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RESEARCH ARTICLE

Association of corneal nerve fiber measures with cognitive function in dementia

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Abstract

Objectives: Corneal confocal microscopy (CCM) is a noninvasive ophthalmic technique that identifies corneal nerve degeneration in a range of peripheral neuropathies and in patients with multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis. We sought to determine whether there is any association of corneal nerve fiber measures with cognitive function and functional independence in patients with MCI and dementia. **Methods**: In this study, 76 nondiabetic participants with MCI (n = 30), dementia (n = 26), and healthy age-matched controls (n = 20) underwent assessment of cognitive and physical function and CCM. **Results**: There was a progressive reduction in corneal nerve fiber density (CNFD), branch density (CNBD), and fiber length (CNFL) ($P < 0.0001$) in patients with MCI and dementia compared to healthy controls. Adjusted for confounders, all three corneal nerve fiber measures were significantly associated with cognitive function ($P < 0.05$) and functional independence ($P < 0.01$) in MCI and dementia. The area under the ROC curve to distinguish MCI with CNFD, CNBD, and CNFL was 69.1%, 73.2%, and 73.0% and for dementia it was 84.8%, 84.2%, and 86.2%, respectively. **Interpretation**: CCM demonstrates corneal nerve fiber loss, which is associated with a decline in cognitive function and functional independence in patients with MCI and dementia.

Introduction

Dementia is a progressive neurodegenerative disease, which currently affects 47 million people world-wide and the estimated 2018 costs were over US $1 trillion.[1] It is a cause of significant cognitive and functional disability, and is the most common cause of death in women over 80 years of age in the United Kingdom.[2] Neurodegeneration underlies accelerated cognitive decline and can be identified by brain atrophy,[3–5] hypometabolism,[6,7] and hypoperfusion.[8] Neurodegeneration can be detected approximately 15 years before overt cognitive decline associated with Alzheimer's disease (AD).[5] The National Institute of Aging and the Alzheimer's Association (NIA-AA) have emphasized the need for biomarkers of neurodegeneration to identify those at greatest risk for cognitive decline or progression from mild cognitive impairment (MCI) to dementia.[9,10]

There is an increasing focus on identifying markers for neurodegeneration, which can detect preclinical disease especially for disease modifying or preventative strategies.[11] There is good evidence that the neurodegenerative process in AD is not limited to the brain but also occurs

in the retina, as a thinner retinal nerve fiber layer (RNFL) is associated with cognitive decline in patients with MCI and AD.[12–14] Corneal confocal microscopy (CCM) is a noninvasive ophthalmic imaging technique which allows quantification of corneal nerve morphology and may act as a potential marker for neurodegeneration. It has been most extensively used to study patients with diabetic neuropathy[15–17] and other peripheral neuropathies including those associated with CIDP,[18] HIV,[19] Fabry disease,[20] and inherited neuropathies such as CMT1A[21] and Friedreich's ataxia.[22] However, more recent studies have shown that CCM can also identify nerve fiber loss in patients with Parkinson's disease,[23,24] amyotrophic lateral sclerosis,[25] and multiple sclerosis.[26–28]

The objectives of this study were to: (1) determine whether there is significant corneal nerve fiber loss in patients with MCI and dementia compared to age-matched controls, (2) determine the association between corneal nerve fiber measurements with cognitive function and functional independence, and (3) define the utility of CCM in diagnosing MCI and dementia.

Methods

Patients with mild cognitive impairment (MCI), dementia, and healthy age-matched controls were recruited from the Geriatric clinic in Rumailah Hospital, Doha, Qatar between September 2016 and May 2018. Patients with severe anxiety, depression, Parkinson's disease, frontotemporal and Lewy body dementia, hypomania, and severe dementia who were unable to cooperate were excluded. Furthermore, patients with systemic diseases that may affect corneal nerve fibers, including diabetes, vitamin B12 deficiency, hypothyroidism, HIV infection, and hepatitis C, were excluded. In addition, patients with dry eyes, corneal dystrophies, ocular trauma or surgery in the preceding 6 months were also excluded. We enrolled 222 people and excluded 117 patients with diabetes, 1 patient with depression, 1 patient with hypomania, 3 people younger than the inclusion age and 24 people who did not complete the assessments to leave a sample size of 76. This study was approved by the Institutional Review Board (IRB) of Weill Cornell Medicine in Qatar (WCM-Q) and Hamad Medical Corporation (HMC) and all participants gave informed consent to take part in the study. The research adhered to the tenets of the declaration of Helsinki.

Demographic and metabolic measures

Data including age, ethnicity, gender, blood pressure, weight, and body mass index (BMI) were recorded. HbA1c, lipids, creatinine, hemoglobin (Hgb), mean corpuscular volume (MCV), serum vitamin B12, vitamin D, free thyroxine (FT4), and thyroid stimulating hormone (TSH) were assessed.

Cognitive screening

Cognitive screening was administered by the occupational therapist using the Montreal cognitive assessment (MoCA) Arabic and English version. The MoCA is a 30-point test and includes seven cognitive domains: visuospatial abilities (clock-drawing, cube copy, and alternation task adapted from the Trail-Making B task), naming (confrontation naming of 3 animals), attention (including the sum of attention, concentration, and working memory items), language (the sum of repetition of sentences and verbal fluency task scores), abstract thinking/executive functions (the 2-item verbal abstraction), short-term memory/recall, and orientation. MoCA scores below 26 were considered to indicate cognitive impairment.[29] A point was added for individuals who had formal education ≤6th grade. Patients with cognitive symptoms of depression were determined based on clinical interview and were excluded from the study. Cognitive symptom duration was estimated from the clinical history obtained from relatives and participants.

Functional Independence assessment

The Functional Independence Measure (FIM) was administered by the occupational therapist, and is an 18-point screening test of which 13 are for motor and 5 for cognitive function and each point is scored from 1 to 7. The total FIM score ranges from 18 to 126. There is no cut-off point for FIM, but a higher score indicates greater independence.[30]

Diagnosis

The diagnosis of MCI and dementia were based on the NIA-AA guideline[31] and the Diagnostic and Statistical Manual 4th edition (DSM IV) diagnostic criteria.[32] A joint consultative model in the Department of Geriatric Medicine run by geriatricians and geriatric psychiatrists with advice and consultation from the neurologists was applied to ensure the correct diagnosis, especially to exclude reversible, complex, and young-onset dementia. The diagnosis of MCI or dementia was based on a comprehensive history and examination, which includes (1) presenting complaint and history of illness; (2) comprehensive history of each of the cognitive domains; (3) psychiatric history for ruling out depression, mood disorders, and psychosis; (4) medical history including episodes of delirium and other medical comorbidities; (5) medication history; (6) functional history of basic daily living activities; (7) components of comprehensive

geriatric assessment; (8) detailed psychiatric mental status examination and cognitive screening using MoCA. Subsequent analysis included a comprehensive organic work-up including blood investigation and brain imaging. It is through this robust diagnostic process that the psychiatrists applied the diagnostic criteria. The final diagnosis (control, MCI, dementia) was made according to consensus decision. Radiological evidence for Alzheimer's disease (AD), included volume loss of hippocampi, entorhinal cortex, and amygdala on MRI, based on the criteria described by Dubois et al.[33] For vascular dementia, the NINDS-AIREN criteria[34] which specify evidence of cerebrovascular disease by brain imaging (MRI) were applied and includes multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or posterior (PCA) or anterior cerebral artery (ACA) territories), multiple basal ganglia, and white matter lacunes, extensive periventricular white matter lesions, or combinations thereof. The neuroradiologists also looked for potentially reversible causes of cognitive decline such as tumors, subdural hematoma, or normal pressure hydrocephalus.

Corneal confocal microscopy

Participants underwent corneal confocal microscopy (CCM), a noninvasive ophthalmic imaging technique using the Heidelberg Retina Tomograph and the Rostock Cornea Module (Heidelberg Engineering GmbH, Heidelberg, Germany).[35,36] The patient's eyes were anesthetized using a drop of 0.4% benoxinate hydrochloride, and Viscotears were applied on the front of the eye for lubrication. A drop of Viscotears was placed between the tip of the objective lens and a sterile disposable TOMO cap allowing optical coupling of the objective lens to the cornea. The patient was instructed to fixate on a target with the eye not being examined. Several scans of the sub-basal nerve plexus in the central cornea were captured per eye for ~2 min. The field of view of each image is 400 × 400 μm. At a separate time, three high clarity images per eye were selected by one researcher blind to the patient diagnosis. Criteria for image selection were depth, focus position, and contrast.[37] Three corneal measures: corneal nerve fiber density (CNFD) (number of main nerve fibers/mm^2), branch density (CNBD) (number of branches/mm^2), and fiber length (CNFL) (length of main nerves and branches mm/mm^2) were quantified manually using CCMetrics, a validated image analysis software.[38]

Statistical analysis

The sample size required to determine a significant difference in corneal nerve fiber measures between the control, MCI, and dementia group was calculated from our previously published data.[39] Given a reported difference in population means of 8 /mm^2 for CNFD, with an estimated standard deviation of 7, we estimated that ~17 participants for each group would be needed to provide a study power of 80% and an alpha of 0.05.

Patients' demographic and clinical characteristics were summarized using means and standard deviations for numeric variables and frequency distribution for categorical variables. Variables were compared between the controls; MCI and dementia group using one-way analysis of variance (ANOVA) with Bonferroni's post hoc test for pairwise comparisons and Chi-square test, respectively. Correlation analysis between the three corneal nerve fiber measures was performed using Pearson's method.

Univariate analysis by simple linear regression was performed with age, gender, systolic and diastolic blood pressure, weight, BMI, HbA1c, cholesterol, triglyceride, HDL, LDL, Hgb, MCV, TSH, FT4, vitamin B12, cognitive function, duration of cognitive impairment, functional independence, MCI, and dementia as independent variables, and the corneal nerve fiber measures as the dependent variables. The multiple linear regression analysis included all variables with $P \leq 0.05$ at the bivariate level. The regression coefficient (beta) and the corresponding 95% confidence intervals (95% CI) are presented. Residual analysis was used to assess the assumptions for fitting a linear regression model. All assumptions were satisfied.

Receiver operating characteristic (ROC) curve analysis was used to determine the ability of CNFD, CNBD, and CNFL to distinguish patients with MCI and dementia from healthy controls. The area under curve (AUC), and two cut-off point with the maximal sum of sensitivity and specificity was calculated.

All analyses were performed using IBM-SPSS (version 23; SPSS Inc, Armonk NY). Dot plots were generated using GraphPad Prism, version 6.05. A two-tailed P value of $\leq$0.05 was considered significant.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics are summarized in Table 1. Participants (n = 76) with mild cognitive impairment (MCI) (n = 30) and dementia (n = 26) were compared with a control group (n = 20). The groups had comparable age, gender, systolic blood pressure (SBP), weight, body mass index (BMI), HbA1c, triglycerides, high-density lipoprotein (HDL), creatinine, hemoglobin (Hgb), and mean corpuscular volume (MCV). The dementia group had a significantly lower diastolic blood pressure compared to the MCI group ($P < 0.05$), a lower

Table 1. Demographic and clinical characteristics of the study population.

	Controls (n = 20)	MCI (n = 30)	Dementia (n = 26)	P value[1]	P value[2]	P value[3]
Demographics						
Age, mean ± SD, years	67.65 ± 9.02	67.83 ± 8.48	72.62 ± 8.53	NS	NS	NS
Gender, n (%)						
Male	14 (28.6)	19 (38.8)	16 (32.7)	NS	NS	NS
Female	6 (22.2)	11 (40.7)	10 (37.0)			
BP sys, mean ± SD, mmHg	137.75 ± 11.39	140.62 ± 14.20	138.35 ± 24.95	NS	NS	NS
BP dias, mean ± SD, mmHg	76.85 ± 10.86	76.97 ± 6.59	70.56 ± 10.37	NS	NS	<0.05
Weight, mean ± SD, kg	73.30 ± 8.74	80.78 ± 18.61	76.61 ± 12.90	NS	NS	NS
BMI, mean ± SD, kg/m^2	27.39 ± 3.06	35.12 ± 24.68	30.14 ± 5.32	NS	NS	NS
HbA1c, mean ± SD, %	5.74 ± 0.41	5.64 ± 0.59	5.61 ± 0.42	NS	NS	NS
Chol. mean ± SD, mmol/L	5.11 ± 0.95	4.96 ± 0.89	4.24 ± 1.10	NS	<0.05	<0.05
Trig. mean ± SD, mmol/L	1.27 ± 0.53	1.28 ± 0.63	1.39 ± 0.68	NS	NS	NS
HDL mean ± SD, mmol/L	1.34 ± 0.37	1.34 ± 0.54	1.27 ± 0.47	NS	NS	NS
LDL mean ± SD, mmol/L	3.18 ± 0.86	2.98 ± 0.83	2.36 ± 0.94	NS	<0.05	NS
Creatinine mean ± SD, μmol/L	82.10 ± 25.39	79.79 ± 27.20	82.75 ± 28.28	NS	NS	NS
Hgb, mean ± SD, gm/dL	14.11 ± 1.65	13.30 ± 1.84	13.28 ± 1.01	NS	NS	NS
MCV, mean ± SD, fL	88.41 ± 5.28	82.59 ± 10.52	86.69 ± 5.90	NS	NS	NS
Cognitive function						
MoCA, mean ± SD	27.30 ± 4.21	24.04 ± 2.93	12.96 ± 5.65	<0.05	<0.0001	<0.0001
Cognitive impairment duration, mean ± SD, years	0 ± 0	1.48 ± 1.66	3.35 ± 3.07	0.05	<0.0001	<0.01
Physical and social function						
FIM, mean ± SD	125.23 ± 1.30	120.9 ± 6.5	84.80 ± 29.01	NS	<0.0001	<0.0001
Corneal nerve fiber measures						
CNFD, mean ± SD, no./mm^2	32.95 ± 6.60	27.38 ± 8.42	20.88 ± 9.36	NS	<0.0001	<0.01
CNBD, mean ± SD, no./mm^2	113.29 ± 51.76	72.83 ± 35.62	52.91 ± 34.88	<0.01	<0.0001	NS
CNFL, mean ± SD, mm/mm^2	24.93 ± 5.70	19.97 ± 6.21	15.58 ± 6.51	<0.05	<0.0001	<0.05

Characteristics of 76 participants presented as mean ± standard deviation for numeric variables and frequency distribution for categorical variables for healthy age-matched controls, people with mild cognitive impairment (MCI) and dementia. Continuous and categorical variables were compared using one-way ANOVA with Bonferroni's post hoc test and Chi-square test, respectively. Abbreviations: MoCA, Montreal cognitive assessment; FIM, Functional independence measure; CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length.

[1]Control versus MCI.

[2]Control versus dementia.

[3]MCI versus dementia.

cholesterol than both the control and MCI group ($P < 0.05$) and lower low-density lipoprotein (LDL) compared to the control group ($P < 0.05$). More patients with dementia were on a statin (n = 12, 46%) compared to controls (n = 4, 20%), which may explain the lower total cholesterol in the dementia group. There was a progressive reduction in cognitive function measured by the Montreal Cognitive Assessment (MoCA) between the control (27.30 ± 4.21), MCI (24.04 ± 2.93, $P < 0.05$) and dementia group (12.96 ± 5.65, $P < 0.0001$). The duration of cognitive impairment was significantly longer in the dementia (3.35 ± 3.07 years) compared to the MCI (1.48 ± 1.66 years, $P < 0.01$) group. The Functional Independence Measure (FIM) was lower in the dementia group (84.80 ± 29.01) compared to the MCI (120.9 ± 6.5, $P < 0.0001$) and control (125.23 ± 1.30, $P < 0.0001$) group, but did not differ between the control and MCI group. The dementia group consisted of participants with Alzheimer's disease (n = 7, 27%), vascular dementia (n = 6, 23%), and mixed dementia (n = 13, 50%).The study cohort was comprised of 16 (21.1%) Qatari Arabs, 30 (39.5%) other Arabs, 21 (27.6%) South Asians, 7 (9.2%) Africans, and 2 (2.6%) Caucasians.

Corneal nerve fiber measures

The corneal nerve fiber morphology and measures in patients with MCI and dementia, and healthy age-matched controls are shown in Figure 1. The MCI group compared to the control group had a significantly lower corneal nerve branch density (CNBD) ($P < 0.01$) and corneal nerve fiber length (CNFL) ($P < 0.05$), with no significant difference in the corneal nerve fiber density (CNFD). CNBD, CNFL, and CNFD ($P < 0.0001$) were all significantly reduced in

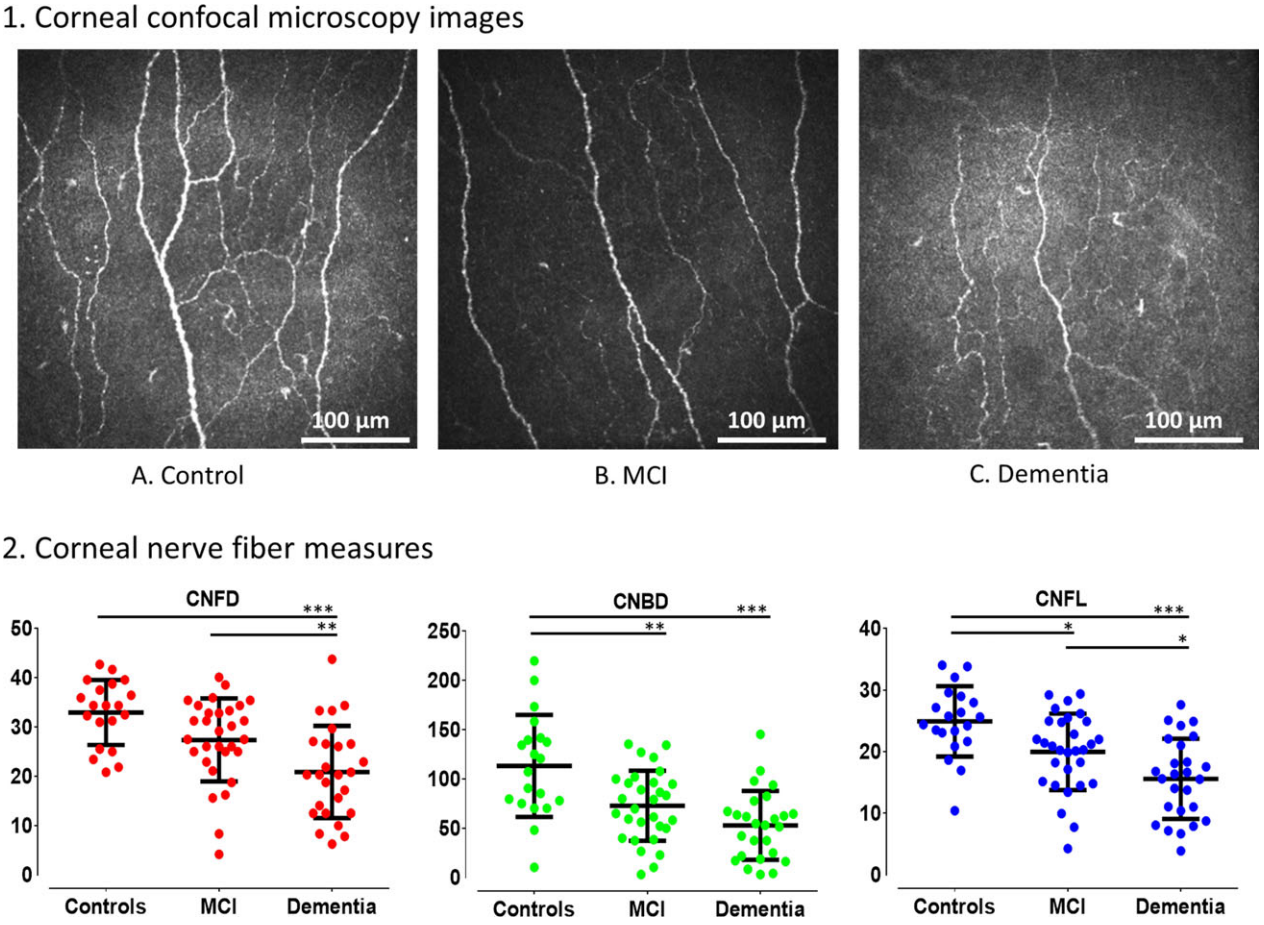

Figure 1. Corneal nerve fiber morphology and measures in healthy age-matched controls, people with mild cognitive impairment (MCI) and dementia. (1) Corneal confocal microscopy (CCM) images of the sub-basal nerve plexus in (A) a 70-year-old control showing normal corneal nerve fiber morphology; (B) a 69-year-old patient with MCI and (C) a 69-year-old patient with dementia showing a progressive reduction in corneal nerve fiber density, branch density, and length. (2) Dot plots of corneal nerve fiber density (CNFD) (red), corneal nerve branch density (CNBD) (green) and corneal nerve fiber length (CNFL) (blue) in controls, people with MCI and dementia. The line that extends from the middle of the vertical line represents the mean and the lines that extend to the top and bottom are the standard deviation with significant differences between the control, MCI and dementia group (*$P \leq 0.05$, **$P \leq 0.01$, ***$P < 0.0001$).

the dementia group compared to the control group and CNFD ($P < 0.01$) and CNFL ($P < 0.05$) were significantly lower in the dementia group compared to the MCI group. All three corneal nerve fiber measures were significantly correlated to each other; CNFD with CNBD ($r = 0.70$, $P < 0.0001$) and CNFL ($r = 0.70$, $P < 0.0001$) and CNBD with CNFL ($r = 0.92$, $P < 0.0001$).

Association of corneal nerve fiber measures with cognitive function, duration of cognitive impairment, and functional independence in MCI and dementia

Univariate analysis with CNFD and CNBD as dependent variables showed a significant association with cognitive function ($b = 0.41$ and 0.39, $P \leq 0.01$), duration of cognitive impairment ($b = -0.32$ and -0.30, $P < 0.05$), functional independence ($b = 0.52$ and 0.45, $P \leq 0.01$), MCI ($b = -0.30$ and -0.28, $P \leq 0.05$), dementia ($b = -0.59$ and -0.58, $P < 0.0001$), and total cholesterol ($b = 0.26$ and 0.25, $P \leq 0.05$). Univariate analysis with CNFL as a dependent variable showed a significant association with cognitive function ($b = 0.42$, $P < 0.0001$), duration of cognitive impairment ($b = -0.30$, $P < 0.01$), functional independence ($b = 0.54$, $P < 0.0001$), MCI ($b = -0.27$, $P = 0.05$), dementia ($b = -0.61$, $P < 0.0001$), age ($b = -0.23$, $P = 0.05$), and total cholesterol ($b = 0.29$, $P \leq 0.05$).

Multiple linear regression analyses to determine the association of corneal nerve fiber measures with

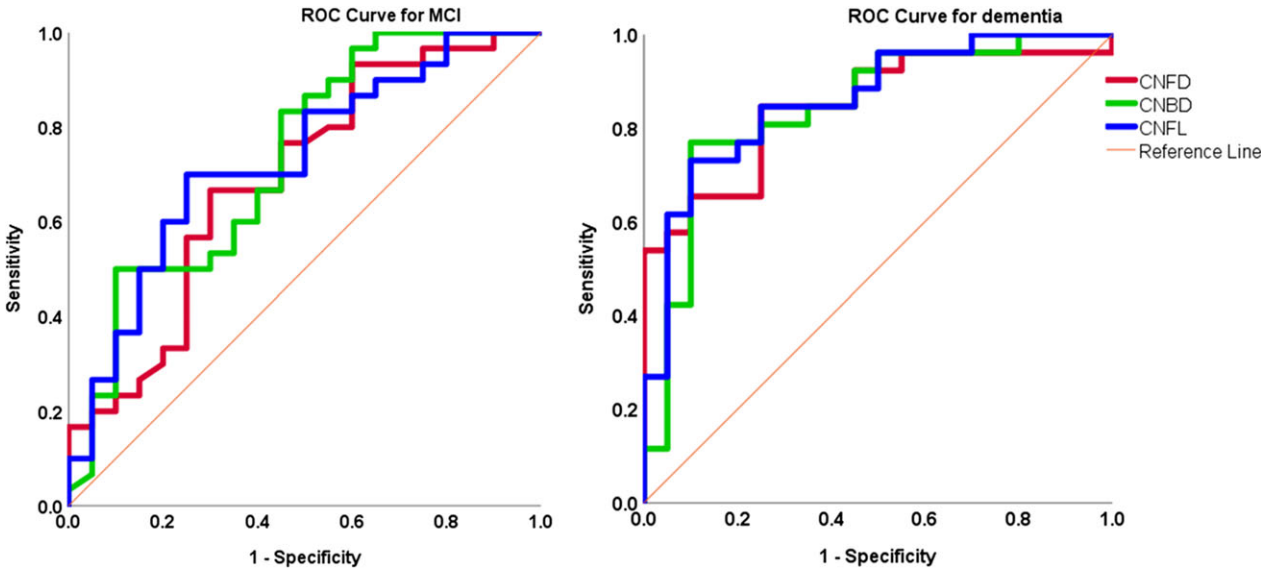

Figure 2. ROC analysis showing the area under the curve for corneal confocal microscopy (CCM) measures in distinguishing people with MCI and dementia from healthy controls. The area under the ROC curve to distinguish MCI with CNFD, CNBD, and CNFL was 69.1%, 73.2%, and 73.0% and for dementia it was 84.8%, 84.2%, and 86.2%, respectively.

cognitive function, functional independence, MCI, dementia, and duration of cognitive impairment are summarized in Table 2. Adjusted for cholesterol, CNFD and CNBD were associated with cognitive function ($b = 0.31$, 0.33, $P < 0.05$), functional independence ($b = 0.50$, 0.67, $P < 0.01$), and dementia ($b = -0.48$, -0.55, $P < 0.01$), but only CNBD was associated with MCI ($b = -0.38$, $P < 0.01$). Adjusted for age and cholesterol, CNFL was associated with cognitive function ($b = 0.31$, $P < 0.05$), functional independence ($b = 0.56$, $P = 0.001$), MCI ($b = -0.33$, $P < 0.05$), and dementia ($b = -0.51$, $P < 0.01$). However, the association of corneal nerve fiber measures with duration of cognitive impairment was lost after adjusting for confounding factors.

CCM sensitivity and specificity

The AUC for MCI with CNFD, CNBD, and CNFL was 69.1% (95% CI, 53.7%–84.4%), 73.2% (95% CI, 58.6%–87.9%), and 73.0% (95% CI, 58.7%–87.3%), respectively, and for dementia it was 84.8% (95% CI, 73.6%–96.0%), 84.2% (95% CI, 72.2%–96.3%), and 86.2% (95% CI, 75.5%–96.9%), respectively (Fig. 2). Using a CNFD cut-off of <34 /mm^2, the sensitivity for MCI and dementia was 76.7% and 92.3%, respectively, and the specificity was 55%. Using a CNBD cut-off of <78 /mm^2, the sensitivity for MCI and dementia was 53.3% and 80.8%, and the specificity was 70% and 75%, respectively. Using a CNFL cut-off of <23 /mm^2 the sensitivity for MCI and dementia was 70.0% and 84.6%, respectively, and the specificity was 75%.

Discussion

This study shows that corneal confocal microscopy (CCM) detects corneal nerve fiber loss in people with mild cognitive impairment (MCI) and people with dementia, compared to age-matched healthy controls. Furthermore, after adjusting for confounding factors, corneal nerve fiber loss was significantly associated with decline in cognitive function and functional independence in patients with MCI and dementia. This is an important observation as it demonstrates cognitive decline is not only associated with brain atrophy[3,4] and retinal nerve fiber layer (RNFL) thinning,[12-14] but also with corneal nerve fiber loss.

The diagnosis of MCI and dementia are based on clinical, cognitive, and functional criteria as well as clinical judgment.[9] However, there is no sharp demarcation between aging cognition and MCI and between MCI and dementia. The NIA-AA proposed a classification scheme for preclinical AD based on biomarkers of β-amyloid, tauopathy, and neurodegeneration to determine the level of certainty for progression from MCI to Alzheimer's disease (AD).[9,10] Current NIA-AA recommended markers for neurodegeneration include brain atrophy,[3-5] hypometabolism,[6,7] and hypoperfusion[8] using magnetic resonance imaging (MRI), PET, and single-photon emission computed tomography (SPECT) imaging, respectively.

Table 2. Multiple linear regression analysis to determine the association of corneal nerve fiber measures with cognitive function, functional independence, mild cognitive impairment (MCI), dementia, and duration of cognitive impairment.

	Coefficient	95% Confidence Interval	*P* value
Montreal cognitive assessment (MoCA)			
CNFD, no./mm^2	0.31	0.06, 0.80	<0.05
CNBD, no./mm^2	0.33	0.54, 4.87	0.01
CNFL, mm/mm^2	0.31	0.04, 0.66	<0.05
Function independence measure (FIM)			
CNFD, no./mm^2	0.67	0.16, 0.38	<0.0001
CNBD, no./mm^2	0.50	0.46, 2.08	<0.01
CNFL, mm/mm^2	0.56	0.08, 0.31	0.001
Mild cognitive impairment (MCI)			
CNFD, no./mm^2	−0.27	−8.21, 0.28	NS
CNBD, no./mm^2	−0.38	−61.08, −9.24	<0.01
CNFL, mm/mm^2	−0.33	−7.67, −0.37	<0.05
Dementia			
CNFD, no./mm^2	−0.48	−7.57, −1.66	<0.01
CNBD, no./mm^2	−0.55	−45.64, −12.50	0.001
CNFL, mm/mm^2	−0.51	−6.20, −1.45	<0.01
Duration of cognitive impairment			
CNFD, no./mm^2	−0.24	−2.19, 0.08	NS
CNBD, no./mm^2	−0.24	−12.76, 0.54	NS
CNFL, mm/mm^2	−0.23	−1.74, 0.10	NS

The following confounding variables were considered: cholesterol for CNFD and CNBD, and age and cholesterol for CNFL. All the variables considered in the fitted model had $P < 0.05$. CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length.

However, the clinical utility of these biomarkers is hampered by the invasiveness of cerebrospinal fluid (CSF) sampling and high costs or limited availability of MRI, PET, and SPECT.[9,31]

There are several studies suggesting that the eye may be a biomarker for dementia.[12,13,40] The European Prospective Investigation of Cancer study of 8623 people in the United Kingdom showed that RNFL thinning was associated with cognitive decline.[13] Similarly, in 32,038 healthy UK Biobank participants RNFL thinning was associated with future cognitive decline.[12] A recent study in patients with Parkinson's disease has shown that a reduction in corneal nerve fiber length was associated with cognitive function as assessed using the Addenbrooke's cognitive examination-revised (ACE-R) score.[40] There are no prior published data examining the association between corneal nerve morphology and cognitive function in people with MCI or dementia. In this study, the diagnostic workup employed the Arabic and English version of the Montreal cognitive assessment (MoCA), which is considered to be a good index of cognitive impairment compared to the Mini-Mental State Examination (MMSE), especially for MCI.[41] All three corneal nerve fiber measures were associated with a decline in cognitive function and functional independence. The ROC curve analysis suggests that CCM may have a good discriminative power to distinguish between healthy people and people with dementia. Paradoxically, we show that patients with a lower CNFL have a lower total cholesterol, which is counter to previous studies showing that corneal nerve fiber loss is associated with increased levels of cholesterol.[42,43] However, this may be explained by the twofold greater use of statins in patients with dementia.

The association between corneal nerve fiber loss and cognitive function should be interpreted with caution, especially with the small cohorts studied. Subanalysis to assess any difference in the corneal nerve fiber measurements for Alzheimer's disease and vascular dementia will be undertaken in future larger cohort studies. We acknowledge, there may be other causes of corneal nerve fiber loss such as impaired glucose tolerance and metabolic syndrome, although we carefully excluded participants with ocular diseases, corneal dystrophies, diabetes, and other causes of neuropathy that may influence corneal nerves. Nevertheless, this study suggests corneal confocal microscopy can identify neurodegeneration in people with MCI and dementia and is associated with cognitive decline and functional independence. Larger, longitudinal studies are required to establish the diagnostic and prognostic utility of CCM in people with MCI and dementia.

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Author Contributions

Malik and Ponirakis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sankaranarayanan, Malik, and Ponirakis.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ponirakis and Malik.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ponirakis and Mahfoud.

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Administrative, technical, or material support: Malik, Al Hamad, Ponirakis, Khan, Tosino, and Elorrabi.

Conflict of Interest

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship and are not listed. We confirm that the order of authors listed in the manuscript has been approved by all authors. None of the authors have received or anticipate receiving income, goods or benefit from a company that will influence the design, conduct, or reporting of the study.

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