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Association of Retinopathy and Retinal Microvascular Abnormalities with Stroke and Cerebrovascular Disease

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Abstract

Background and purpose—Abnormalities of the retinal circulation may be associated with cerebrovascular disease. We investigated associations between retinal microvascular abnormalities and 1) strokes and subclinical cerebral infarcts and 2) cerebral white matter lesions in a UK-based tri-ethnic population-based cohort.

Methods—1185 participants (age 68.8±6.1y; 77% male) underwent retinal imaging and cerebral MRI. Cerebral infarcts and white matter hyperintensities (WMH) were identified on MRI, retinopathy was graded and retinal vessels were measured.

Results—Higher retinopathy grade (odds ratio (OR) = 1.40 (1.16, 1.70)), narrower arteriolar diameter (OR = 0.98 (0.97, 0.99)), fewer symmetrical arteriolar bifurcations (OR = 0.84 (0.75, 0.95)), higher arteriolar optimality deviation (OR = 1.16 (1.00, 1.34)) and more tortuous venules (OR = 1.20(1.09, 1.32)) were associated with strokes/infarcts and WMH. Associations with quantitative retinal microvascular measures were independent of retinopathy.

Conclusions—Abnormalities of the retinal microvasculature are independently associated with stroke, cerebral infarcts and white matter lesions.

Keywords

stroke; white matter lesions; infarcts; retinal

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Conflicts of Interest
None

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Introduction

Stroke is a leading cause of death and disability worldwide, however symptomatic strokes represent only a sub-fraction of the burden of cerebrovascular disease.1 White matter lesions may also be indicative of cerebral microvascular disease and stroke risk.2 Retinopathy is associated with incident and prevalent stroke, subclinical infarcts and white matter lesions; 3 however associations with quantitative retinal microvascular measures have been inconsistent.4 This study investigated associations between retinal microvascular abnormalities and 1) cerebral infarcts/stroke and 2) white matter lesions in a UK-based tri-ethnic population-based cohort, and if associations with quantitative measures were independent of retinopathy status.

Methods

Participants

Southall and Brent REvisited (SABRE) is a population-based tri-ethnic cohort (Europeans, South Asians and African Caribbeans).5 Surviving participants attended for re-investigation between 2008 and 2011. Ethics approval was granted by St Mary's Hospital Research Ethics Committee (07/H0712/109), and written informed consent obtained.

The fundus of both eyes was imaged using a Zeiss FF450+ fundus camera and an Oscar 510C CCD following administration of 1% tropicamide and 2.5% phenylephrine eye drops. Refraction was measured using a Nidek AR-310 auto-refractometer. Retinopathy grading was according to the NHS Diabetic Eye Screening Programme classification.6 Quantitative retinal vessel measurements were made using an automated program.7, 8 MRI was performed as previously published.9 Cerebral infarcts and strokes were categorised as: 0 = no stroke or large infarct (>3mm); 1 = 1 large infarct; 2 = stroke and/or ≥2 large infarcts. White matter hyperintensities (WMH) were graded as none, mild (one WMH); moderate (2 WMH) or severe (≥ 3 WMH). Additional details of methods and participant characteristics are given in supplementary data (see http://stroke.ahajournals.org; Supplemental Tables 1 & II).

Analysis was restricted to 1185 individuals (aged 69±6y; 77% male; 37% South Asian, 15% African Caribbean) who underwent imaging and retinopathy grading (Supplemental Figure). Associations between retinopathy/quantitative retinal microvascular measures and infarcts/strokes or WMH were analysed using ordered logistic regression adjusted for age, sex and ethnicity. The assumption of proportional odds was tested using a Brant test. Additional models were constructed to include potential confounders chosen *a priori* - hypertension, body mass index (BMI), HbA1c, diabetes, total cholesterol, high density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), coronary artery disease, years of education and smoking habit (model 2); potential confounders plus retinopathy for quantitative measures (model 3).

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Results

A higher retinopathy grade was associated with higher OR for cerebral infarcts and stroke (Table 1) and WMH (Table 2). Narrower arteriolar diameter, fewer symmetrical arteriolar bifurcations, higher venular tortuosity and lower AVR were also significantly associated with greater OR for cerebral infarct and strokes (Table 1) and WMH (Table 2). Adjustment for confounders had little or no effect. Further adjustment for urinary microalbuminuria had minimal effects on associations (not shown).

Discussion

Retinopathy and quantitative abnormalities of the retinal microvasculature are associated with prevalent clinical and sub-clinical cerebrovascular disease in a tri-ethnic population-based cohort. Associations were independent of risk factors, and adjustment for presence of retinopathy had little effect on associations with quantitative measures. Previous studies examining the retina in relation to cerebral disease have yielded inconsistent results.10–14 Our data provide additional information in a large well-characterised tri-ethnic sample including first generation migrants to the UK who are at increased risk of stroke.2

This study has a number of limitations. It is cross-sectional so the issue of causality cannot be resolved. By design the majority were male and only ~40% of original participants attended for re-assessment. People who attended clinic were slightly younger and tended to be healthier than those who failed to attend or who had died in the intervening period. Nevertheless, it seems unlikely that this would substantially influence the validity of cross-sectional associations observed within the sample.

In summary, retinopathy, arteriolar narrowing, reduced density of the retinal arteriolar network (rarefaction) and increased venular tortuosity are associated with cerebral infarcts, stroke and white matter lesions in an older tri-ethnic cohort. These associations are independent of conventional risk factors, including diabetes, elevated blood pressure and renal microvascular disease and associations with quantitative measures were independent of retinopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Associations between retinopathy and quantitative retinal microvascular measures with cerebral infarcts and stroke

Variable	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P	Model 3 OR (95% CI)	P
Retinopathy						
R0	Reference		Reference		NR	
R1	1.47 (1.08, 2.00)	0.015	1.41 (1.01, 1.96)	0.04		
R2	3.62 (1.75, 7,48)	0.001	2.79 (1.30, 5.99)	0.008		
Trend		*<0.001*		*0.004*		
Quantitative measures						
Arteriolar diameter	0.98 (0.97, 0.99)	0.04	0.97 (0.96, 0.99)	0.003	0.97 (0.96, 0.99)	0.002
Number of arterioles	0.94 (0.87, 1.01)	0.08	0.94 (0.87, 1.02)	0.1	0.93 (0.86, 1.01)	0.09
Number of symmetrical arteriolar bifurcations	0.84 (0.75, 0.95)	0.004	0.83 (0.73, 0.94)	0.003	0.82 (0.73, 0.93)	0.002
Arteriolar tortuosity	1.05 (0.98, 1.12)	0.2	1.04 (0.97, 1.12)	0.3	1.04 (0.97, 1.12)	0.3
Log arteriolar optimality deviation	1.16 (1.00, 1.34)	0.05	1.13 (0.97, 1.32)	0.1	1.13 (0.97, 1.32)	0.1
Venular diameter	1.00 (0.99, 1.01)	>0.9	0.99 (0.98, 1.01)	0.3	0.99 (0.98, 1.01)	0.3
Number of venules	0.97 (0.90, 1.04)	0.3	0.99 (0.92, 1.07)	0.8	0.99 (0.92, 1.07)	0.8
Venular tortuosity	1.20(1.09, 1.32)	<0.001	1.17 (1.05, 1.29)	0.003	1.16 (1.05, 1.29)	0.004
Arteriovenous ratio	0.29 (0.08,1.01)	0.05	0.25 (0.07, 0.93)	0.04	0.23 (0.06, 0.85)	0.03

Model 1, adjusted for age, sex ethnicity; model 2, model 1 plus adjustment for hypertension, BMI, HbA1c, diabetes, total cholesterol, high density lipoprotein (HDL) cholesterol, log C-reactive protein, coronary artery disease, years of education and smoking habit; Model 3: model 2 plus adjustment for presence of retinopathy.

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Table 2

Association between retinopathy and quantitative retinal microvascular measures with white matter hyperintensities

Variable	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P	Model 3 OR (95% CI)	P
Retinopathy						
R0	Reference		Reference		NR	
R1	1.14 (0.89, 1.46)	0.3	1.03 (0.79, 1.33)	0.9		
R2	5.64 (2.64, 12.09)	<0.001	4.35 (1.98, 9.56)	<0.001		
Trend		*0.001*		*0.04*		
Arteriolar diameter	0.99 (0.97, 1.00)	0.02	0.98 (0.97, 0.99)	0.01	0.98 (0.97, 0.99)	0.002
Number of arterioles	0.91 (0.86, 0.967)	0.002	0.92 (0.87, 0.98)	0.006	0.92 (0.87, 0.98)	0.03
Number of symmetrical arteriolar bifurcations	0.90 (0.83, 0.98)	0.02	0.88 (0.81, 0.97)	0.007	0.88 (0.80, 0.96)	0.006
Arteriolar tortuosity	0.97 (0.92, 1.03)	0.4	0.96 (0.90, 1.02)	0.2	0.96 (0.90, 1.02)	0.2
Log arteriolar optimality deviation	0.98 (0.88, 1.09)	0.7	1.00 (0.90, 1.12)	>0.9	1.01 (0.90, 1.12)	>0.9
Venular diameter	0.99 (0.99, 1.01)	0.9	1.00 (0.99, 1.01)	0.6	1.00 (0.99, 1.01)	0.6
Number of venules	0.94 (0.89, 0.99)	0.03	0.96 (0.90, 1.01)	0.1	0.96 (0.90, 1.01)	0.1
Venular tortuosity	1.14 (1.04, 1.23)	0.003	1.11 (1.01, 1.21)	0.02	1.11 (1.02, 1.21)	0.02
Arteriovenous ratio	0.40 (0.15, 1.04)	0.06	0.32 (0.12, 0.86)	0.02	0.31 (0.12, 0.84)	0.02

Models and abbreviations as for table 1.