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Retinal Imaging

Retinal thickness in Alzheimer disease? A systematic review and meta-analysis

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Abstract

Introduction: Retinal characteristics are increasingly recognized as biomarkers for neurodegenerative diseases. Retinal thickness measured by optical coherence tomography may reflect the presence of Alzheimer disease (AD). We performed a meta-analysis on retinal thickness in AD and mild cognitive impairment (MCI) patients and healthy controls (HCs).

Methods: We selected 25 studies with measurements of retinal thickness including 887 AD patients, 216 MCI patients, and 864 HCs that measured retinal thickness. Outcomes were peripapillary retinal nerve fiber layer (RNFL) and macular thickness. The main outcome was the standardized mean differences (SMDs). We used STATA to perform the meta-analysis.

Results: Relative to HCs, AD and MCI patients had lower peripapillary RNFL (SMD 0.98 [CI −1.30, −0.66, $P < .0001$] and SMD 0.71 [CI −1.24, −0.19, $P = .008$]). Total macular thickness was decreased in AD patients (SMD 0.88 [CI −1.12, −0.65, $P = .000$]).

Discussion: Retinal thickness is decreased in AD and MCI patients compared to HC. This confirms that neurodegenerative diseases may be reflected by retinal changes.

Keywords: Meta-analysis; Optical coherence tomography (OCT); Retinal thickness; Eye; Biomarkers; Alzheimer's disease (AD); Mild cognitive impairment (MCI)

1. Introduction

Alzheimer disease (AD) is the most common form of dementia. It is neuropathologically characterized by amyloid-beta (Aβ)-plaques and neurofibrillary tangles containing tau. These neuropathological changes are believed to develop 15–20 years before symptom onset. AD is diagnosed in subjects with MCI or dementia using clinical criteria combined with abnormal biomarkers for Aβ pathology or neuronal injury [1,2]. Aβ pathology is reflected by decreased Aβ levels in cerebrospinal fluid (CSF) or on an amyloid positron emission tomography (PET). Neuronal injury is reflected by either cortical atrophy on magnetic resonance imaging (MRI), hypometabolism on fluorodeoxyglucose-PET (FDG-PET), or increased tau and/or phosphorylated tau (pTau) levels in CSF [3]. These biomarkers however, are invasive, expensive, or time consuming. Thus, there is an urgent need for an early, patient-friendly, inexpensive AD biomarker, that preferably detects AD pathology before severe neurodegeneration [4].

The retina is embryologically derived from the cranial part of the neural tube, similar to the brain, and therefore shares many similarities with its tissue. The retina is easily accessible, and retinal neurons can be visualized through high-resolution optical methods such as optical coherence tomography (OCT) visualizing thickness of retinal layers (Fig. 1). With OCT, retinal changes are visualized both in ophthalmological disease and in neurodegenerative disease. Previous studies have shown that the retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL) thickness are reduced in subjects with multiple sclerosis (MS) [5], Parkinson disease (PD) [6], and AD [7–31].

J.d.H. performed statistical analysis.

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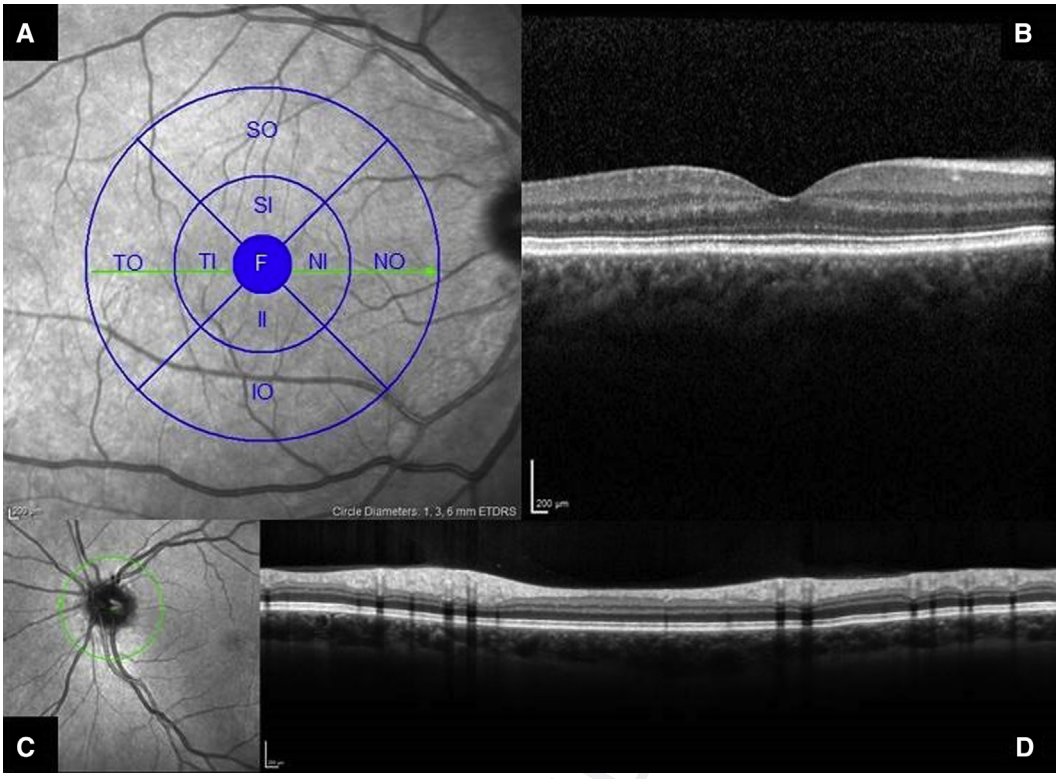

Fig. 1. Optical coherence tomography (Heidelberg Spectralis). OCT image of the macula (A) with an overlay of the Early Treatment Diabetic Retinopathy Q7 Study regions and transversal OCT image showing the macula (B). Image of optic disk (C) and a transversal OCT image through the optic disk (D). Abbreviations: F, Fovea; II, inferior inner; IO, inferior outer; NI, nasal inner; NO, nasal outer; OCT, optical coherence tomography; SI, superior inner; SO, superior outer; TI, temporal inner; TO, nasal inferior.

In this study, we perform a meta-analysis to assess the retinal layer thickness in AD and MCI patients and cognitively normal subjects. OCT is an optical method that accurately measures retinal layer thickness and therefore potentially a patient-friendly noninvasive method for detection of neurodegenerative diseases. We also assess the role of concomitant ophthalmological disease on retinal thickness, in particular glaucoma and the possible confounding role of age and disease severity.

2. Methods

2.1. Search strategy

We searched PubMed and EMBASE for studies analyzing OCT measurements in AD patients, MCI patients, and/or healthy controls (HCs) using the following search terms: "Alzheimer Disease," "senile dementia," "Mild Cognitive Impairment," "MCI," "optical coherence tomography," and "OCT" between 1990 and February 2016.

2.2. Inclusion

We included 25 studies that used NINCDS-ADRDA and/or DSMIV criteria for AD diagnosis, Petersen or Winblad criteria for MCI, and OCT to assess retinal layer thickness. Eight of these studies included an MCI group. Ten studies used first-generation time domain (TD)-OCT, and 15 studies used spectral domain (SD)-OCT. Twenty-four studies performed a peripapillary RNFL protocol (of which 16 studies presented data for separate quadrants). One study performed a macular protocol only, and six studies performed both a peripapillary and macular protocol. Eight studies included neuroimaging (MRI or CT), and two studies included CSF analysis (Table 1 characteristics of the included studies).

Of the 637 records identified, 612 were excluded due to their title, topic, method, or design. Others were excluded due to their abstracts, reviews, posters, communications in response to an article, or in the case of duplicate data. Studies with nondemented subjects or studies that use different techniques such as RNFL thickness with Heidelberg Retinal Tomography (HRT), fundus autofluorescence, and electroretinography were also excluded (Fig. 2 flowchart of included and excluded articles).

2.3. Data extraction

We extracted mean and quadrant RNFL and macular thickness with standard deviations for AD and MCI patients and HC. In one study, data were presented as box plots [25]. Estimates of the mean and standard deviation were therefore calculated using the lower and upper quartiles, mean, and sample size following the methods described in Wan et al. [32].