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Featured Articles

Microvascular network alterations in the retina of patients with Alzheimer's disease

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Abstract

Background: Although cerebral small-vessel disease has been implicated in the development of Alzheimer's disease (AD), the cerebral microcirculation is difficult to visualize directly in vivo. Because the retina provides a noninvasive window to assess the microcirculation, we determined whether quantitatively measured retinal microvascular parameters are associated with AD.

Methods: We conducted a case-control study (case:control matching ≈ 1:2). Retinal photographs were analyzed using a computer program, and a spectrum of quantitative retinal microvascular parameters (caliber, fractal dimension, tortuosity, and bifurcation) were measured. Logistic regression models were used to compute the odds ratio (OR) and 95% confidence interval for AD adjusting for age, gender, ethnicity, smoking, hypertension, diabetes, hypercholesterolemia, and history of myocardial infarction.

Results: We included 136 demented patients with AD and 290 age-gender-race-matched controls. Persons with narrower venular caliber (OR per standard deviation [SD] decrease, 2.01 [1.27–3.19]), decreased arteriolar and venular fractal dimension (OR per SD decrease 1.35 [1.08–1.68], 1.47 [1.17–1.84], respectively) and increased arteriolar and venular tortuosity (OR per SD increase, 1.84 [1.40–2.31], 1.94 [1.48–2.53], respectively) were more likely to have AD. These associations still persisted when only AD cases without a history of cerebrovascular disease were included.

Conclusions: Patients with AD have altered microvascular network in the retina (narrower retinal venules and a sparser and more tortuous retinal vessels) compared with matched nondemented controls. These changes in retinal microvasculature may reflect similar pathophysiological processes in cerebral microvasculature in the brains of patients with AD.

Keywords: Retina; Retinal vasculature; Alzheimer's disease; Microcirculation; Small-vessel disease

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is a major global medical, social, and economic public health issue [1,2]. There has been a

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long-standing interest in determining whether vascular mechanisms contribute to the development of AD [3,4]. Accumulating evidence suggests that vascular factors, especially those affecting the cerebral microcirculation (e.g., hypertension, diabetes), play an important role in the pathogenesis of AD [5]. Nevertheless, data directly showing the involvement of the cerebral microcirculation in AD are sparse because there is no means to visualize the cerebral microcirculation [6].

The retinal and cerebral small blood vessels share similar embryological origin, anatomical features, and physiological properties (e.g., nonanastomotic end arteries, blood-brain and blood-retina barrier) [7,8]. Retinal vessels, measuring 100 to 300 μm in size, allow for a noninvasive visualization of the human microcirculation in vivo, offering a unique and easily accessible "window" to study cerebral microvascular pathology.

Previous studies using retinal photography have demonstrated a link between the presence of clinically visible retinal microvascular abnormalities (e.g., retinopathy signs) and clinical (e.g., stroke) and subclinical (white matter lesions on magnetic resonance imaging [MRI]) cerebral small-vessel disease [9–15]. There is now the ability to assess a range of newer retinal parameters (fractal dimension, tortuosity, and bifurcation) that are a global reflection of "optimality" and "efficiency" of blood distribution in the retinal network [16,17]. These new retinal features reflect the integrity of the cerebral microcirculation and have been recently linked to stroke [18], in particular lacunar stroke [19,20], providing the first direct evidence that early microvascular network abnormalities may contribute to the pathophysiology of these conditions [21].

In this study, we examined the associations of a spectrum of quantitative-measured retinal vascular parameters in AD. We hypothesize that microvascular network alterations in the retina, reflecting changes in the cerebral microcirculation, are seen in patients with AD.

2. Methods

2.1. Study population

We conducted a case-control study of patients with AD and age-gender-race-matched population controls.

2.1.1. AD cases

A total of 192 AD patients were enrolled consecutively from July 2009 to October 2012 from three tertiary hospitals (dementia/memory clinics from the National University of Hospital, Khoo Teck Puat Hospital and Singapore General Hospital, Singapore). All patients underwent clinical neurologic and neuropsychiatric assessment. Computed tomography (CT) or MRI was reviewed as part of the diagnostic process. The dementia syndrome was diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, and the diagnosis of AD followed the National Institute of Neurological Disorders and Stroke (NINDS)–Alzheimer Disease and Related Disorders Association (ADRDA) criteria.

Of the 192 AD patients, we excluded 56 patients because of ungradable retinal photographs (poor fixation, $n = 11$; poor image quality [e.g., cataract, small pupil size], $n = 44$; and those without at least four large, gradable arterioles or venules, $n = 1$), leaving 136 subjects for the final analysis.

2.1.2. Population controls

The controls were selected from population-based studies under the Singapore Epidemiology of Eye Disease (SEED) program, which includes the Singapore Chinese Eye Study (SCES), the Singapore Indian Eye Study (SINDI), and the Singapore Malay Eye Study (SiMES). The methodology and objectives of these studies are reported in detail elsewhere [22,23]. All SEED participants aged 60 years or above were administered the Abbreviated Mental Test (AMT) for assessment of cognitive function. The AMT is a 10-question cognitive screening instrument (with minimum score of 0 and maximum score of 10) that has been modified for the local Singapore context and validated [24]. All of the selected controls were screened using the locally validated AMT and found not to be cognitively impaired on the basis of established education and age cut-offs for Singaporeans older than 60 years of age. All of the selected controls had no self-reported history of stroke or dementia.

Written informed consent was obtained from each participant or legal representative; the study conducted adhered to the Declaration of Helsinki. Ethical approval was obtained from the Singapore Eye Research Institute Institutional Review Board and the National Healthcare Group Pte Ltd Domain Specific Review Board.

2.2. Retinal photography and quantitative measurements of retinal microvasculature

Digital fundus photography was taken using a 45° digital retinal camera (Canon CR-DGi 10D or Canon CR-1 40D; Canon, Japan) after pupil dilation using 1% tropicamide and 2.5% phenylephrine hydrochloride. Two retinal images of each eye were obtained: one centered at the optic disc and the other centered at the fovea.

We used a semiautomated computer-assisted program (Singapore I Vessel Assessment [SIVA], software version 3.0) to quantitatively measure the retinal vascular parameters from the photographs. SIVA automatically identifies the optic disc, places a grid with reference to the center of the optic disc, identifies vessel type, and calculates retinal vascular parameters. Trained graders, masked to participant characteristics, were responsible for the visual evaluation of SIVA automated measurement and manual