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A systematic review and meta-analysis of retinal nerve fiber layer change in dementia, using optical coherence tomography

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Abstract

Introduction: Retinal nerve fiber layer (RNFL) thinning, assessed by optical coherence tomography (OCT), has recently been reported in various dementias.

Methods: We conducted a systematic review and meta-analysis to investigate the diagnostic utility of RNFL thickness measurement using OCT in dementia (including Alzheimer's disease [AD] and mild cognitive impairment [MCI]) compared with healthy controls (HC).

Results: Seventeen studies comparing AD with HC (702 AD eyes and 790 HC eyes) were included, demonstrating a significant reduction in mean RNFL thickness in AD (weighted mean difference [WMD] 12.44, 95% confidence interval or CI [−16.64, −8.25], P <.0001). Five studies comparing MCI and HC (214 MCI eyes and 421 HC eyes) were included demonstrating a significant reduction in mean RNFL thickness in MCI (WMD −8.23, 95% CI [−14.00, −2.45], P =.005). No relevant studies were identified for other dementias.

Discussion: OCT measurement of RNFL thickness appears diagnostically useful in discriminating between AD, or MCI, and HC.

Keywords: OCT; Alzheimer's disease; Dementia; Mild cognitive impairment; Optical coherence tomography; Retinal imaging

1. Introduction

Pathological changes in the eye have recently been reported in a range of neurodegenerative diseases. The retina is essentially an extension of the brain, and shares embryological origins with regions responsible for cognition [1]. Visual symptoms, including impaired visual fields and acuity are commonly reported in early Alzheimer's disease (AD) [2]. Optical coherence tomography (OCT) is a noninvasive, noncontact optical scanning method, for cross-sectional imaging of the internal retinal structure. As a clinical imaging device, the operation is straightforward and patient satisfaction is extremely high thanks to its fast acquisition (just a few seconds) and noncontact scan. Advancements in the technology of the light source and detector in recent years now permit extremely detailed visualization and precise measurement of the retinal layers, including the retinal nerve fiber layer (RNFL). The RNFL consists of the unmyelinated axons of the retinal ganglion cells, which together form the optic nerve and anterior visual pathways [3]. Measurement of the RNFL thickness in the retina is therefore a measurement of axonal loss in the anterior visual pathways.

Thinning of the RNFL has been described in a range of neurological disorders including multiple sclerosis [3], Parkinson's disease [4], and neuromyelitis optica [4]. Recently, RNFL thinning in patients with AD [4–13] and mild cognitive impairment (MCI) [11,12,14] have also been reported.

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RNFL thinning in AD has been hypothesized to occur because of retrograde degeneration of the retinal ganglion cell axons [9], and these changes have been suggested to occur even before memory is affected [15]. There is also a suggestion that neuroretinal atrophy may occur as a result of amyloid-β plaque deposits within the retina, although this hypothesis remains more speculative [7].

We aimed to conduct a systematic review and meta-analysis of the literature to determine the diagnostic utility of OCT measurement of the RNFL thickness in various dementias, including AD, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VaD), and MCI.

2. Methods

2.1. Search strategy and study selection

We systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Excerpta Medica Database (EMBASE) via OVID for all human studies published until September 2014, in all languages. The Medical Subject Heading (MeSH) search terms used were: (1) "dementia", (2) "Alzheimer disease", (3) "dementia, vascular", (4) "dementia, multi-infarct", (5) "Lewy body disease", (6) "mild cognitive impairment", and (7) "tomography", (8) "tomography, optical coherence", and (9) "OCT". We searched Web of Knowledge, Scopus, and Google Scholar for all studies published before and including September 2014 using the MeSH terms: (1) "optical coherence tomography", (2) "OCT", and (3) "dementia", (4) "Alzheimer", (5) "mild cognitive impairment", and (6) "MCI". Further studies were identified through reference and citation searching of relevant articles, and hand-searching of relevant journals.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (1) original study; (2) study of diagnostic utility of OCT; (3) diagnosis of dementia based on appropriate criteria for the diagnosis of AD, such as the National Institute of Neurological, Communicative Diseases and Stroke and Alzheimer's Disease and Related Disorders Association [16]; (4) diagnosis of AD, FTD, DLB, VaD, or MCI; (5) comparison of RNFL thickness in patients versus control; (6) total subjects in the study of at least 10; and (7) age and sex-matched control group.

We excluded the following studies: (1) review articles; (2) abstract-only studies; (3) case reports; and (4) studies of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy dementia.

2.3. Data extraction

We initially screened all studies identified in the systematic search of the online databases by abstract and title. Irrelevant or duplicate studies were removed, and the remaining articles were assessed for eligibility by full-text review. Data extracted from these studies included: title; authors; center; publication year; aim of study; study type; disease focus; number of patients and controls; characteristics of patients including male:female ratio, mean age, and participant selection criteria; diagnostic criteria; method of OCT used; and results and authors' suggestions.

2.4. Quality assessment

We assessed all full-text studies included in data analysis using the Quality Assessment for Diagnostic Accuracy Studies tool to determine the risk of bias and variability in each study [17].

2.5. Statistical analysis

We extracted original data from the studies (means, standard deviations, sample sizes) and where required calculated data which were not available. We used RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) [18] for the meta-analysis of these continuous outcomes, calculating the summary estimates including 95% confidence intervals (CIs). We used the means, standard deviations, and sample sizes extracted from the studies to calculate the weighted mean difference (WMD) using the inverse-variance random-effects model. A P value of less than .05 was considered to be statistically significant. To assess heterogeneity, we used the chi-squared test, tau-squared, and the Higgins I^2 test, with an I^2 value of more than 50% being significantly heterogeneous. We performed subgroup analysis according to the type of OCT used and whether one or both eyes were used per subject. We also performed sensitivity analysis to further evaluate the heterogeneity by excluding studies where the required data had to be calculated from the data provided. We used funnel plot to assess for possible publication bias.

3. Results

Five hundred and fifty-five studies were identified in the literature search, with a further three identified through citation searching and hand-searching. Two hundred and thirty-six were duplicates and therefore removed, leaving 322 studies which were screened by abstract and title only; 288 were deemed ineligible at this stage, and a further eight studies were excluded as these were abstract only conference presentations. Seven studies were removed; three were deemed ineligible after full text review as they did not measure the RNFL, one study was a duplicate, another study did not compare RNFL thickness in patients to controls, and two studies reported insufficient data for analysis. Nineteen articles were therefore eligible; 17 compared AD to controls (totalling 702 AD eyes and 790 control eyes) with 5 studies comparing MCI to controls (totalling 214 MCI eyes and 421 control eyes); 3 of these 19 studies compared both AD and MCI.

Thirteen studies determined the RNFL thickness in patients with AD compared with healthy controls (HC), seven