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Retinal blood flow in mild cognitive impairment and Alzheimer's disease

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Abstract

Background: Patients with Alzheimer's disease (AD) demonstrate the narrowing of retinal veins and decreased retinal venous blood flow compared with control subjects. We assessed whether these abnormalities are present in patients with mild cognitive impairment (MCI).

Methods: After the determination of the global clinical dementia rating, 52 subjects (10 AD, 21 MCI, and 21 normal controls) underwent retinal hemodynamic profiling. Blood column diameter, blood speed, and blood flow were measured in a major temporal retinal vein using retinal laser Doppler flowmetry. In addition, peripapillary retinal nerve fiber layer (RNFL) thickness was measured using optical coherence tomography.

Results: Blood column diameter in AD was narrower than in both MCI ($P = .004$) and controls ($P = .002$). However, blood speed in both AD ($P = .024$) and MCI ($P = .005$) was lower than in controls. As a result, the differences in blood flow between AD and MCI ($P = .036$), AD and controls ($P < .0001$), and MCI and controls ($P = .009$) were significant. Although there were no differences in RNFL thickness among the groups, blood flow was correlated ($P = .047$) with superior RNFL thickness in the AD group, but not in the MCI ($P = .40$) or control ($P = .84$) groups.

Conclusions: Retinal blood flow in MCI is intermediate between what is measured in control subjects and in AD patients. Our findings suggest that blood flow abnormalities may precede the neurodegeneration in AD.

Keywords: Mild cognitive impairment; Alzheimer's disease; Retinal venous blood column diameter; Retinal blood speed; Retinal blood flow

1. Introduction

Transcranial Doppler ultrasonography [1], single photon emission computed tomography, and magnetic resonance imaging (MRI) [2] all demonstrate that cerebral blood flow is diminished in Alzheimer's disease (AD). The findings of diminished blood flow correlate with pathology studies that show decreased vascular density, tortuous arterioles, and deposition of excessive collagen in veins and venules [3,4]. However, there is as yet no consensus on whether decreased cerebral blood flow is a cause or a consequence of AD [5]. It has been suggested that impaired nitric oxide signaling may contribute to the pathology associated with AD [6,7]. There is evidence that cerebral blood flow is already decreased in patients with mild cognitive impairment (MCI) [8], the condition thought to be the predementia stage of AD. Reduced blood flow compared with controls in specific regions of the cerebral circulation in MCI patients has also significantly predicted the progression to AD in studies with follow-up periods ranging from 2 to 7 years [9–11].

There is evidence that the dysregulation of cerebral blood flow contributes to the pathogenesis of AD [12]. Resting cerebral blood flow is reduced, and the incremental blood flow response to neuronal stimulation is attenuated in AD [13].

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Retinal and cerebral tissues share a common embryological origin, and their microvasculatures share anatomical and physiological similarities such as the presence of a tightly controlled blood-tissue barrier and autoregulatory capacity. Retinal vascular circulatory abnormalities are thus likely to reflect cerebrovascular pathology [14,15]. Because the retina is accessible to sensitive, noninvasive optical diagnostic methodologies, structural and functional abnormalities analogous to those established to occur in the brain in AD may also be observed in this tissue [16].

Structural retinal vascular abnormalities in AD patients include significant thinning of the blood column diameters in the larger retinal vessels and significantly decreased vessel density in the retinal microvascular network compared with controls [17,18]. Only one prior study also reported reduced retinal blood flow in patients with AD compared with control subjects [19]. There have not been any studies of retinal vascular structural abnormalities or of retinal blood flow abnormalities in patients with MCI. In this study, we sought to confirm the observations of altered retinal circulation in AD patients and to determine whether these abnormalities are also present in patients with milder clinical symptoms or MCI, that is, earlier in the course of the disease.

2. Methods

2.1. Study subjects

Subjects referred for the study underwent prior cognitive testing at either the Massachusetts Alzheimer's Disease Research Center or the Boston University Alzheimer's Disease Center. Subjects with MCI met the 2004 MCI Working Group Criteria [20] for amnestic MCI and had a global clinical dementia rating (CDR) of 0.5. Subjects with AD met both *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* [21] diagnostic criteria for dementia and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [22] for probable AD. Subjects with AD had a global CDR of either 1.0 or 2.0. Control subjects had normal cognition and a global CDR of 0.0. All diagnoses were made by a multidisciplinary consensus diagnostic conference. The Institutional Review Boards at the Massachusetts Eye and Ear Infirmary (MEEI), Massachusetts General Hospital, and the Boston University Medical Center approved this study. Written informed consent to participate was obtained from each subject before the ophthalmoscopic examinations that were performed at the MEEI. The investigators performing the retinal assessments were blind to the cognitive status of the subjects.

2.2. Study procedures

Each subject received a complete ophthalmic examination including visual acuity assessment, intraocular pressure (IOP) measurement using Goldmann applanation tonometry (Haag Streit USA, Mason, OH), slit lamp biomicroscopy, indirect ophthalmoscopy, and digital fundus photography in both eyes. We added tropicamide 1% in both eyes for pupillary dilation. To facilitate the retinal blood flow measurements, only subjects with refractive error within the range −10 to +10 diopters, no significant cataract or cataract surgery within the prior 6 months, and pupillary dilation of at least 6 mm after mydriasis were tested. Subjects with a history of diabetes mellitus or evidence of glaucoma on examination were excluded from the analysis. Brachial artery blood pressure and pulse rate were measured using a Keller vital signs monitor (Keller Medical Specialties, Antioch, IL). Mean arterial pressure (MAP) was automatically displayed.

2.3. Laser Doppler retinal blood flow measurements

Blood column diameter, centerline blood speed, and retinal blood flow rate were reliably measured in a major temporal retinal vein of each subject using a Canon 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 [23]. The blood flow rate in units of microliter 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 segments of the largest temporal vein approximately one disc diameter away from the optic disc margin. The instrument is equipped with an internal fixation target and an automatic eye tracking system that maintains centration of the measuring laser beam on the target blood vessel to compensate for eye movements. Results are acquired at 50 measurements per second for 2 seconds. Bilateral measurements were not successful in all study subjects because of media opacities or the anatomical arrangement of the retinal vessels. Measurements in all subjects were performed during the midday hours, between 12 p.m. and 4 p.m., by the same experienced examiner (GTF). Only one eye of each subject was included in the analysis. If both eyes had reliable measurements, the eye with the larger diameter temporal retinal vein was designated as the study eye. The retinal vein with the largest diameter drains the largest retinal area and carries the greatest fraction of the total retinal blood flow. The blood flow in this vein is thus representative of the total retinal blood flow. Veins rather than arteries were chosen for measurement because of technical reasons. The instrument eye tracking system performs more efficiently when the target vessel has a larger diameter and carries deoxygenated blood. The designated eye was used in all subsequent analyses.

2.4. Retinal nerve fiber layer thickness measurements

To quantify retinal neuronal loss due to the pathological mechanisms associated with AD, peripapillary retinal nerve