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Retinal neurodegeneration on optical coherence tomography and cerebral atrophy

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HIGHLIGHTS

- Cerebral atrophy and retinal neuronal damage have been linked to cognitive decline.
- Retinal neuronal damage is reflected by RNFL and GC-IPL thinning.
- GC-IPL thinning was associated with occipital and temporal lobe grey matter loss.
- No association was found with regional white matter volumes.

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ABSTRACT

Neurodegeneration in dementia is mainly evaluated by assessing cerebral atrophy, while retinal neurodegeneration can be quantified *in vivo* using optical coherence tomography (OCT). We examined the association of retinal nerve fibre layer (RNFL) and ganglion cell-inner plexiform layer (GC–IPL) thinning with global and regional cerebral atrophy on magnetic resonance imaging (MRI).

Malay participants aged 60–80 years from the Epidemiology of Dementia in Singapore Study underwent comprehensive examinations, including 3-Tesla cranial MRI. RNFL and GC-IPL thicknesses were obtained from spectral domain-OCT; and cerebral grey and white matter volumes were obtained from MRI scans using a validated segmentation tool. Linear regression models were constructed with adjustment for age and sex; and additionally for vascular risk factors and MRI markers including intracranial volume.

164 participants without glaucoma with gradable quality MRI and OCT scans were included for analysis. GC-IPL thinning was associated with reduction in total brain volume in the occipital (mean change in GC-IPL per standard deviation (SD) decrease in occipital lobe volume: −1.77 μm, 95% confidence interval (CI) −6.55 to 0.01 μm) and temporal lobes (mean change in GC-IPL per SD decrease in temporal lobe volume: −3.45 μm, 95%CI −5.40 to −1.49 μm) in multivariate adjusted models. In particular, GC-IPL thinning was primarily associated with grey matter volume, whereas no association was found with white matter changes.

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Retinal neuronal damage, as reflected by GC-IPL thinning, was independently associated with grey matter loss in the occipital and temporal lobes, suggesting that retinal OCT may provide insights for assessing neurodegeneration in the brain.

1. Introduction

Alzheimer's disease is characterized by brain atrophy in cortical and subcortical grey and white matter especially the hippocampus and entorhinal cortex. Structural neuroimaging has shown that diffuse atrophy is present even in the early stages of dementia [6,14,24]. Advanced automated segmentation techniques, such as voxel based morphometry, allow quantification of grey and white matter volumes using magnetic resonance imaging (MRI) [26]. Grey matter loss is related to progressive mild cognitive impairment (MCI) and conversion to dementia in the MCI group [9,17,27]. Global and regional grey matter volume measurements are now crucial biomarkers in detecting neuronal loss and progression of cognitive decline. However, MRI remains a time-consuming and expensive technique. Moreover, some patients have contraindications for undergoing MRI such as claustrophobia, cardiac pacemakers, and inability to tolerate the procedure.

As the retina shares developmental, physiological and anatomical features with the brain [12,19], retinal imaging is now increasingly used in studying neurodegenerative disease. Both histopathological and clinical studies have shown that patients with Alzheimer's disease have functional visual deficits and anatomical changes in retinal structures [3,13].

Structural changes to the optic nerve can be non-invasively measured *in vivo* using techniques such as spectral domain-optical coherence tomography (SD-OCT). Recent advances in SD-OCT have made it possible to automatically measure the retinal nerve fibre layer (RNFL) and the ganglion cell-inner plexiform layer (GC-IPL). Unmyelinated axons of retinal ganglion cells form the RNFL, while the GC-IPL contains the cell bodies and dendrites of these cells. Previous studies have linked RNFL thinning to a number of brain diseases, such as Alzheimer's disease [1,15,22], Parkinson's disease and multiple sclerosis [7,8]. However, studies have not examined if neuronal changes in the retina are associated with global or regional cerebral atrophy assessed from MRI. Therefore, we examined the relationship of RNFL and GC-IPL thickness, with cerebral white and grey matter volumes on MRI in an elderly population from Singapore.

2. Materials and methods

2.1. Study population

The on-going Epidemiology of Dementia in Singapore (EDIS) study draws participants from the Singapore Epidemiology of Eye Disease (SEED) study, a multi-ethnic population-based study among persons aged 40 to 85 years. For this study, we focused on participants drawn from the first follow-up examination of the Singapore Malay Eye Study (SiMES-2) component of the SEED study who had OCT data available [23]. In order to use limited MRI imaging resources efficiently, it was decided to focus on subjects most likely to have cognitive problems. Hence, participants from SiMES-2 aged ≥60 years ($n = 1014$) were screened using the abbreviated mental test (AMT) and a self-report of progressive forgetfulness. Screen-positive subjects ($n = 448$) were invited to take part in the second phase of this study, which included an extensive neuropsychological test battery and brain MRI. Of these 448 participants, 307 agreed to participate in phase II. Cognitive impairment no dementia (CIND) was defined as impairment in one or more domains in the neuropsychological test battery [10]. Dementia was diagnosed in accordance to Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Details of the study methodology have been described elsewhere [10]. Ethics approval was obtained from the SingHealth Institutional Review Board and the National Healthcare Group Domain-Specific Review Board. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to recruitment.

2.2. Neuroimaging

MRI was performed on a 3 T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre of the National University of Singapore. Subjects with claustrophobia, contraindications for MRI, or those who were unable to tolerate the procedure were excluded.

Intracranial volume (ICV), grey matter and white matter volumes were quantified by automatic segmentation at the Erasmus University Medical Center Rotterdam, The Netherlands [5,25]. Brain tissue segmentation was quantified by Proton density T1 and T2 weighted images. Imaging parameter and classification algorithms for automated segmentation have been described elsewhere [10]. Total brain volume was calculated as the sum of grey matter and white matter volumes of the five regions; frontal, parietal, occipital, temporal and central regions.

2.3. Optical coherence tomography

After pupil dilation using tropicamide 1%, SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) was used to acquire macular scans and optic disc scan using the macular cube 200×200 and optic nerve head cube 200×200 scan protocols, respectively, in each eye, as described previously [4,16]. The supplementary figure illustrates measurement areas from the macular and optic disc scans, with cross-sections showing automatic segmentation and thickness measurement of the macular GC-IPL and peripapillary RNFL. Participants were excluded if OCT scans had poor signal strength, GC-IPL or RNFL algorithm segmentation failure, retinal pathology affecting GC-IPL or RNFL thickness measurement (such as epiretinal membrane, macula edema, vitreomacular traction, etc), or artifacts due to eye movement. Additionally, participants were also excluded if they had a diagnosis of glaucoma from study ophthalmologists.

2.4. Assessment of other vascular risk factors

Demographic and risk factors including age, sex, smoking, hypertension, diabetes, hyperlipidemia, height and weight were collected and verified by medical records. Blood tests included full blood count, fasting blood glucose and total cholesterol. Systolic and diastolic blood pressures were measured using a digital automatic blood pressure monitor (OMRON-HEM 7203, Japan) after resting for five minutes. Mean arterial blood pressure (MABP) was calculated as two-thirds of the diastolic blood pressure plus one-third of the systolic blood pressure. Subjects were categorized into non-smokers and smokers (past and current smokers). Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Hypertension