Retinal Vascular Fractal Dimension Is Associated with Cognitive Dysfunction

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Fractal analysis is a method used to quantify the geometric branching complexity and density of retinal vessels. This study examined the relationship of retinal vascular fractal dimension and other retinal vascular parameters with cognitive dysfunction in an older Asian population. Subjects aged 60 years and older from the Singapore Malay Eye Study were selected for analysis. Retinal vascular fractal dimension (D_f) and other quantitative retinal vascular parameters (branching angle, tortuosity, and caliber) were measured based on a standardized grading protocol from photographs of the retinal fundus using a computer-assisted program. Qualitative retinal signs were also assessed from photographs. Cognitive dysfunction was defined as a locally validated Abbreviated Mental Test (AMT) score ≤6/10 in participants with 0-6 years of formal education and an AMT score ≤8/10 in those with more than 6 years of formal education. Cognitive dysfunction was identified in 262 of the 1202 participants (21.8%). Decreased retinal vascular D_f was significantly associated with lower AMT score ($P = .019$). In multivariate logistic regression analysis, participants with lower retinal vascular D_f values were more likely to have cognitive dysfunction (odds ratio, 1.71; 95% confidence interval, 1.03-2.82, comparing the lowest and highest D_f quintiles). In subgroup analysis stratified for cardiovascular risk factors, this association was present in participants with hypertension and current smokers. Other retinal vascular signs were not associated with cognitive dysfunction. Decreased retinal vascular D_f is associated with cognitive dysfunction in older persons. Rarefaction of the retinal vasculature may reflect similar changes in the cerebral microvasculature that may contribute to cognitive deterioration. **Key Words:** Cognitive dysfunction—fractal—imaging—retinal vasculature.

Dementia is a significant and growing medical, social, and economic problem worldwide, but its pathogenesis remains poorly understood.[1,2] Although cerebrovascular disease, especially cerebral small-vessel disease, is considered to play a role in the pathogenesis of dementia, to date research has been limited by an inability to directly visualize the cerebral microcirculation.[3] Retinal and cerebral small vessels share similar embryologic origins, anatomic

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features, and physiological properties.[4,5] Because the retina allows noninvasive visualization of the human circulation in vivo, it offers a unique "window" to study cerebrovascular disease.

Numerous studies have reported a strong link between the presence of retinal vascular abnormalities and both clinical (cognitive impairment and stroke) and subclinical (white matter lesions detected on magnetic resonance imaging) cerebrovascular diseases.[6-12] These studies suggest that changes in retinal vasculature reflect similar cerebral microvasculopathy, and that their study may provide further insight into the underlying pathogenic mechanisms.

Although previous studies have focused mainly on qualitative "retinopathy signs" and widths of retinal vessels, a range of newer retinal vascular features are now being explored. Retinal vascular fractal dimension (D_f) measures the complexity of the retinal circulation and is a reflection of its optimality and the efficiency of blood distribution with the least amount of energy.[13,14] Changes in retinal vascular D_f, and other features, including tortuosity and branching angle, have been linked to stroke,[15-17] diabetes,[18,19] hypertension,[20-23] and chronic kidney disease (CKD),[24] providing additional insight into early microvascular abnormalities before the appearance of clinical disease.[19]

In the present study, we examined the associations between retinal vascular D_f and a spectrum of other quantitative and qualitative retinal vascular changes with cognitive function in a population-based cohort. We hypothesized that abnormal D_f in retinal vasculature, measured by retinal imaging, is related to cognitive dysfunction.

Methods

Study Population

The data for this analysis were derived from the Singapore Malay Eye Study (SiMES), a population-based cross-sectional study of eye diseases in urban Malay adults aged 40-80 years residing in southwestern Singapore. In brief, participants were selected using an age-stratified (by 10-year age group) random sampling method from a computer-generated list provided by the Singapore Ministry of Home Affairs. Of 4168 eligible persons, 3280 (78.7%) participated in the study between August 2004 and June 2006. Study methodology and objectives are described in detail elsewhere.[25] The study was performed in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Singapore Eye Research Institute's Institutional Review Board. Each participant provided written informed consent and underwent a standardized interview, systemic and ocular examinations, and laboratory tests.

Retinal Photography

Digital fundus photography was performed using a 45-degree digital retinal camera (Canon CR-DGi with a 10D SLR digital camera back; Canon, Tokyo, Japan) after pupil dilation with tropicamide 1% and phenylephrine hyprochloride 2.5%. Two retinal images were obtained for each eye, one centered at the optic disc and the other centered at the fovea.

Quantitative Measurements of Retinal Microvasculature

We used a semiautomated computer-assisted program (Singapore I Vessel Assessment [SIVA], version 1.0, National University of Singapore, Singapore) to quantitatively measure the retinal vascular parameters from digital photographs. Trained graders, masked to participants' characteristics, used the SIVA program to measure the parameters according to a standard protocol. The measured area was standardized and defined within the region 0.5-2.0 disc diameters from the disc margin. Intragrader and intergrader reliability has been reported previously.[20]

Retinal vascular D_f was calculated from a skeletonized line tracing using the box-counting method, and represents a "global" measure that summarizes the entire branching pattern of the retinal vascular tree.[22] Larger values indicate a more complex branching pattern. Figure 1 shows examples of retinal D_f measurements by SIVA.

Retinal Vascular Tortuosity

Retinal vascular tortuosity reflects the straightness/curliness of the vessels; a smaller tortuosity value indicates a straighter retinal vessel. Retinal vascular tortuosity was computed as the integral of the curvature square along the path of the vessel, normalized by the total path length; this measure is dimensionless, representing a ratio measure.[26] The estimates were summarized as retinal arteriolar and venular tortuosity separately, representing the average tortuosity of arterioles and venules, respectively.

Retinal Vascular Branching Angle

Retinal vascular branching angle was defined as the first angle subtended between 2 daughter vessels at each vascular bifurcation (ω).[27] The estimates were summarized as retinal arteriolar branching angle and retinal venular branching angle, representing the average branching angle of arterioles and venules, respectively.

Retinal Vascular Caliber

Retinal vascular caliber was measured using the SIVA program,[28] following the standardized protocol used in the Atherosclerosis Risk in Communities Study.[29] Based on the revised Knudtson-Parr-Hubbard formula,[30] the retinal arteriolar and venular calibers were summarized as central retinal artery equivalent and central retinal vein equivalent, respectively.

As reported previously, a subset of 50 retinal images from 50 SiMES participants were selected at random and measured independently by 2 graders, using the SIVA