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Retinal Imaging Biomarkers

Retinal thickness correlates with parietal cortical atrophy in early-onset Alzheimer's disease and controls

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Abstract

Introduction: The retina may reflect Alzheimer's disease (AD) neuropathological changes and is easily visualized with optical coherence tomography (OCT). Retinal thickness decrease has been correlated to AD, however, without information on amyloid status. We correlated retinal (layer) thickness to AD biomarkers in amyloid-positive early-onset AD (EOAD) patients and amyloid-negative controls.

Methods: We measured macular thickness and peripapillary retinal nerve fiber layer thickness with OCT in 15 EOAD patients and 15 controls and correlated retinal thickness to visual rating scores for atrophy on magnetic resonance imaging.

Results: Total macular thickness correlated to parietal cortical atrophy in both groups (Spearman ρ −0.603, $P = .001$). Macular and peripapillary retinal nerve fiber layer thicknesses were not significantly decreased in EOAD compared to controls.

Discussion: Retinal thickness does not discriminate EOAD from controls but is correlated to parietal cortical atrophy in both groups. These findings may suggest reflection of cerebral cortical changes in the retina, independent of amyloid.

Keywords: Optical coherence tomography (OCT); Retinal thickness; Biomarker; Alzheimer's disease; Retina; Cortical atrophy

1. Introduction

With the currently increasing amount of clinical trials for Alzheimer's disease (AD) and its prodromal stage, a patient-friendly and sensitive diagnostic method for an early diagnosis is urgently needed. The retina is embryologically derived from the neural tube, and as a protrusion from the brain, it shares many similarities with brain tissue. Through the pupil, the retina and its neurons are easily examined with optical coherence tomography (OCT) thus serving as a potential noninvasive diagnostic target in neurodegenerative diseases such as AD, Parkinson's disease (PD), and dementia with Lewy bodies [1–4].

Currently, cortical atrophy on magnetic resonance imaging (MRI), as a biomarker for neurodegeneration, can be assessed with visual rating scores for global cortical atrophy, medial temporal lobe atrophy, and parietal cortical atrophy [5–7]. Typically, late-onset Alzheimer's disease (LOAD) shows medial temporal lobe atrophy, whereas early-onset Alzheimer's disease (EOAD) shows a diffuse pattern including parietal cortical atrophy [8]. Retinal thickness decrease measured with OCT might serve as a noninvasive proxy of cortical atrophy on MRI. Previous research showed both total macular and peripapillary retinal nerve fiber layer (RNFL) thinning in AD measured with OCT; however, this was not consistent in all studies. In a recent meta-analysis,

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we found an absolute decrease of peripapillary RNFL of 10 μm and of total macular thickness of 16 μm in AD compared to controls [9].

Similar to AD, glaucoma is a complex neurodegenerative disease and shows considerable overlap of neuroretinal changes with AD [10–14]. Previous studies did not account for the possible confounding effect of glaucoma on OCT measurements in AD patients, nor did they include established AD biomarkers as part of AD clinical diagnosis (NIA-AA) [10,11,15].

The objective of this study was to assess retinal layer thickness in amyloid-positive early-onset AD patients compared to amyloid-negative healthy controls, with the exclusion of glaucoma. In addition, correlation of retinal measures with established biomarkers in AD, such as cortical atrophy on MRI, was assessed.

2. Methods

2.1. Subjects

Fifteen subjects with EOAD and 17 controls (age $<$ 70 years, Mini–Mental State Examination $\geq$17, thus capable of giving informed consent) were included from the screening program of the Alzheimer Center of the VU University Medical Center embodying the basis of the Alzheimer Dementia Cohort (ADC) [16]. Controls comprised subjects with subjective cognitive decline, defined as subjective cognitive complaints without objective cognitive impairment on neuropsychological assessment, no signs of neurodegeneration on neuroimaging, and absence of amyloid pathology based on cerebrospinal fluid (CSF) and/or amyloid positron emission tomography (PET). Patients and controls underwent a standardized ADC screening program including MMSE, MRI, and lumbar puncture for amyloid-$\beta_{(1–42)}$, tau_{181}, and phosphorylated tau (pTau) levels. MRI visual rating scores for cortical atrophy were used for medial temporal lobe atrophy (MTA), global cortical atrophy (GCA), and parietal cortical atrophy (PCA) [6,7]. MRI scans were scored by a blinded rater before a multidisciplinary consensus meeting where a clinical diagnosis was made by consensus. All AD patients fulfilled NIA-AA criteria and had evidence of amyloid pathology in CSF and/or amyloid PET (florbetaben n = 13, florbetapir n = 9) [15]. CSF tau_{181}/amyloid $\beta_{(1–42)}$ ratio $>$0.52 was considered indicative for AD [17]. Parametric images of amyloid-PET scans were assessed by experienced raters and visually interpreted as amyloid positive or amyloid negative following FDA guidelines for florbetaben and florbetapir. Exclusion criteria were (ophthalmological) conditions interfering with OCT quality/retinal thickness: severe cataract, age-related macular degeneration, and glaucoma, and neurological or systemic chronic conditions known to interfere with retinal thickness (e.g., multiple sclerosis, PD, diabetes mellitus, rheumatoid arthritis, sarcoidosis, Crohn's disease, and colitis ulcerosa). In addition, we excluded subjects with ischemic stroke and/or mild-to-severe white-matter hyperintensities on MRI, operationalized as a Fazekas score $>$1 [18].

2.2. Eye examinations

Subjects were included within a year after the ADC screening program and underwent the following eye examinations: best corrected visual acuity, intraocular pressure (IOP) using noncontact tonometry (if IOP $>$ 20 mm Hg, we used contact applanation tonometry), slit-lamp examination of the anterior and posterior segment and fundus photography (Topcon TRC 50DX type IA), Heidelberg Retinal Tomography (HRT) optic nerve head analysis, and Frequency Doubling Technology for visual fields. Tropicamide 0.5% was administrated for pupil dilation to facilitate optimal ophthalmic examination.

We followed the fourth European Glaucoma Guideline criteria: glaucoma was diagnosed when two of the three following measurements were abnormal: ocular pressure ($>$21 mm Hg), structural glaucomatous changes (examined with HRT using the Moorfields Regression Analysis), and functional changes (examined with Frequency Doubling Technology) [19]. All examinations were interpreted by an ophthalmologist and resident in ophthalmology (F.D.V. and S.F.J.). This study was designed and conducted according to the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of the VU University Medical Center. All patients gave their written informed consent in the presence of their caregiver.

2.3. Optical coherence tomography

Two protocols for both eyes were performed in each subject with Heidelberg Spectralis Spectral-Domain OCT: (1) central retina (macula) dense horizontal scanning; central 20° $\times$ 20° area; 49 B-scans (averaging 16 frames per B-scan); 512 A-scans per B-scan and (2) axonal ring scan around the optic nerve head for RNFL.

Peripapillary RNFL was measured in six sectors provided by Heidelberg software. Macular thickness was measured in the Early Treatment of Diabetic Retinopathy Study (ETDRS) map (fovea [Ø 1 mm], and the mean of four quadrants of both the inner ring [Ø 3 mm], area 2 to 5, and the outer ring [Ø 6 mm], area 6 to 9) (Fig. 1). In the fovea, the inner and the outer ring segmentation analysis was performed with Heidelberg segmentation software (version 1.9.204.0) to calculate thickness of the following retinal layers: RNFL, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, and retinal pigment epithelium (Fig. 1).

2.4. Statistical analysis

2.4.1. Sample size calculation

In our previous meta-analysis with 887 AD patients and 864 controls, we found a mean RNFL difference of 10 μm