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Fractal Dimension of the Retinal Vasculature and Risk of Stroke:

A Nested Case-control study.

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INTRODUCTION

Recent studies show associations between retinal vascular changes and either small infarcts detected on brain imaging, or with clinical stroke.¹ The retinal vascular fractal dimension has been used as a global measure of the geometric pattern of the vasculature^{2,3} potentially representing the complexity of the branching pattern of vessels in the body, including the cerebral microvasculature. A loss of complexity of the cerebral microvasculature may lead to limited collateral formation at cerebral infarction sites.⁴ To date, studies have reported cross-sectional associations between retinal fractal dimension and lacunar stroke.^{4,5} However, no prospective data are available about the relation of retinal fractal dimension and the incidence of stroke.

A limitation of retinal vessel measurement is measurement noise in segmentation; we therefore developed a method to use the Fourier-transformed images to assess spectrum fractal dimension (SFD) of the retinal vasculature^{6,7} With this new measurement, we expect to detect vasculature changes that may signal a risk of future stroke. In this study we examined the association between baseline SFD and stroke incidence using a case-control sample nested in the Blue Mountains Eye Study (BMES) cohort.

METHODS

The BMES is a population-based cohort study of an urban Australian population aged 49 years or older (n=3,654), representing 82.4% of eligible population in a defined two-postcode area of the Blue Mountains region, Australia.¹ Written informed consent was obtained from all participants at enrollment.¹

Stroke cases were defined among participants who had no history of stroke at baseline (1992-94) but who developed incident stroke over the subsequent 5 years (1997-99), or who had died from stroke or stroke-related causes in the period up to December 31, 2005. The definitions used to identify stroke events and mortality are shown in **Table e-1**. We identified 130 cases with either stroke event or stroke-related mortality, however 26 persons were excluded due to missing

photographs or clinical information on hypertension or diabetes. As a result, we included 21 stroke events and 86 stroke-related deaths, including 3 persons overlapped in both, which gave a total of 104 cases. Two controls per case were selected from the remaining participants matched for age, gender, diabetes and hypertension status. Of these, 97.1% (101/104) cases and 88.5% (184/208) controls had digitized, baseline retinal photographs of sufficient quality to enable SFD assessment. Images centered at the optic disc were re-sampled to 778 x 519 pixels for efficient image processing. An area centered on the optic disc covering 2.5 disc radii was cropped and enhanced using the Gabor-wavelet transform ^{6,7} (**Figure e-1**). The SFD, a mono-fractal of retinal vascular image spectrum, represents a slope of linear association between the natural log-scaled image intensity (“magnitude”) and the natural log-scaled pixel density frequency distribution (“frequency”).^{6,7} This system is fully automated. To assess the reproducibility of image cropping, we performed a Monte Carlo type simulation for image cropping; the repeated estimates of SFD were highly replicated on 100 simulated grading with a correlation of 0.93.⁷

Statistical analysis

We used SFD measures from the left eye, given the high correlation between two eyes ($r=0.63$). We constructed conditional logistic regression models to determine odds ratio (OR) and 95% confidence intervals (CI) for each SD decrease in SFD or for lower quartiles: unadjusted (**Model 1**) or adjusted for stroke risk factors (**Model 2**: body mass index, smoking, total cholesterol, high-density-lipoprotein cholesterol, and triglycerides; **Model 3**: plus systolic blood pressure and glucose level; and **Model 4**: further plus age). Stepwise selection method was applied in **Model 4** to identify significant risk factors for incident stroke. Stata 11.1 (StataCorp, College station, TX) was used.

RESULTS

Overall the mean age was 73.8 (standard deviation [SD] 8.2) years, 58% were female, 49.5% were hypertensive and 4.6% had diabetes. There were no significant differences in the matched

characteristics or other stroke risk factors between cases and controls (**Table**). The mean SFD was 1.509 (SD 0.026).

Cases had significantly smaller SFD (1.504) compared to controls (1.511; $p=0.044$). Each SD decrease in baseline FFD was associated with 40% greater risk of stroke (OR 1.39, 95%CI 1.06-1.83). This remained statistically significant after adjusting for stroke risk factors (Model 4: OR 1.36, 95% CI 1.00-1.84). Persons in the smallest quartile of SFD (<1.494) were twice more likely to have a subsequent stroke than those with the largest quartile (>1.527) (stroke incidence 42.3% vs. 27.8%; OR 2.30, 95% CI 1.06-4.97) (Table e-2). This association remained significant after adjusting for body mass index, smoking, total cholesterol, HDL cholesterol, and triglycerides (Model 2: OR 2.42, 95% CI 1.04-5.62), or further adjusting for systolic blood pressure and glucose (Model 3: OR 2.43, 95% CI 1.04-5.68). However, it became attenuated after further adjusting for age (Model 4: OR 2.13, 95% CI 0.90-5.04). Using the stepwise backward selection method, the incremental (per SD decrease) in the FFD was the only significant factor remained.

DISCUSSION

We found that low SFD of retinal vasculature was associated with 2-fold risk of incident stroke compared to persons with high SFD, independent of stroke risk factors. Previous cross-sectional studies found inconsistent findings between retinal vascular fractal dimension and lacunar stroke ⁴.
⁵. We provide the first longitudinal data in this regard, although limitations present, including potential selection bias from excluding cases with poor quality images, and the lack of stroke subtype information.

While our study supports the concept that structural retinal microvascular changes may represent a subclinical biomarker of stroke, what SFD changes indicate in the context of stroke pathogenesis remains unclear. We speculate that reduced SFD indicates reduced complexity in branching pattern of the microvasculature, leading to reduction in perfusion and limited ability to form collaterals, which could increase vulnerability to cerebral hypoxia.⁶

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Table 1. Comparison of characteristics of stroke cases and matched controls.

	Controls (n=184)	Stroke cases (n=101)	
Matched characteristics	Mean (SD)	Mean (SD)	p-value
Age, years	73.6 (8.1)	74.0 (8.5)	0.73
	n (%)	n (%)	
Gender, male	78 (41.7%)	42 (41.6%)	0.98
Hypertension, present	89 (47.6%)	52 (51.5%)	0.13
Diabetes, present	7 (3.7%)	6 (5.9%)	0.39
Other clinical characteristics	Mean (SD)	Mean (SD)	p-value
Systolic blood pressure, mmHg	154.5 (25.7)	152.7 (22.7)	0.55
Diastolic blood pressure, mmHg	82.6 (10.7)	83.5 (10.9)	0.51
Fasting plasma blood glucose, (mmol/L)	5.0 (1.3)	5.1 (4.3)	0.98
Body mass index (kg/m ²)	24.9 (3.6)	25.0 (4.3)	0.99
Total cholesterol (mmol/L)	6.0 (1.0)	6.1 (1.1)	0.34
HDL cholesterol (mmol/L)	1.49 (0.46)	1.48 (0.50)	0.86
Triglycerides (mmol/L)	1.5 (1.2 - 2.1)	1.4 (1.1-1.8)	0.08
(Median and Inter-quartile range)			
	n (%)	n (%)	
Current smoker	16 (8.6%)	13 (12.9%)	0.25
Central Retinal Artery Equivalent (μm)	159.2 (1.1)	159.7(1.6)	0.77
Central Retinal Vein Equivalent (μm)	237.7 (1.8)	236.1 (2.6)	0.62
	Mean (95 % CI)	Mean (95 % CI)	p-value
SFD of retinal vascular pattern	1.511 (1.507, 1.515)	1.504 (1.499, 1.510)	0.044

HDL: High-density lipoprotein. SFD: Spectrum fractal dimension. Data are expressed as numbers (%) or means and standard errors.