always present in the central cornea but increase rapidly in response to various exogenous factors.[37] It is therefore likely that influences of exogenous factors on the corneal DC presence outweigh effects potentially attributable to MS. Thus, DC count at one single time point might not be a reliable marker to draw any firm conclusion regarding differences in DC dynamics in MS in comparison to HC.

This study is an exploratory pilot study, and results should be replicated in an independent study. Our study shows that corneal SNP nerve fibre density is substantially reduced in MS patients in comparison to healthy subjects. The association of reduced corneal SNP density with higher clinical disability prompts further investigations on the applicability of this new measure as potential imaging biomarker for disease severity and progression in MS.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Vor der Promotion

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1. No Evidence for Retinal Damage Evolving from Reduced Retinal Blood Flow in Carotid Artery Disease
   Heßler H, Zimmermann H, Oberwahrenbrock T, Kadas EM, **Mikolajczak J**, Brandt AU, Kauert A, Paul F, Schreiber SJ
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3. Comparison of Standard Versus Wide-Field Composite Images of the Corneal Subbasal Layer by In Vivo Confocal Microscopy
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   Neurology, April 2015
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5. Afferent visual system damage in patients with MOG-antibody seropositive opticospinal inflammatory disease – a case series reporting data from seven patients.
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Während der Promotion

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1. Visual dysfunction, but not retinal thinning, following anti-NMDA receptor encephalitis
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2. Vision-related quality of life in patients with neuromyelitis optica spectrum disorders in comparison to patients with multiple sclerosis.

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