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Retinal Imaging

Change in retinal structural anatomy during the preclinical stage of Alzheimer's disease

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Abstract

Introduction: We conducted a 27-month longitudinal study of mid-life adults with preclinical Alzheimer's disease (AD), using spectral domain optical coherence tomography to compare changes in volume and thickness in all retinal neuronal layers to those of age-matched healthy control subjects.
Methods: Fifty-six older adults (mean age = 65.36 years) with multiple risk factors for AD completed spectral domain optical coherence tomography retinal imaging and cognitive testing at baseline. Twenty-seven months later, they completed the same examinations and an ^{18}F-florbetapir positron emission tomography imaging study.
Results: Compared to healthy control subjects, those in the preclinical stage of AD showed a significant decrease in macular retinal nerve fiber layer (mRNFL) volume, over a 27-month follow-up interval period, as well as a decrease in outer nuclear layer and inner plexiform layer volumes and thickness in the inferior quadrant. However, only the mRNFL volume was linearly related to neocortical positron emission tomography amyloid standardized uptake value ratio after controlling for any main effects of age ($R^2 = 0.103$; $\rho = 0.017$). Furthermore, the magnitude of mRNFL volume reduction was significantly correlated with performance on a task of participants' abilities to efficiently integrate visual and auditory speech information (McGurk effect).
Discussion: We observed a decrease in mRNFL, outer nuclear layer, and inner plexiform layer volumes, in preclinical AD relative to controls. Moreover, the largely myelinated axonal loss in the RNFL is related to increased neocortical amyloid-β accumulation after controlling for age. Volume loss in the RNFL, during the preclinical stage, is not related to performance on measures of episodic memory or problem solving. However, this retinal change does appear to be modestly related to relative decrements in performance on a measure of audiovisual integration efficiency that has been recently advanced as a possible early cognitive marker of mild cognitive impairment.

Keywords: Preclinical; Alzheimer's disease; Retinal; Cognition; RNFL; OCT; Optical coherence tomography; McGurk effect; Amyloid

1. Background

The formation of the eye begins in the third week of human embryologic development, with the retina being a crucial component of the ocular globe and the central nervous system. The retina is derived from pluripotent neuroectodermal

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cells that migrate from the diencephalic invagination of the neural tube [1], and so it is structurally, physiologically, and functionally brain tissue—with the retina sometimes described as a "protrusion" from the brain. As is the case throughout the neocortex, the retina consists of discrete neuronal cell layers, with multiple types of neurons and neurotransmitter systems, glial cells, and microvasculature. Unlike the rest of the central nervous system, however, the retinal neuronal cell layers can be noninvasively visualized through high-resolution optical methods such as spectral domain optical coherence tomography (SD-OCT) [2].

A recent review [3] cites the wide variety of retinal biomarkers that have been explored in patients with Alzheimer's disease (AD), ranging from retinal anatomical and vascular markers to curcumin binding studies [4] and retinal oximetry and electroretinogram studies. Clinically, it is reasonable to suspect the presence of early ocular involvement in AD because visual system changes such as decreased vision, abnormal pupillary reaction, visual field changes, motion detection abnormalities, impaired color vision, and decreased contrast sensitivity have been identified in mild-to-moderate AD [3,5].

SD-OCT allows for the precise segmentation and measurement of the retinal cell layers, thereby promoting exploration of neuronal changes that might be directly related to specific neurodegenerative diseases. Over the past 2 decades, there have been over 70 peer-reviewed publications exploring retinal optical coherence tomographic (OCT) correlates of AD, in humans, nonhuman primates, and other animal models of AD disease. With respect to humans, most prior reports have consisted of cross-sectional studies comparing groups of AD patients to groups of seemingly "healthy controls". When compared with healthy age-matched controls, patients with AD have reduced numbers of ganglion cell axons and are three times more likely to have an increased optic nerve cup-to-disc ratio, a potential consequence of ganglion cell and nerve fiber loss [6]. Such reports have confirmed an earlier report of substantial loss of ganglion cells in AD patients, based on histopathology of autopsy materials [7]. Furthermore, peripapillary retinal nerve fiber layer (pRNFL) thickness has been found to be significantly thinner, suggesting the presence of optic atrophy in patients with mild cognitive impairment (MCI) and mild-to-moderate AD when compared with age-matched controls [8]. Reduction of macular RNFL (mRNFL) volume also has been identified in AD [9]. The loss of RNFL tissue in the retina may constitute an early biomarker of AD. If so, a reduction in RNFL thickness or volume may be observed before widespread damage to the mesiotemporal central nervous memory system that is characteristic of AD [10–12].

With respect to the RNFL, we have surveyed all available literature, including those studies relying on other imaging approaches, such as 2D fundus photography and histological analyses, and we have found variable reports of decreased RNFL and/or ganglion cell layer (GCL) thicknesses in AD and MCI. A search on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) was performed (25 August, 2017) to find all published articles, using the search terms "Alzheimer's" and "retinal layer". This search led to 134 articles identified and, of these, only 34 articles consisted of human studies that compare retinal layer morphology changes in Alzheimer's patients to healthy individuals (see Table 1).

Nearly all of these 34 publications resulted from cross-sectional studies based on comparisons of cases to putatively "healthy controls". Most often the healthy controls had no biomarker confirmation to indicate that they did not fall within the preclinical stage of AD. One study did search for thickness differences in all 10 retinal layers [20], with the remaining 33 studies concentrating on measurement differences for the mRNFL, pRNFL, and the GCL. Of note, the GCL was only once reported as a single layer [20], being most often considered in conjunction with an adjacent cell layer, either as the ganglion cell–inner plexiform layer complex (GC-IPL) or as the retinal nerve fiber layer–GCL complex (RGCL or GCC).

From the 33 articles seeking to compare group differences for the RNFL, 29 found RNFL thinning in AD compared with age-matched controls (see Table 1). Only seven of these 29 published reports appear to have accounted for participants' age as a statistical covariate in their analyses. This is important because there is normal age-related thinning of the RNFL and other retinal layers [44]. Of these seven publications that did account for effects of aging, one determined that the observed thinning was due primarily to the main effect of aging rather than disease burden [26]; one study found RNFL thinning in MCI but not in AD [30]; two studies reported RNFL thinning solely in one or two specific quadrants [13,32]; and three studies reported robust disease burden after accounting for age [15,17,18]. Only two of the 33 reviewed studies reported within-subjects longitudinal results (both in symptomatic AD patients vs. controls), and they both reported increased RNFL thinning compared with controls [18,27].

AD-related amyloid-β (Aβ) plaques can start to accumulate abnormally in the brain up to 20 years before symptom onset, and this stage is classified as preclinical AD [45,46]. Only two of the studies reviewed previously, both relying solely on cross-sectional data, recruited individuals in the preclinical stage of the disease. One from the same larger study that we draw from in the current report [16] found a thicker inner plexiform layer (IPL) in preclinical AD compared with healthy controls. Another study [14] found no difference in the RNFL thickness between AD, preclinical AD, and healthy controls. Golzan et al. reported a significant difference in the RGCL thickness across the three groups, and yet they found no association between retinal structural measurements and positron emission tomography (PET) Aβ binding in the neocortex. Aside from these two cross-sectional studies of preclinical AD [14,16], none of the other published reports compared PET imaging evidence of neocortical amyloidosis with the retinal OCT measurements for this earliest stage of the disease. In this