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## Retinopathy in Ischaemic Stroke Subtypes

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### Abstract

**Background and Purpose**—Lacunar stroke is associated with an intrinsic cerebral small vessel disorder of unknown aetiology although possible causes include increased blood brain barrier permeability. Retinal arterioles are similar to cerebral small vessels and retinopathy occurs secondary to increased blood retinal barrier permeability. We hypothesized that there would be higher rates of retinopathy in patients with acute lacunar versus cortical stroke.

**Methods**—We prospectively recruited patients presenting with acute lacunar and cortical ischaemic stroke. An experienced stroke physician diagnosed and subtyped the stroke based on clinical features and cerebral magnetic resonance imaging. We performed 6 dilated digital retinal photographs of each eye in all patients. A carefully trained physician graded retinopathy (one or more of hard or soft exudates, microaneurysms or haemorrhages) blind to stroke type as definitely present/absent or uncertain.

**Results**—We recruited 220 patients; 6 were excluded with ungradeable photographs leaving 214 patients for analysis (105 lacunar and 109 cortical strokes). Mean age was 68 years (SD 11 years) and median NIHSS 2. Similar proportions of each group had diabetes (17% lacunar v 10 % cortical) and hypertension (56% lacunar and 66% cortical). 18% of lacunar and 19% of cortical patients had any retinopathy. After adjusting for baseline differences in age, hypertension and diabetes, retinopathy was not associated with ischaemic stroke subtype.

**Conclusions**—We have not demonstrated a strong association between retinopathy and ischaemic stroke subtype. However larger samples or assessment of other retinal vascular abnormalities may yield positive associations.

### Keywords

Retinopathy; Lacunar Stroke; Aetiology

### Introduction

Although accounting for 25% of all of ischaemic stroke<sup>1</sup> the exact aetiology of lacunar stroke remains unknown.<sup>2</sup> Lacunar strokes are thought to arise from disease in a single perforating artery causing small deep cerebral lesions. Possible mechanisms include local large or small vessel atheroma, vasospasm and micro-emboli blocking these arteries. Conventional causes of stroke probably account for only 15-20% of lacunar strokes, suggesting other mechanisms may be responsible in the majority.<sup>2</sup> More recently it has been

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Conflicts of Interest

None of the authors have any conflicts of interests to declare.

suggested that disordered small vessel endothelium or blood-brain barrier dysfunction may contribute.<sup>3;4</sup> The retinal and cerebral small vessels are developmentally related, are of similar size and share physiological characteristics. The blood-retinal barrier is analogous to the blood-brain barrier.<sup>5</sup> Large population studies show associations between retinopathy (defined as the presence of hard or soft exudates, haemorrhage or microaneurysms) and previous as well as future stroke risk.<sup>6;7;8;9</sup> Retinopathy is associated with increased permeability of the blood-retinal barrier<sup>10</sup> and we therefore hypothesized that there could be higher rates of retinopathy in patients with acute ischaemic lacunar stroke compared to acute ischaemic cortical stroke controls where the mechanism is largely atherothromboembolic.

## Patients and Methods

We recruited patients prospectively with acute clinical lacunar or mild cortical ischaemic stroke from our hospital stroke service which serves a largely urban population of approximately 400,000 people. We included patients who presented up to 3 months after symptom onset who had a definite diagnosis of stroke and who could provide informed consent. We excluded patients with severe total anterior circulation stroke (as the atherothromboembolic disease mechanisms responsible for severe cortical stroke are present in patients with milder cortical stroke) or who were medically unstable, had contraindications to Magnetic Resonance Imaging (MRI) or who were unwilling to participate. The hospital sees approximately 550 patients with possible stroke a year of whom 250 might have been eligible with a lacunar or mild cortical stroke and the study ran for 2.5 years. We used a control group of patients with cortical ischaemic stroke to control for having a stroke, risk factor profiles and secondary stroke prevention medications (as opposed to normal age-matched controls which would not have controlled for any of these factors). All patients were examined by an experienced stroke physician and classified initially into lacunar or cortical stroke clinical syndromes according to the Oxfordshire Community Stroke Project classification.<sup>11</sup> Patients had diagnostic cerebral MRI (including diffusion-weighted imaging, DWI) at presentation to identify the site of the recent infarct and quantify white matter hyperintensities. All scanning was performed on a 1.5-T MR scanner (Signa LX; General Electric) with 22 mT m<sup>-1</sup> maximum strength gradients. Diagnostic MRI also included axial T2-weighted, fluid-attenuated inversion recovery (FLAIR), and gradient echo sequences (details available on request). All patients underwent usual investigations for stroke (carotid Doppler ultrasound, electrocardiogram, blood tests, and other tests if indicated). We recorded age, gender, National Institutes of Health Stroke Scale (NIHSS),<sup>12</sup> presence of atrial fibrillation (AF), history of diabetes, hypertension, ischaemic heart disease (IHD), peripheral vascular disease (PVD) and previous stroke/transient ischaemic attack. All patients had six field retinal photography (centred on the disc, macula, lateral macula, nasal to the disc, upper arcade and lower arcade) of the left and right eyes, with 1% tropicamide eye drops where possible, using a Canon CR-DGi digital retinal camera (Canon USA Inc.).

Mild cortical stroke syndrome was defined as maximum clinical deficit of either weakness or sensory loss in the face, arm or leg or loss of higher cerebral dysfunction (eg, dysphasia or neglect), or weakness in more than one limb in the presence of loss of higher cerebral function equivalent to a partial anterior circulation stroke syndrome or homonymous hemianopia suggestive of occipital cortical infarct. Lacunar stroke syndrome was defined as one of the classical lacunar syndromes (eg pure motor weakness and/or sensory loss of face and arm, arm and leg or all three, ataxic hemiparesis or clumsy hand dysarthria syndrome).<sup>11</sup> Following initial clinical classification, we further classified stroke subtype using radiological criteria (ie whether the recent infarct on MRI was cortical or lacunar) and used both the clinical and radiological classification to assign the final stroke subtype classification. Where the clinical classification differed from the radiological classification,

the radiological classification was used as cortical syndromes can arise from lacunar strokes and vice versa. If no definite recent lesion was visible on the scan, the clinical classification was used. No patients had concurrent acute lacunar and cortical infarcts. If a patient had old lesions present we recorded their presence and type (infarct/haemorrhage and cortical/lacunar) but subtyped stroke based upon the acute lesion. The study was approved by the Local Research Ethics Committee and all patients gave written informed consent.

## Image analysis

All MRI scans were coded by an experienced neuroradiologist (JW) for the presence, location and size of the recent symptomatic infarct, any old infarcts or haemorrhages. A recent infarct was defined as a hyperintense area on diffusion imaging (with corresponding reduced signal on the Apparent Diffusion Co-efficient image), with or without increased signal on FLAIR or T2 weighted imaging, in a distribution compatible with an arterial territory. Lacunar infarcts were in the cerebral hemispheric white matter, basal ganglia or brain stem and <2cm diameter if recent (lesions >2cm were classed as striatocapsular/cortical as they have large artery disease causes). Retinal photographs were graded by a single trained physician (FD) for retinopathy (defined as the presence of haemorrhage, microaneurysms or hard or soft exudates) in either eye as being absent, questionably present or present according to an established, validated proforma,<sup>13</sup> blinded to clinical details. Training was performed using standard test images and with ophthalmologists performing regular diabetic screening. All lesions identified using previously defined criteria<sup>14</sup> that were questionably present or present were checked by a consultant ophthalmologist (BD). The intra-rater repeatability Kappa score for the presence versus absence of retinopathy (for 30 randomly chosen cases in this study) was 0.84 (excellent). This technique was based upon a retinopathy grading scale (microaneurysms and haemorrhages) with a published intra-rater Kappa score of 0.9.<sup>15</sup>

## Statistical Analysis

We used 2 sample t-tests, Fishers Exact Test and Chi Square test for association to investigate baseline characteristics between the lacunar and cortical groups and associations with retinopathy and multiple binary logistic regression to assess multivariate effects of explanatory variables. All analysis was performed with Minitab software (version 14, Minitab Inc, PA, USA). Sample size calculation based on existing literature on retinal findings in stroke suggested that 197 patients would be needed to detect a difference of prevalence in retinopathy of 10% with 80% power at the 0.05 significance level.

## Results

We recruited 220 patients of whom 6 were excluded with photographs of inadequate quality (due to cataract, poor compliance and inadequate dilatation) to assess retinopathy leaving 214 patients for analysis. The mean age was 68.4 years (SD 11.6 years), 62% were male, and the median NIHSS was 2. There were 109 patients with acute cortical stroke and 105 with acute lacunar stroke. Acute stroke lesions were seen on MRI (DWI and/or T2/FLAIR based on signal characteristics and lack of focal atrophy) in 159/214 (74%) patients of whom 144/214 (67%) of the cohort had DWI positive lesions (the rate reflecting the small nature of the lesions and occasional delays to scanning). Consistent with previous studies<sup>16</sup> 38/214 (18%) patients had their stroke subtype classification changed by MRI findings from cortical to lacunar or vice versa. 73/214 patients had old infarcts on imaging – in 16 the old infarct was of a different subtype to the acute lesion and 4 had both old cortical and lacunar infarcts.

The baseline characteristics of the lacunar and cortical groups are shown in Table 1. The cortical patients were older than the lacunar stroke patients (mean 70.6 years v 66.3 years, 2 sample t test estimate of difference 4.25 95% CI 1.15-7.34 yrs p=0.007) with lower NIHSS (median 2 v 3 Mann-Whitney U test p<0.01) and had higher rates of atrial fibrillation (14% v 4% p=0.009) and ischaemic heart disease (29% v 13% p=0.004). There were no significant differences between the two groups in gender or rates of hypertension, diabetes or PVD.

Of 214 patients, 40 patients (18.7%) had retinopathy present: 19/105 patients (18%) with lacunar stroke and 21/109 patients (19%) with cortical stroke had retinopathy (Chi squared statistic 0.48, p=0.8). Table 2 shows individual components of retinopathy by stroke subtype. There were no significant differences between individual components of retinopathy and stroke subtype.

With univariable analysis only the presence of diabetes was associated with retinopathy (Chi square statistic 4.8, p=0.028) but not age, NIHSS, hypertension, diabetes, IHD, PVD, previous TIA/Stroke or AF. After correcting for mild baseline differences in age, hypertension and diabetes with multivariable binary logistic regression, there was no association between ischaemic stroke subtype and presence of retinopathy (OR 0.76 – 95% CI 0.37-1.57 p=0.46) see Table 3. The only variable independently associated with the presence of retinopathy after correction for age, stroke subtype and hypertension was diabetes (OR 3.02 -95% CI 1.24-7.34 p= 0.01). To examine possible effect modifiers, we assessed all two way interactions (between age, hypertension, diabetes and stroke subtype) and sequentially removed those interactions contributing least to the model where their effect was non significant. After this process the only significant interaction that remained was between hypertension and age in predicting retinopathy (OR for a combined age multiplied by presence of hypertension explanatory variable of 0.94 95% CI 0.88 -1.00 p=0.04) when modelled with age, hypertension, diabetes and stroke subtype, but this did not significantly alter the associations shown in Table 3.

To ensure accurate ischaemic stroke classification, we performed a pre-specified subgroup analysis excluding patients who had an old lesion of a different type to the acute stroke classification e.g. a patient presenting with an acute lacunar stroke who had an old cortical lesion. Multivariable logistic regression correcting for age, diabetes and hypertension in these 194 patients did not change the size, direction and significance of the results in Table 3.

## Discussion

We have not demonstrated an association between ischaemic stroke subtype and the presence of any retinopathy. In this study the only variable which was associated with retinopathy on multivariable analyses was diabetes.

The strengths of the study are that stroke was diagnosed by an expert at the time of the stroke, all patients had diagnostic MRI at presentation to permit accurate diagnosis and subtyping, we used a pre-specified clinical and imaging based hierarchy to classify stroke subtype and our sample size exceeded our original calculated estimate that would be required to detect a 10% difference between stroke subtypes. We can therefore be reasonably confident that we have not missed an important difference in retinopathy prevalence simply through inadequate study design. Furthermore all patients had retinal photography performed at the time of the stroke and no previous studies have compared retinopathy in ischaemic stroke subtypes. The limitations are that the cross-sectional design means that we can only report on associations between retinopathy and stroke. There were

modest imbalances in baseline variables which may not have been completely corrected with multivariate analyses. Although we recruited beyond the number indicated in our sample size calculation, more patients would be needed to show differences in overall prevalence of less than 10%, or in specific subtypes of retinopathy. Fluorescein angiography may have demonstrated subclinical differences in microvascular perfusion between stroke subtypes, however is more invasive than colour fundus photography, and therefore would have restricted recruitment and was not feasible in this study. The study sample size was perhaps limited by exclusion of patients with severe strokes (equivalent to total anterior circulation strokes) and the need for patients to have a definite diagnosis of stroke rather than a possible diagnosis of stroke. However retinal photography would have been difficult in severely unwell patients (the subject needs to sit up, hold their head still and follow commands) and the atherothromboembolic disease mechanisms present in severe cortical strokes will be represented in the included milder cortical strokes. We subtyped acute ischaemic stroke into lacunar and cortical stroke using the OCSF classification modified by the results of the brain MRI, and therefore unbiased by using risk factors to classify stroke (eg as in the TOAST classification). This study focused on patients with acute clinically proven strokes, however some patients had old lesions on their MRI scans that may or may not have represented clinical strokes (most appeared not to – we did not ascertain a past history of clinically-evident stroke in 65/73 of patients with old infarcts). We repeated the analysis excluding the few patients who had an old lesion type that differed from the acute ischaemic type and this sensitivity analysis did not change the main results shown in Table 3.

How does our study relate to previous information on retinopathy and stroke? In the large population-based Atherosclerosis Risk in Communities (ARIC) study, the presence of any retinopathy predicted future ischaemic stroke during 3.5 years follow up with a relative risk (RR) of 2.58 (95% CI 1.59-4.20) corrected for diabetes, hypertension, age and other vascular risk factors.<sup>7</sup> A similar finding is reported for diabetic subjects with a longer follow up from the same study.<sup>6</sup> Furthermore baseline retinopathy in the Blue Mountains Eye Study was reported as being significantly associated with future risk of stroke and TIA with a RR of 1.7 (95% CI 1.0-2.8).<sup>13</sup> Although demonstrating a link between retinopathy and future stroke in general, none of these studies reported or compared associations with different subtypes of ischaemic stroke. The evidence for an association between retinopathy and history of stroke is less compelling (perhaps reflecting the inherent difficulties in obtaining accurate medical histories) – the Cardiovascular Health Study (CHS) reported that retinopathy was associated with a clinical history of stroke (OR 2.0 95% CI 1.1-3.6)<sup>8</sup> and MRI defined cerebral infarction of unspecified subtype (OR 1.18 95% CI 1.05-1.34).<sup>17</sup> There have been no published studies thus far that have compared retinopathy between ischaemic stroke subtypes.

We demonstrated a prevalence of retinopathy of 19% in patients with mild ischaemic stroke and mean age 68 yrs. This is slightly higher than population-based prevalences of 7.0% (ARIC)<sup>7</sup> and 8.3% (CHS)<sup>8</sup> probably reflecting the fact that the patients in the present study had higher rates of vascular disease than community-dwelling healthy subjects. The prevalence in the present study was slightly lower than in diabetic patients with ischaemic stroke of 33% (ARIC),<sup>6</sup> but similar to that in patients in CHS who had a history of ischaemic stroke, 19% of whom had retinopathy.<sup>8</sup> These differences may be explained by different rates of diabetes and stroke severity.

What do our results mean? The aim of the present study was to investigate whether there were higher rates of retinopathy in patients with lacunar stroke as this might reflect blood-retinal barrier breakdown. There is growing evidence that cerebral small vessel disease may be associated with dysfunctional blood-brain barrier<sup>4</sup> and retinal imaging offers an excellent

non-invasive method of studying blood vessels that are similar to cerebral vessels. That the rates of retinopathy do not differ between acute ischaemic stroke subtypes may be due to several reasons other than our hypothesis being incorrect. One of the first stages in the development of diabetic retinopathy is subtle breakdown of the blood-retinal barrier which eventually leads to characteristic retinopathy<sup>18</sup> (visible on techniques like fluorescein angiography). In the present study we have looked at any retinopathy (haemorrhage, exudates and microaneurysms). Perhaps only certain retinopathic components are associated with blood-retinal barrier leak whilst others reflect other pathological processes. Although we have reported the findings, this study was not powered to identify differences in individual retinopathy features, only in any retinopathy. Although very similar, it may be that retinal vessels do not behave exactly like cerebral vessels and the changes are too subtle to be identified without retinal fluorescein angiography. Microvascular changes in the brain and the retina may not move in parallel – it is possible that in these patients (with a low NIHSS and stroke severity) the retinal changes may have not yet developed and perhaps studying patients with more severe stroke may have revealed subtype-specific retinopathic differences. Alternatively, it may be that retinopathy is a marker of vascular risk and is co-associated with stroke but not stroke subtypes, as lacunar and cortical strokes have similar hypertension and diabetes risk profiles.<sup>19</sup> Future research should perhaps concentrate on carefully subtyping stroke and investigating the use of retinopathy as a marker of risk factor effects on end organs in the individual and how this relates to any future stroke risk.

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**Table 1**

Baseline characteristics of lacunar and cortical stroke subtypes. Statistical test used – Mean age (2 sample t test), median NIHSS (Mann-Whitney U test), PVD and AF (Fishers Exact Test), all others Chi square test for association.

Characteristic	Lacunar Stroke	Cortical Stroke	P value for difference
n	105	109	-
Age years (SD)	66.3 (11.6)	70.6 (11.4)	0.007
Male n (%)	60 (57%)	74 (68%)	0.10
Median NIHSS	3	2	<0.01
Atrial Fibrillation n (%)	4 (4%)	15 (14%)	0.01
<b>Past Medical History of:</b>			
Diabetes n (%)	18 (17%)	11 (10%)	0.13
Ischaemic heart disease n (%)	14 (13%)	32 (29%)	0.004
Peripheral vascular disease n (%)	5 (5%)	5 (5%)	0.95
Hypertension n (%)	59 (56%)	62 (66%)	0.14
TIA n (%)	16 (15%)	13 (12%)	0.46
Stroke n (%)	9 (9%)	12 (11%)	0.55
Old infarct on MRI n (%)	35 (33%)	38 (35%)	0.81

**Table 2**

Number of patients with individual components of retinopathy by stroke subtype. There are no significant differences in proportions with retinopathy features between stroke subtypes.

Characteristic	Lacunar Stroke	Cortical Stroke	% Difference (95% CI)	P value
n	105	109		
Hard Exudates (%)	4 (4%)	8 (7%)	3.5% (-2.6%, 9.6%)	0.26
Soft Exudates (%)	6 (6%)	5 (5%)	1.1% (-4.8%, 7.0%)	0.71
Haemorrhage/ microaneurysm(%)	14 (13%)	12 (11%)	2.3% (-6.4%, 11.0%)	0.60

**Table 3**

Multivariable analysis of associations with retinopathy for all 214 patients. All OR are corrected for the other variables in the table.

Variable	Multivariable OR for association with retinopathy	95% CI	P value
Lacunar stroke subtype	0.76	0.37-1.57	0.46
Age	0.98	0.95-1.01	0.25
Hypertension	0.82	0.80-1.75	0.61
Diabetes	3.02	1.24-7.34	0.01