Corneal nerve and brain imaging in mild cognitive impairment and dementia: A cross-sectional study

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Research

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Abstract

Background: Visual rating of medial temporal lobe atrophy (MTA) is an accepted biomarker of Alzheimer's disease. Corneal confocal microscopy (CCM) is a non-invasive ophthalmic imaging biomarker of neurodegeneration. We sought to determine the diagnostic accuracy of CCM to distinguish mild cognitive impairment (MCI) and dementia from no cognitive impairment (NCI) in relation to MTA rating.

Methods: Subjects aged 60-85 with NCI, MCI and dementia were recruited from the geriatric and memory clinic in Rumailah Hospital, Doha, Qatar between 18/09/16 and 31/07/19. The diagnosis of MCI and dementia were based on the International Classification of Diseases (ICD-10) criteria. Subjects underwent cognitive screening using the Montreal Cognitive Assessment (MoCA), CCM and MTA rating on MRI. Statistical tests used were ANOVA with Bonferroni's post hoc test, kappa statistics and receiver operating characteristic (ROC) curve analysis. A two-tailed P value of ≤ 0.05 was considered significant.

Results: 182 subjects with NCI (n=36), MCI (n=80) and dementia (n=66), including AD (n=19, 28.8%), VaD (n=13, 19.7%) and combined AD (n=34, 51.5%) were studied. CCM showed a progressive reduction in corneal nerve fiber density (CNFD, fibers/mm^2) (32.0±7.5 vs 24.5±9.6 vs 20.8±9.3, p<0.0001), branch density (CNBD, branches/mm^2) (90.9±46.5 vs 59.3±35.7 vs 53.9±38.7, p<0.0001), and fiber length (CNFL, mm/mm^2) (22.9±6.1 vs 17.2±6.5 vs 15.8±7.4, p<0.0001), in subjects with MCI and dementia compared to NCI. The MTA rating in the dementia group was significantly higher compared with the NCI and MCI group in the right (1.9±1.0 vs 0.5±0.6 and 0.6±0.8, p<0.0001) and left (2.1±1.1 vs 0.6±0.7 and 0.8±0.8, p<0.0001) hemispheres. The area under the ROC curve (95% CI) for the diagnostic accuracy of CNFD, CNBD, CNFL vs MTA-right and -left for MCI was 78% (67-90%), 82% (72-92%), 86% (77-95%) vs 53% (36-69%) and 40% (25-55%), respectively, and for dementia it was 85% (76-94%), 84% (75-93%), 85% (76-94%) vs 86% (76-96%) and 82% (72-92%), respectively.

Conclusions: The diagnostic accuracy of CCM, a non-invasive ophthalmic biomarker of neurodegeneration was high and comparable with MTA rating for dementia and superior to MTA rating for MCI.

Background

Dementia is a progressive neurodegenerative disease affecting 40-50 million people worldwide.(1, 2) Therapeutic and psychological interventions for people with early stage dementia can improve cognition, independence, and quality of life.(3) However, the clinical diagnosis of mild cognitive impairment (MCI) or early dementia can be challenging due to the insidious onset of disease and gradual cognitive decline. The National Institute on Aging and the Alzheimer's Association (NIA-AA) has proposed a number of biomarkers that reflect the underlying pathology of the disease to support the diagnosis of MCI and dementia.(4, 5)

Medial temporal lobe atrophy (MTA) rating is an established biomarker for neurodegeneration in Alzheimer's disease (AD).(4, 5) There is progressive MTA in subjects with MCI and dementia compared to those with no cognitive impairment (NCI).(6, 7) MTA rating has been shown to have high diagnostic accuracy for probable(8) and established AD.(9, 10) It can distinguish subjects with and without amnestic MCI and predict transition from NCI to MCI and from MCI to probable AD(11) as well as cognitive decline.(12) MTA has also been reported in patients with vascular dementia (VaD).(13, 14)

Corneal confocal microscopy (CCM) is a rapid non-invasive ophthalmic imaging technique which was originally pioneered for identifying neurodegeneration in diabetic peripheral neuropathy(15-19) and subsequently in a range of other peripheral neuropathies.(20) CCM has recently also been used to identify neuronal injury in a number of central neurodegenerative disorders, including MCI, dementia,(21) Parkinson's disease,(22) amyotrophic lateral sclerosis(23) and multiple sclerosis.(24-26) CCM generates *in vivo* images of the sub-basal nerve plexus and image analysis of corneal nerve morphology is performed using validated image analysis software (27) to reduce inter- and intra-rater variability for quantification of corneal nerve morphology.(15, 28, 29)

The objective of this study was to compare the diagnostic accuracy of CCM with MTA rating for MCI and dementia, including AD, VaD and combined AD.

Methods

Patients with MCI, dementia, including AD, VaD and combined AD and no cognitive impairment (NCI) were recruited from the Geriatric and Memory clinic in Rumailah Hospital, Doha, Qatar between 18/09/16 and 31/07/19. Patients with severe anxiety, severe depression, Parkinson's disease, frontotemporal dementia and Lewy body dementia, hypomania, and severe dementia who were unable to cooperate were excluded. Additionally, patients with other potential causes of peripheral neuropathy including vitamin B12 deficiency, hypothyroidism, HIV infection and hepatitis C were excluded. Diabetes was not excluded because there is high prevalence of diabetes in patients aged ≥50 years in Qatar.(30) Patients with dry eyes, corneal dystrophies, ocular trauma or surgery in the preceding 6 months were excluded. This study was approved by the Institutional Review Board of Weill Cornell Medicine in Qatar and Hamad Medical Corporation 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

Age, gender, ethnicity, blood pressure, weight, body mass index (BMI), HbA1c, cholesterol, triglycerides, thyroid stimulating hormone (TSH), free thyroxine (FT4) and vitamin B12 were recorded.

Cognitive screening

Cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) test. The MoCA assesses seven cognitive domains including visuospatial/executive, naming, memory, attention,

language, abstraction and delayed recall giving a total score of 30. A score of £ 26 indicates cognitive impairment. A point was added for individuals who had formal education ≤6th grade. Cognitive symptom duration was estimated from the clinical history obtained from relatives and participants.

Diagnosis

The diagnosis of MCI and dementia were based on the ICD-10 criteria.(31) The diagnosis was made according to consensus decision by geriatricians, geriatric psychiatrists and neurologists to exclude reversible, complex and young-onset dementia. The diagnosis of MCI and dementia were based on a patient history and examination, which include (1) presenting complaint and history of illness; (2) comprehensive history of each of the cognitive domains using MoCA; (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. A comprehensive organic work-up including blood tests and brain imaging was undertaken to exclude other potentially reversible causes of cognitive decline such as tumors, subdural hematoma or normal pressure hydrocephalus. Radiological evidence for AD, included volume loss of hippocampi, entorhinal cortex, and amygdala on MRI, based on the criteria described by Dubois et al.(32) The diagnosis of probable or possible VaD was based on the NINDS-AIREN criteria(33), which include multiple large vessel infarcts or a single strategically placed infarct including angular gyrus, thalamus, basal forebrain, or posterior (PCA) or anterior cerebral artery (ACA) territories, and multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or combinations thereof.

MRI brain procedures

MRI was performed on a superconductive magnet operated at 3T (Skyra, Siemens). A T1-weighted 3D magnetisation prepared rapid acquisition gradient echo sequence (MPRAGE) was obtained in the sagittal plane with a 1 mm slice thickness, repetition time of 1900 ms, echo time of 2.67 ms and 2.46 ms, inversion time of 1100 ms and 900 ms, flip angle of 9 degree and 15 degree, and FOV= 240 x 100. Coronal and axial reformatted MPRAGE images were made from the sagittal 3D sequence.

Medial temporal lobe atrophy visual rating

Two board certified neuroradiologists blinded to diagnosis and clinical data assessed MRI images. T1-coronal images at the level of the midbrain were used to score for right and left medial temporal lobe atrophy (MTA). The right and left hippocampi, entorhinal cortices, perirhinal cortices were separately rated according to the five-point scale developed and validated by Duara et al, and a combined visual MTA score for each hemisphere was calculated averaging the three measurements.(11) The coronal reformatted MRI slice at the level of the mammillary bodies seen in the sagittal plane was used to define the outline of the medial temporal lobe. The outline of the entorhinal cortex in this slice was defined by the anterior parahippocampal gyrus and adjacent white matter (seen medial to the collateral sulcus and inferior to the hippocampus). The outline of the perirhinal cortex was defined by the fusiform gyrus and adjacent white matter (seen lateral to the collateral sulcus and medial to the occipitotemporal sulcus).

Corneal confocal microscopy

CCM analysis was performed with the Heidelberg Retinal Tomograph III Rostock Cornea Module (Heidelberg Engineering GmbH, Heidelberg, Germany). The cornea was locally anesthetized by instilling 1 drop of 0.4% benoxinate hydrochloride (Chauvin Pharmaceuticals, Chefaro, UK) and Viscotears (Carbomer 980, 0.2%, Novartis, UK) was used as the coupling agent between the cornea and the TomoCap as well as between the TomoCap and the objective lens. Subjects were 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 400X400 μm. At a separate time, three high clarity images per eye were selected by one researcher blind to the patient diagnosis using established criteria based on depth, focus position and contrast.(29) Corneal nerve fiber density (CNFD) (fibers/mm^2), branch density (CNBD) (branches/mm^2) and fiber length (CNFL) (total fiber length mm/mm^2) were quantified using CCMetrics, a validated image analysis software.(27)

Power analysis

Based on data from a previous study showing a reported difference in population means of CNFD 10 fibers/mm^2, CNBD 4.96 branches/mm^2 or CNFL 9.3 mm/mm^2,(21) a sample size of 6, 22 and 7 subjects, respectively was calculated to have 80% power to detect a significant difference between the NCI, MCI and dementia group.

Statistical analysis

Patients' demographics and clinical characteristics were summarized using means and standard deviations for numeric variables and frequency distribution for categorical variables. Variables were compared between the NCI, 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.

To assess inter-rater reliability, the neuroradiologists independently scored for MTA in 30 subjects with NCI (n=10), MCI (n=10), and dementia (n=10), blind to the identity and diagnosis of the subjects. To assess intra-rater reliability, one of the neuroradiologists repeated ratings in all 30 subjects after an interval of approximately four weeks. Inter-rater and intra-rater reliability was assessed using kappa statistics.

Receiver operating characteristic (ROC) curve analysis was used to determine the ability of CNFD, CNBD, CNFL, MTA-R, and MTA-L to distinguish between patients with MCI and dementia from NCI. The area under the ROC curve (AUC) and a cut-off point with the maximal sensitivity and specificity were 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 ≤ 0.05 was considered significant.

Results

We enrolled 207 people and excluded 1 patient with severe depression, 1 patient with hypomania and 23 people who did not complete all assessments to leave a sample size of 182.

Demographic and clinical characteristics

182 subjects with NCI (n=36), MCI (n=80) and dementia (n=66) were studied. The demographic and clinical characteristics of these three groups are summarized (Table 1). The study cohort comprised of 111 (61.0%) males and 71 (39.0%) females. There were 63 (34.6%) Qatari Arabs, 62 (34.1%) other Arabs, 37 (20.3%) South Asians, and 20 (11.0%) other ethnicities. The prevalence of Type 2 diabetes was 110 (60.4%) and was comparable between subjects with NCI (n=22, 61.1%), MCI (n=46, 57.5%) and dementia (n=42, 63.6%), p=0.71. Gender proportion and the mean age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body weight, BMI, HbA1c, cholesterol and triglycerides were comparable between groups. There was a progressive reduction in cognitive function measured by MoCA between NCI (27.4 ± 4.1), MCI (22.1 ± 5.5, p<0.0001) and dementia (12.7 ± 4.1, p<0.0001) group. The mean duration of cognitive impairment was significantly shorter in the MCI group compared to the dementia group (1.5 ± 1.6 years vs 3.2 ± 2.8 years, p<0.0001). The dementia group comprised of AD (n=19, 28.8%), VaD (n=13, 19.7%) and combined AD and vascular lesions (n=34, 51.5%).

Visual rating of medial temporal lobe atrophy

The inter-rater reliability for MTA rating between two raters was 0.57 and 0.67 for the right and left MTA, respectively. The intra-rater reliability was 1.00 for both the right and left MTA.

The atrophy rating of the right and left hippocampi, entorhinal cortices, perirhinal cortices and medial temporal lobe were comparable between the NCI and MCI group (Fig 1 & Table 1). The MTA rating of the dementia group was significantly higher compared with the NCI and MCI group on the right (1.9±1.0 vs 0.5±0.6 and 0.6±0.8, p<0.0001) and left (2.1±1.1 vs 0.6±0.7 and 0.8±0.8, p<0.0001) hemispheres. The average MTA rating in the group with AD (1.9±1.0) and combined AD with vascular lesions (2.3±1.0) was higher than the group with VaD (1.5±0.8) but was not significant (P=0.08).

Corneal nerve fiber measures

The corneal nerve fiber measures in subjects with NCI, MCI and dementia are shown in Figure 2. Compared to NCI the MCI and dementia group had a significantly lower corneal nerve fiber density (CNFD, fibers/mm^2) (32.0±7.5 vs 24.5±9.6 and 20.8±9.3, p<0.0001), branch density (CNBD, branches/mm^2) (90.9±46.5 vs 59.3±35.7 and 53.9±38.7, p£0.001) and fiber length (CNFL, mm/mm^2) (22.9±6.1 vs 17.2±6.5 and 15.8±7.4, p<0.0001). CNFD (20.8±10.7 vs 19.8±9.1 vs 21.0±8.8, P=0.93), CNBD (58.1±45.8 vs 51.2±37.2 vs 51.9±36.0, P=0.84) and CNFL (16.4±8.7 vs 15.9±8.4 vs 15.3±6.4, P=0.88) were comparable between subjects with AD, VaD and dementia with combined AD, respectively.

CNFD was comparable in subjects with NCI (30.3±8.0 vs 34.4±6.2, p=0.10), MCI (23.0±10.0 vs 26.7±8.7, p=0.12) and dementia (20.2±9.4 vs 21.8±9.2, p=0.53), with and without diabetes. CNBD was comparable in subjects with NCI (91.6±44.1 vs 89.8±51.4, p=0.92), MCI (55.1±36.0 vs 65.8±34.9, p=0.23) and dementia (52.8±41.2 vs 55.9±34.5, p=0.74), with and without diabetes. CNFL was comparable in subjects with NCI (22.3±6.4 vs 23.9±5.4, p=0.43), MCI (16.2±6.6 vs 18.7±6.1, p=0.12) and dementia (16.3±8.0 vs 16.3±6.3, p=0.68), with and without diabetes.

MTA sensitivity and specificity

The area under the ROC curve (AUC) (95% CI) to distinguish MCI from NCI for MTA-R and MTA-L was not significant 53% (36-69%) and 40% (25-55%), respectively, whilst for dementia it was 86% (76-96%) and 82% (72-92%) (p<0.0001), respectively (Fig 3 & Table 2). The sensitivity and specificity for dementia was 85% and 71% with MTA-R cut-off <0.8 and 79% and 62% with MTA-L cut-off <1.2.

CCM sensitivity and specificity

The area under the ROC curve (95% CI) to distinguish MCI from NCI for CNFD, CNBD, and CNFL was 78% (67-90%), 82% (72-92%), and 86% (77-95%) (p<0.0001), respectively, and for dementia it was 85% (76-94%), 84% (75-93%), and 85% (76-94%) (p<0.0001), respectively (Fig 3 and Table 2). The sensitivity and specificity for MCI was 57% and 81% with CNFD cut-off <27 fibers/mm^2, 77% and 76% with CNBD cut-off <85 branches/mm^2 and 81% and 81% with a CNFL cut-off <22 mm/mm^2. The sensitivity and specificity for dementia was 77% and 81% with a CNFD cut-off <27 fibers/mm^2, 79% and 81% with a CNBD cut-off <78 branches/mm^2 and 79% and 91% with a CNFL cut-off of <21mm/mm^2.

Discussion

This study compared the diagnostic accuracy of corneal confocal microscopy (CCM) a non-invasive ophthalmic imaging biomarker of neurodegeneration for mild cognitive impairment (MCI) and dementia(21) with medial temporal lobe atrophy (MTA) rating, an established biomarker for Alzheimer's disease.(4, 5) The diagnostic accuracy of corneal nerve measures of neurodegeneration was high and equivalent to MTA rating for dementia, but it was superior to MTA rating for MCI. MTA rating could not distinguish subjects with MCI from subjects with NCI.

Dementia is a neurodegenerative condition characterized with an insidious onset and a slow progression.(4) A diagnosis of MCI requires a change in cognition, evidence of impairment in at least one cognitive domain and preserved ability to function independently in daily life.(5) However, cognitive assessment tests are influenced by age, educational and cultural background.(4) A method that allows for greater diagnostic certainty to distinguish normal cognition due to aging from MCI and dementia is required. Biomarkers can support the diagnosis of MCI and dementia by providing direct or indirect evidence of the underlying pathology of the disease and identify subtypes of MCI which do or do not progress to dementia.(4)

MTA rating as a biomarker of neuronal injury is included in the NIA-AA guidelines to support the diagnosis of AD.(4, 5) Pathological changes occurring in the medial temporal lobe have been demonstrated at autopsy in patients with dementia in the earliest stages of the disease.(34) MTA also occurs in vascular dementia (VaD) but not to the same extent as in AD.(13, 14) A gradual accumulation of infarcts or white matter ischemia is associated with hippocampal neuronal loss. In this study, MTA was detected in subjects with AD, VaD and combined AD and vascular lesions. MTA visual rating was developed for use in clinical practice as it is easy to learn and can be quickly scored to support the diagnosis of AD.(35) However, there are conflicting data about the diagnostic accuracy of MTA visual rating for AD. Duara et al.(11) reported that MTA can discriminate probable AD from no cognitive impairment with a good sensitivity (85%) and specificity (82%), above the 80% threshold.(8) Heo et al.(9) and Cavedo et al.(10) also reported that MTA scoring has high diagnostic accuracy for AD. Our findings are in line with the study of Falgas et al.(36) showing that MTA visual rating can distinguish between AD and healthy controls with 94% specificity but 77% sensitivity using ≥1.5 cut-off or 90% sensitivity with 56% specificity using ≥1 cut-off. However, previous studies reporting a high diagnostic accuracy for AD with MTA rating assessed patients with late-onset AD who have more atrophy compared to patients with early-onset AD. Furthermore, Duara et al.(11) used different MTA visual rating cut-offs for different age groups, ≥2 for 63-75 years and ≥3 for ≥75 years, whilst our cut-off was independent of age. Falgas et al.(36) also reported that MTA rating cannot distinguish patients with early-onset AD and subjects with MCI. The area under the curve (AUC)/sensitivity/specificity were 63%/30%/93% for non-amnesic and 67%/34%/93% for amnesic early-onset AD. In this study, the left and right MTA scores could not distinguish subjects with NCI from MCI.

Corneal nerve morphology has been evaluated using CCM in a number of central neurodegenerative disorders, including MCI, dementia,(21) Parkinson's disease,(22) amyotrophic lateral sclerosis(23) and multiple sclerosis.(24-26) Ponirakis et al.(21) reported corneal nerve loss and reasonable diagnostic accuracy in a small cohort of subjects with MCI and dementia. In the present study with a greater number of participants we show improved diagnostic accuracy with an AUC (86% vs 73%), sensitivity (81% vs 70%) and specificity (81% vs 75%) for MCI and a comparable AUC (85% vs 86%) and sensitivity (79% vs 85%) but improved specificity (91% vs 75%) for dementia. This study also shows that the severity of corneal nerve loss was comparable between AD, VaD and dementia with combined AD and vascular lesions.

The diagnostic accuracy of MTA visual rating and CCM for MCI should be interpreted with caution because diagnosis of MCI was based on clinical evaluation and cognitive examination using the ICD-10 criteria.(31) This is a significant limitation when comparing the diagnostic accuracy of these two techniques for MCI without biological confirmation of the disease including cerebrospinal fluid (CSF) concentrations of amyloid beta (Aβ) 42, Aβ40, tau/phosphorylated tau(37, 38) or Aβ deposition using positron emission tomography (PET).(39, 40) This could have led to higher rate of misdiagnosis of MCI. We acknowledge, there may be other causes of corneal nerve fiber loss such as impaired glucose tolerance(41) and diabetes.(42) However, our findings are in line with a recent report(43) showing the CCM measures were comparable between patients with type 2 diabetes and good glycemic control,

compared to healthy controls. We also carefully excluded participants with ocular diseases, corneal dystrophies and other causes of neuropathy that may cause corneal nerve loss.

In conclusion, this study shows that CCM has high diagnostic accuracy for MCI and dementia, whereas MTA rating has high diagnostic accuracy for dementia but cannot distinguish subjects with NCI from those with MCI. This suggests that CCM should be considered as an ophthalmic imaging biomarker of neurodegeneration to support the diagnosis of MCI and dementia.

Abbreviations

ACA Anterior Cerebral Artery

AD Alzheimer's Disease

ANOVA Analysis of Variance

AUC Area Under the Curve

BMI Body Mass Index

CCM Corneal Confocal Microscopy

CNBD Corneal Nerve Branch Density

CNFD Corneal Nerve Fiber Density

CNFL Corneal Nerve Fiber Length

CSF Cerebrospinal Fluid

DBP Diastolic Blood Pressure

FT4 Free Thyroxine

ICD International Classification of Diseases

MCI Mild Cognitive Impairment

MoCa Montreal Cognitive Assessment

MPRAGE Magnetisation Prepared Rapid Acquisition Gradient Echo

MTA Medial Temporal Lobe Atrophy

NCI No Cognitive Impairment

NIA-AA National Institute on Aging and the Alzheimer's Association

PCA Posterior Cerebral Artery

PET Positron Emission Tomography

ROC Receiver Operating Characteristic

SBP Systolic Blood Pressure

TSH Thyroid Stimulating Hormone

VaD Vascular Dementia

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Review Board of Weill Cornell Medicine in Qatar and Hamad Medical Corporation and all participants gave informed consent to take part in the study. The research adhered to the tenets of the declaration of Helsinki.

Consent for publication:

Not applicable

Availability of data and materials:

Data and materials generated and analyzed during this study are available from the corresponding author on reasonable request.

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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: Malik and Ponirakis.
- Acquisition, analysis, or interpretation of data: All authors.
- Drafting of the manuscript: Al-Janahi, Ponirakis and Malik.
- Critical revision of the manuscript for important intellectual content: All authors.

- Statistical analysis: Al-Janahi, Ponirakis and Mahfoud.
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- Administrative, technical, or material support: Malik, Al Hamad, Ponirakis, Khan, Tosino and Elorrabi.

Potential 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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Tables

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

	NCI (*n* = 36)	MCI (*n* = 80)	Dementia (*n* = 66)	*P* value[1]	*P* value[2]	*P* value[3]
Demographics						
Age, years	71.7 ± 6.2	71.6 ± 5.4	73.9 ± 6.9	NS	NS	NS
Female	11 (30.6%)	34 (42.5%)	26 (39.4%)	NS	NS	NS
Systolic BP, mmHg	140.3 ± 17.0	138.6 ± 17.4	138.6 ± 21.4	NS	NS	NS
Diastolic BP, mmHg	73.7 ± 19.8	71.4 ± 8.3	69.1 ± 10.0	NS	NS	NS
Weight, kg	76.4 ± 10.7	80.7 ± 19.2	75.8 ± 13.8	NS	NS	NS
BMI, Kg/m^2	27.6 ± 4.0	30.6 ± 7.2	30.0 ± 4.9	NS	NS	NS
HbA1c, %	6.7 ± 1.3	7.0 ± 1.7	6.6 ± 1.3	NS	NS	NS
Chol. mmol/L	4.3 ± 1.1	4.3 ± 1.0	3.9 ± 1.2	NS	NS	NS
Trig. mmol/L	1.5 ± 0.7	1.5 ± 0.7	1.4 ± 0.7	NS	NS	NS
Cognitive function						
MoCA	27.4 ± 4.1	22.1 ± 5.5	12.7 ± 4.1	<0.0001	<0.0001	<0.0001
Cognitive impairment duration, years	N/A	1.5±1.6	3.2±2.8			<0.0001
Corneal nerve fiber measures						
CNFD, $fibers/mm^2$	32.0 ± 7.5	24.5 ± 9.6	20.8 ± 9.3	<0.0001	<0.0001	NS
CNBD, $branches/mm^2$	90.9 ± 46.5	59.3 ± 35.7	53.9 ± 38.7	0.001	<0.0001	NS
CNFL, mm/mm^2	22.9 ± 6.1	17.2 ± 6.5	15.8 ± 7.4	<0.0001	<0.0001	NS
Medial Temporal Atrophy Measures						
Medial temporal atrophy (right & left)	0.7 ± 0.7	0.6 ± 0.6	2.0 ± 1.0	NS	<0.0001	<0.0001
Medial temporal atrophy (right)	0.6 ± 0.8	0.5 ± 0.6	1.9 ± 1.0	NS	<0.0001	<0.0001

Hippocampus (right)	1.1 ± 1.1	1.3 ± 0.9	2.8 ± 0.9	NS	<0.0001	<0.0001
Entorhinal cortex (right)	0.4 ± 0.9	0.2 ± 0.6	1.6 ± 1.2	NS	<0.0001	<0.0001
Perirhinal cortex (right)	0.3 ± 0.6	0.2 ± 0.5	1.4 ± 1.1	NS	<0.0001	<0.0001
Medial temporal atrophy (left)	0.8 ± 0.8	0.6 ± 0.7	2.1 ± 1.1	NS	<0.0001	<0.0001
Hippocampus (left)	1.3 ± 0.9	1.2 ± 1.0	2.8 ± 0.9	NS	<0.0001	<0.0001
Entorhinal cortex (left)	0.7 ± 0.9	0.3 ± 0.7	1.8 ± 1.3	NS	<0.0001	<0.0001
Perirhinal cortex (left)	0.6 ± 0.7	0.3 ± 0.7	1.8 ± 1.3	NS	<0.0001	<0.0001
[1]NCI versus MCI.						
[2]NCI versus Dementia						
[3]MCI versus Dementia						

Characteristics of 182 participants presented as mean ± standard deviation for numeric variables and frequency distribution for NCI, 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; NCI, no cognitive impairment, MCI, mild cognitive impairment, CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length.

Table 2. Receiver operating characteristic (ROC) curve analysis for the diagnostic accuracy of corneal confocal microscopy and medial temporal lobe atrophy rating for MCI and dementia.

	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	*P*-value
NCI vs. MCI					
CNFD, fibers/mm^2	0.78 (0.67-0.90)	26.6	57%	81%	<0.0001
CNBD, branches/mm^2	0.82 (0.72-0.92)	84.9	77%	76%	<0.0001
CNFL, mm/mm^2	0.86 (0.77-0.95)	22.1	81%	81%	<0.0001
MTA-R	0.53 (0.36-0.69)				NS
MTA-L	0.40 (0.25-0.55)				NS
NCI vs. Dementia					
CNFD, fibers/mm^2	0.85 (0.76-0.94)	26.8	77%	81%	<0.0001
CNBD, branches/mm^2	0.84 (0.75-0.93)	77.9	79%	81%	<0.0001
CNFL, mm/mm^2	0.85 (0.76-0.94)	21.1	79%	91%	<0.0001
MTA-R	0.86 (0.76-0.96)	0.8	85%	71%	<0.0001
MTA-L	0.82 (0.72-0.92)	1.2	79%	62%	<0.0001

Abbreviations: no cognitive impairment (NCI), mild cognitive impairment (MCI), corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), medial temporal atrophy (MTA).

Figures

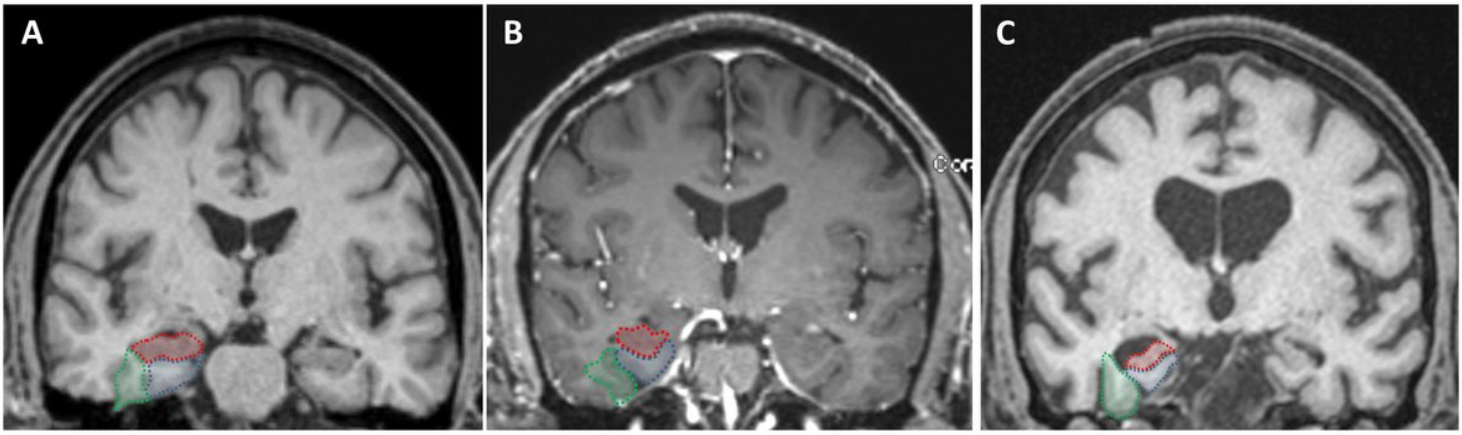

Figure 1

Visual rating system for assessing medial temporal atrophy. The three regions of interest are outlined in the right hemisphere in color (hippocampus in red; entorhinal cortex in blue; perirhinal cortex in green). Control subject (A) and subject with MCI (B), all showing no atrophy (MTA score=0) in both hemispheres. Subject with dementia (C), all structures have atrophy, (right MTA score=3.3 and left MTA score=2.3).

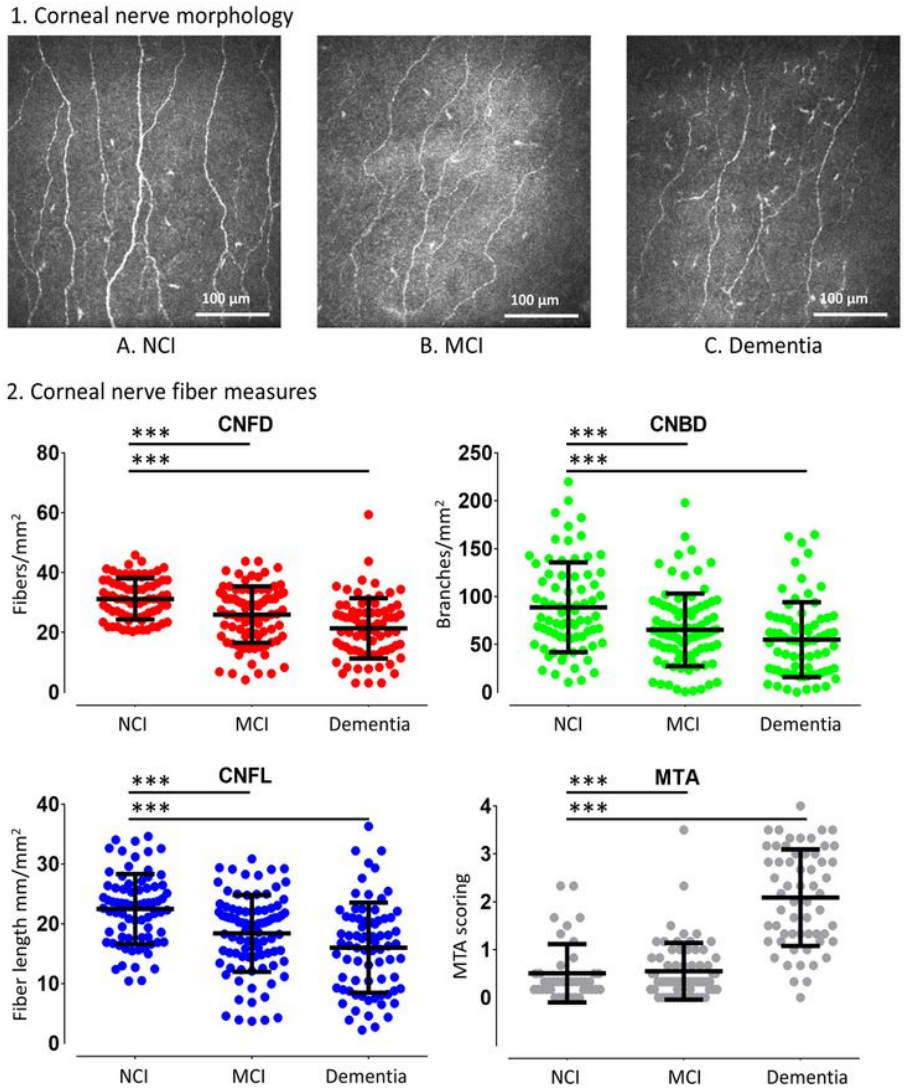

Figure 2

Corneal nerve fiber measures, and medial temporal lobe atrophy in NCI, MCI and dementia. (1) Corneal confocal microscopy (CCM) images of the sub-basal nerve plexus in (A) a 73-year old subject with NCI showing normal corneal nerve fiber morphology; (B) a 69-year old subject with MCI and (C) a 74-year old subject 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), branch density (CNBD) (green), fiber length (CNFL) (blue) and MTA scoring (grey) in controls, subjects 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 NCI, MCI and dementia group (***P<0.0001).

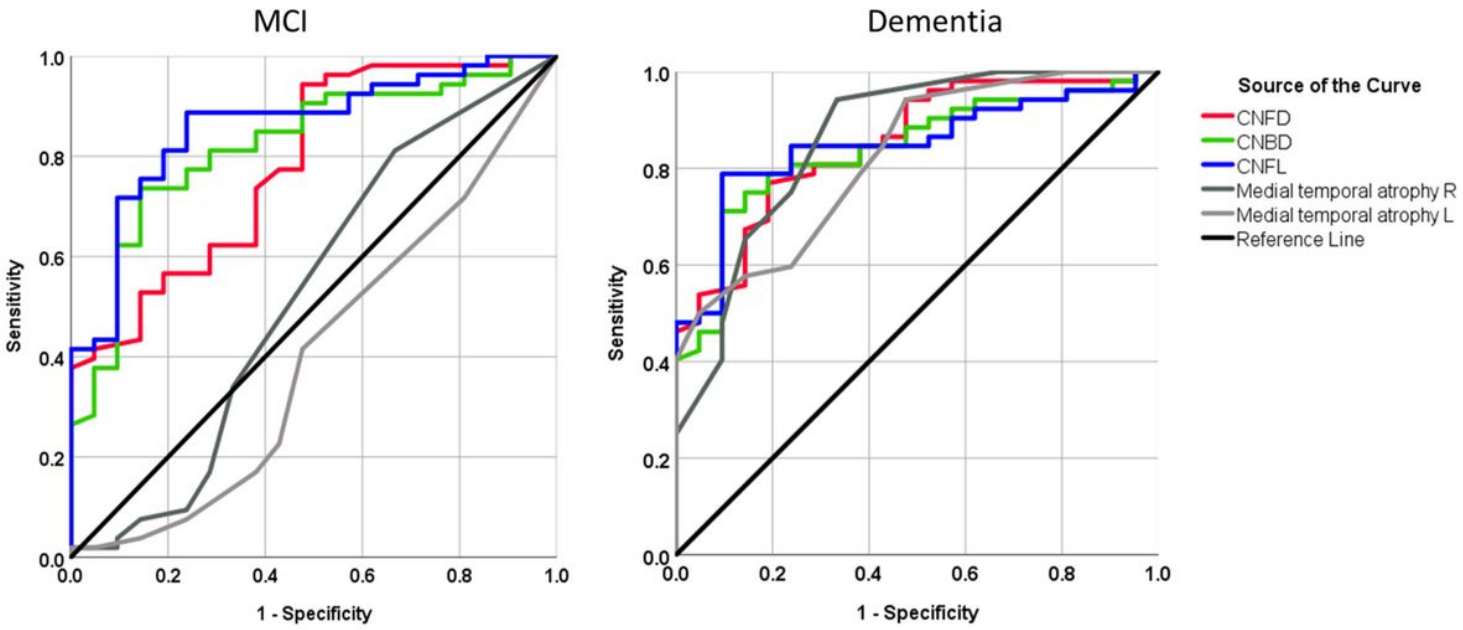

Figure 3

Diagnostic accuracy of corneal nerve measures and medial temporal atrophy rating for MCI and dementia. ROC analysis showing the area under the curve for corneal nerve fiber measures and right and left medial temporal lobe atrophy (MTA) rating.