Investigative Ophthalmology & Visual Science
www.iovs.org

doi: 10.1167/iovs.06-1029
Invest. Ophthalmol. Vis. Sci. **May 2007** vol. 48 no. 5 **2285-2289**

Retinal Abnormalities in Early Alzheimer's Disease

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Abstract

PURPOSE. There is evidence suggesting that visual disturbances in patients with Alzheimer's Disease (AD) are due to pathologic changes in the retina and optic nerve, as well as to higher cortical impairment. The purpose of this study was to evaluate retinal hemodynamic parameters and to characterize patterns of retinal nerve fiber layer (RNFL) loss in patients with early AD.

METHODS. Nine patients with mild to moderate probable AD (mean Mini Mental State Examination score 24 of a possible 30 (age 74.3 ± 3.3 years; mean ± SD) and eight age-matched control subjects (age, 74.3 ± 5.8 years) were included in this prospective cross-sectional study. Blood column diameter, blood velocity, and blood flow rate were measured in the major superior temporal retinal vein in each subject by using a laser Doppler instrument. Peripapillary RNFL was measured by optical coherence tomography.

RESULTS. Patients with AD showed a significant narrowing of the venous blood column diameter (131.7 ± 10.8 μm) compared with control subjects (148.3 ± 12.7 μm, $P = 0.01$), and a significantly reduced venous blood flow rate (9.7 ± 3.1 μL/min) compared with the control subjects (15.9 ± 3.7 μL/min, $P = 0.002$). A significant thinning of the RNFL was found in the superior quadrant in patients with AD (92.2 ± 21.6 μm) compared with control subjects (113.6 ± 10.7 μm, $P = 0.02$). There were no significant differences in the inferior, temporal, or nasal RNFL thicknesses between the groups.

CONCLUSIONS. Retinal abnormalities in early AD include a specific pattern of RNFL loss, narrow veins, and decreased retinal blood flow in these veins. The results show that AD produces quantifiable abnormalities in the retina.

Introduction

Visual symptoms are often among the earliest complaints of patients with Alzheimer's Disease (AD).[1 2] Visual function testing in patients with AD has revealed abnormalities in contrast sensitivity,[3 4] and in depth[5] and motion[6 7] perception. Historically, the impairments experienced by these patients have been attributed to disease localized to the cerebral cortex.[8 9] Based on an extensive clinical neuro-ophthalmic examination of patients with AD, Rizzo et al.[10] concluded that visual impairments in patients with AD are related to pathologic changes in the visual association cortex rather than to changes in the retina or optic nerve. Trick et al.[11] reported visual field defects that were most pronounced in the inferior hemifield in patients with AD. Armstrong[12] measured the density of plaques and tangles in specific regions of the primary visual cortex (i.e., the lingual and cuneal gyri), and compared the pathologic data with the visual field data collected by Trick et al.[11] A greater density of senile plaques and neurofibrillary tangles was found in the cuneal gyrus compared with the lingual gyrus, indicating that the regional differences in cortical disease are consistent with, and would explain, the predominantly inferior field defects in AD.

Whether the visual field defects found in AD are related solely to the cortical disease or whether disease extends to the optic nerve and retina as well remains an open question. Abnormalities in pattern electroretinogram (PERG) parameters consistent with retinal ganglion cell dysfunction have been measured in patients with AD.[13 14 15] Rizzo et al.[10] reported a mixture of normal and abnormal PERG results in their patients with AD, but were reluctant to base any conclusions on their results.

The first histopathologic evidence of retinal ganglion cell loss and optic nerve degeneration in patients with AD was reported by Hinton et al.[16] These histopathologic changes in AD were confirmed in several follow-up studies.[17 18 19 20] Other histopathologic studies,[21 22] however, failed to confirm these findings and suggested that methodological differences were responsible for the different results.

Clinical studies of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) using photographic methods have suggested that an optic neuropathy with RNFL abnormalities occurs as a component of AD.[23 24] More recently, a generalized reduction of the peripapillary RNFL thickness in patients with AD compared with age-matched control subjects as evaluated by optical coherence tomography (OCT) has been reported.[15 25] In addition, Iseri et al.[25] reported a reduced total macular volume in patients with AD that was correlated with the severity of the disease. Another recent study using confocal scanning laser ophthalmoscopy also reported a reduction of optic nerve fibers in patients with AD.[26] In contrast, Kergoat et al.[27] found no differences in RNFL thickness between patients with AD and healthy control subjects evaluated with scanning laser polarimetry.

It has been shown that RNFL thickness measurements using OCT are useful in identifying the early changes associated with glaucomatous optic neuropathy (GON).[28] Inferior RNFL loss corresponding to superior visual field loss is a typical pattern found in early GON.[28] The predominant inferior visual field loss seen in patients with AD[11] would correspond structurally to superior RNFL losses. We therefore hypothesized that a specific pattern of superior RNFL loss could be detected by using OCT in patients with early AD.

Our second hypothesis was that there might be abnormalities in the retinal blood circulation accompanying the neuronal damage in the retina of these patients with early AD. There have been no prior studies of the retinal circulation in patients with AD. It is well documented, however, that cerebral blood flow velocity measured by transcranial Doppler ultrasonography is abnormally decreased in AD.[29] Whether the decrease in blood flow is secondary to a diminished metabolic demand accompanying neuronal degeneration, or whether it precedes and contributes to the degeneration remains an open question.[30] In this regard, it is interesting to note that other studies using single-photon emission computed tomography[31] and color duplex sonography[32] have reported reduced cerebral perfusion in patients diagnosed with mild cognitive impairment (MCI), widely considered to be the preclinical stage of AD. An abnormal retinal circulation in early AD is thus a definite possibility.

The goals of this study were thus to determine whether regional thinning of the RNFL occurs in patients with early AD and to determine whether the retinal circulation is abnormal in these patients.

Methods

Study Subjects

Patients with a diagnosis of probable AD with mild or moderate dementia, as determined by referring neurologists according to the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[33] and the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria,[34] were subjects for the study. The study protocol adhered to the guidelines of the Declaration of Helsinki, was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations, and was performed at the Schepens Retina Associates Foundation, Boston. Nine patients with a diagnosis of probable AD, six classified as having mild dementia and three classified as having moderate dementia were enrolled in this prospective cross-sectional study. Patients with severe dementia were not included because we were focused on investigating early changes in the retina related to AD in these patients. In addition, reliable test results are more likely obtained in patients with early AD than in patients with severe dementia. Patient age was 74.3 ± 3.3 years (mean ± SD). Eight age-matched control subjects (age, 74.3 ± 5.8 years) were recruited by advertisement. After written informed consent was obtained, each subject underwent a screening evaluation including medical history and medications, and the Mini Mental State Examination (MMSE).[35 36]

A complete ophthalmic examination including visual acuity, intraocular pressure (IOP) measurement, slit lamp biomicroscopy, indirect ophthalmoscopy, and digital fundus photography was performed in both eyes of each subject. The examiners were not masked to the diagnosis. Tropicamide 1% was used for pupillary dilation. The IOP was measured by applanation tonometry after instillation of anesthetic eye drops (proparacaine 0.5%) and a fluorescein strip. Patients with AD were included if there was no history or evidence of other neurologic or psychiatric disorders or other types of dementia. All subjects, patients or control subjects, were excluded if there was a history of diabetes mellitus, hypertension, heart disease, or other serious chronic medical conditions. All subjects were required to have best corrected visual acuity better than 20/60, refractive error −6 to +6 D, pupillary dilation greater than 6 mm, no significant cataract, no cataract surgery within the prior 6 months, and no history or evidence of glaucoma, retinal vascular occlusive disease or any other ocular disease.

Laser Doppler Retinal Blood Flow Measurements

Blood column diameter, centerline blood velocity, and retinal blood flow rate were reliably measured in the major superior temporal retinal vein in at least one eye of each subject by a laser Doppler retinal blood flow instrument (CLBF 100; Canon, Tokyo, Japan). The basic principles, technical characteristics, and reproducibility of measurements using the instrument have been described previously.[37] The blood flow rate in actual units of microliters per minute in a retinal vessel is determined from simultaneous measurements of the blood column diameter and the centerline blood velocity. Measurement sites were along relatively straight sections of the superior temporal vein approximately one disc diameter away from the disc margin. The instrument is equipped with an internal fixation target and an automatic eye tracking system that maintains centration of the laser beam on the target blood vessel, even during eye movements. The measurement of the velocity is based on the principle of bidirectional laser Doppler velocimetry.[37] The beam from a red 675-nm diode laser is used for blood velocity measurements. A tracking beam provided by a green 543-nm HeNe laser and oriented perpendicular to the target vessel is used to measure vessel diameter. Results are acquired at 50 measurements per second for 2 seconds.

Attempts were made to measure the retinal venous hemodynamic parameters in both eyes of each subject. However, bilateral measurements were not successful in all study subjects because of media opacities or the anatomic arrangement of the retinal vessels. Measurements in the patients were limited to retinal veins because they are more reliably tracked during eye movements than are arteries. The measurements in all the subjects were performed during the midday hours, between 12 and 4 PM, by the same experienced examiner (GTF). Superior rather than inferior temporal veins were chosen as the primary targets, because they are technically easier to measure. The instrument internal fixation target is elevated for these measurement locations, making it easier for the subjects to simultaneously maintain target fixation and an elevated eyelid. Only one eye of each subject was included in the analysis. If both eyes had reliable measurements, the eye with the larger-diameter superior temporal retinal vein measured with the CLBF was designated as the study eye. The designated eye was used in all subsequent analyses.

Optical Coherence Tomography

Peripapillary RNFL thickness and optic nerve head (ONH) parameters were measured in both eyes of each subject (Stratus OCT 3000; Carl Zeiss Meditec, Inc., Dublin, CA). OCT is a noninvasive technique that allows high-resolution cross-sectional imaging of the retina. The basic principles and technical characteristics of the OCT have been described previously.[38 39] The ONH scan is obtained from six linear scans centered on the ONH, and the OCT software automatically derives the ONH parameters, including the horizontal and vertical cup-to-disc ratios. For the RNFL measurements the standard RNFL thickness circle scan mode consisting of three circular scans with a diameter of 3.4 mm centered on the ONH was used. Average overall and quadrant (superior, inferior, temporal and nasal) RNFL thicknesses were automatically calculated. The OCT measurements were performed by an experienced operator, who was not masked to the subjects' diagnosis. During the examination, the subject was instructed to fixate on an internal target to bring the ONH within view of the examiner. The best-quality scan (focused image of the fundus, an adequate signal-to-noise ratio, and the presence of a centered, circular ring around the ONH) was chosen for RNFL thickness analysis. OCT results only from the eye previously designated as the study eye in each subject were included in the analysis. Average RNFL thicknesses in each quadrant of the study eye were compared between the patients with AD and the control subjects.

Statistical Analysis

All data were analyzed with commercial statistical software (StatView for Windows; ver. 5.0; SAS Institute, Cary, NC). Unpaired *t*-tests were used to compare outcome variables between the patient and control groups. Differences between ratios of nominal variables were compared by χ^2 tests. Data are presented as the mean ± SD. In all statistical analyses, $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of the patients with AD and control subjects are shown in Table 1 . The mean MMSE score was 23.8 of a possible 30 (range, 17–30) in the patients with AD. The mean MMSE score in the control subjects was 29.5 (range, 29–30). The patient with AD who had the MMSE score of 30 also had the greatest number of years of education (22 years). No significant differences in visual acuity, IOP, or cup-to-disc ratio were found between patients with AD and control subjects.

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TABLE 1.

Characteristics of Patients with AD and Control Subjects

Figure 1 shows retinal photographs of a control subject and a patient with AD. The only noticeable difference clinically is that the retinal veins in the patient appear to be somewhat narrower than those in the control subject. This impression is borne out by the laser Doppler measurements.

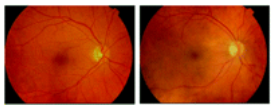

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FIGURE 1.

Retinal photographs of a control subject (*left*) and a patient with Alzheimer's Disease (*right*). The retinal veins in the patient appear narrower than those in the control subject.

Table 2 shows the comparison of retinal hemodynamic parameters between the AD and control groups. There was a statistically significant difference in the venous blood column diameter between patients with AD and control subjects ($P = 0.01$) (Fig. 2) . Although lower in the AD group, the venous centerline blood speed was not significantly different from the blood speed in the control group ($P = 0.07$). The blood flow rate was significantly lower in patients with AD compared with control subjects ($P = 0.002$; Fig. 3).

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TABLE 2.

Retinal Hemodynamic Parameters in Patients with AD and Control Subjects

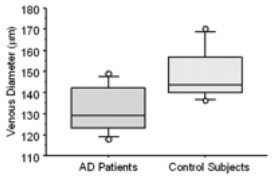

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FIGURE 2.

Retinal venous blood column diameter in patients with Alzheimer's Disease and age-matched control subjects. *Horizontal lines*, *bottom to top*: 10th, 25th, 50th (median), 75th, and 90th percentiles. Values above the 90th and below the 10th percentile are plotted as *circles*.

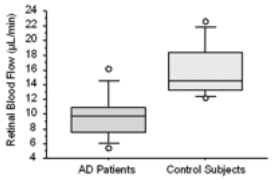

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FIGURE 3.

Retinal blood flow rate in patients with Alzheimer's Disease and age-matched control subjects. Percentiles are marked as described in Figure 2 .

RNFL thicknesses measured in each of the four quadrants in the patients with AD and in the control subjects are shown in Table 3 . A significant RNFL thinning was found in the superior quadrant in the patients with AD compared with the control subjects ($P = 0.02$; Fig. 4). There were no significant differences in the inferior, temporal, or nasal RNFL thicknesses between the groups. In addition, there was no significant correlation between superior RNFL thickness and retinal blood flow in the patients with AD.

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TABLE 3.

Peripapillary RNFL Thickness Values in Patients with AD and Control Subjects

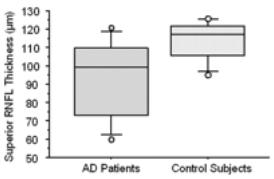

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FIGURE 4.

RNFL thickness in the superior quadrant in patients with Alzheimer's Disease and age-matched control subjects. Percentiles are marked as described in Figure 2 .

Discussion

In this study, retinal hemodynamic data obtained in patients with mild or moderate AD showed a marked narrowing of the retinal venous blood column diameter and a reduction in retinal blood flow rate compared with age-matched control subjects. To our knowledge, this is the first study to demonstrate abnormalities in the retinal circulation of patients with AD.

OCT data showed a significant thinning of the peripapillary RNFL that was most pronounced in the superior quadrant. Our RNFL results are consistent with the visual field findings reported by Trick et al.[11] They observed predominantly inferior visual field defects in patients with AD, which correspond structurally to superior RNFL

defects. Anatomically, axons from the superior retina project via the parietal lobe portion of the optic radiation to the cuneal gyrus of the primary visual cortex, whereas axons from the inferior retina project to the lingual gyrus. In a histopathology study of cortical damage in AD, Armstrong[12] found a greater density of senile plaques and neurofibrillary tangles in the cuneal gyrus than in the lingual gyrus, and suggested that this difference could explain the predominantly inferior field defects in AD reported by Trick et al.[11] What was not clear was whether the cortical disease alone was responsible for the visual field loss. Our finding of superior RNFL thinning in this study suggests that field deficits in AD may also be related to neuronal degeneration in the retina.

Other investigators, also using OCT, reported RNFL thinning in patients with AD extending to all four quadrants.[15 25] Those studies, however, included patients with AD with dementia that was more advanced than in our group. The range of MMSE scores in the patients studied by Parisi et al.[15] was 11 to 19; the range in the patients studied by Iseri et al.[25] was 8 to 28. In our group, the scores were higher, ranging from 17 to 30. A comparison of our results with those of Parisi et al.[15] and Iseri et al.[25] thus suggests that the earliest retinal damage due to AD may be localized to the superior quadrant.

Regarding our retinal circulatory findings, it is likely that the mechanisms producing reduced blood flow in the retina are related to those that produce cerebral blood flow abnormalities which are known to occur in AD. Of note, vascular disease was also evident in the original case of Alzheimer,[40] which we use today to define AD. The large population-based prospective Rotterdam Study suggests that cerebral hypoperfusion precedes the onset of clinical dementia.[29] Cerebral amyloid angiopathy, characterized by β-amyloid deposition in the walls of arteries and arterioles has been well documented in AD,[41 42 43] and Suo et al.[44] demonstrated a direct and specific constrictive effect of β-amyloid on cerebral arteries leading to a decrease in cerebral blood flow in an in vivo animal experiment.

In addition to amyloid angiopathy, deposition of collagen fibrils in the walls of capillaries[45 46] and veins[47 48] resulting in narrowed lumina and even occlusion has been found in patients with AD. Van Horssen et al.[49] reported collagen XVIII accumulation in all types of cerebral blood vessels including arteries, arterioles, capillaries, venules, and veins in patients with AD. They suggested that collagen XVIII is associated with amyloid deposition in blood vessel walls and may be involved in the pathogenesis of AD. It is likely that the mechanisms leading to the reduced blood flow found in the retina of our patients with AD are related to those that produce the cerebral blood flow abnormalities in AD. It is reasonable to speculate that the narrowing of the retinal venous diameter observed in our study is related to an increased venous wall thickness due to collagen deposition, as found in cerebral veins.

We found no correlation between RNFL thickness and retinal blood flow in the patients with AD. One reason for this could be that the sample size was relatively small. It is possible, however, that different mechanisms lead to these structural and physiologic abnormalities in the retina of patients with AD. The time points at which the abnormalities in RNFL thickness and in retinal blood flow occur during the course of the disease need to be clarified. Cerebral blood flow is known to be impaired in patients with MCI, the preclinical stage of AD.[31 32] Whether retinal hemodynamic abnormalities or retinal neuronal loss is also present in MCI must be determined.

The major limitation of the study is the relatively small sample size. Ideally, the study should be repeated with a larger sample, and the examiners should be masked as to whether the subjects are patients with AD or control subjects. The strengths of the study are that the primary outcome measures were obtained objectively with state-of-the-art instruments, and that the study subjects were free of conditions such as diabetes or hypertension which might influence the retinal circulation.

Footnotes

Supported in part by a grant from The Stranahan Foundation, Toledo, Ohio.

Submitted for publication August 30, 2006; revised December 8, 2006, and January 10, 2007; accepted February 20, 2007.

Disclosure: **F. Berisha**, None; **G.T. Feke**, None; **C.L. Trempe**, None; **J.W. McMeel**, None; **C.L. Schepens**, None

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