Retinopathy and Lobar Intracerebral Hemorrhage

Insights Into Pathogenesis

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Background: The vascular pathogenesis underlying lobar intracerebral hemorrhage (ICH) is unclear.

Objective: To determine whether certain retinal microvascular signs are associated with lobar ICH to improve understanding of its underlying cerebral vasculopathy.

Design: Prospective cohort study.

Setting: Royal Melbourne Hospital and Westmead Hospital.

Patients: Of 655 patients with acute stroke, 25 had lobar ICH, 51 had deep ICH, 93 had lacunar infarction, and 486 had nonlacunar cerebral infarction.

Main Outcome Measures: Retinal photographs were assessed for retinopathy lesions (microaneurysms, retinal hemorrhages, cotton-wool spots, and hard exudates) and retinal arteriolar wall signs (focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar wall light reflex) masked to the cerebral pathologic abnormalities and the study hypothesis.

Results: In patients without diabetes mellitus, retinopathy lesions were more likely to be present in persons with lobar ICH than in those with either lacunar infarction (47.8% vs 30.4%; adjusted odds ratio, 3.5; 95% confidence interval, 1.1-10.9) or nonlacunar cerebral infarction (47.8% vs 24.6%; 3.3;1.4-8.1). Most retinal arteriolar wall signs were less frequent in lobar ICH than in deep ICH, although this difference was significant only for focal arteriolar narrowing.

Conclusions: Patients with lobar ICH were more likely than patients with lacunar or nonlacunar cerebral infarction to have retinopathy lesions, suggesting breakdown of the blood-retina barrier in patients with lobar ICH. These findings support a distinct vasculopathy in lobar ICH compared with other acute stroke subtypes resulting from cerebral small vessel disease or ischemic infarction.

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Lobar intracerebral hemorrhage (ICH) accounts for approximately one-third of primary ICH. Unlike small deep ICH and infarcts, thought to be caused mainly by intracranial small vessel disease, and nonlacunar cerebral infarcts, usually caused by embolism of a thrombus from a proximal source in the heart, aortic arch, or other extracranial large arteries, the pathogenesis of lobar ICH is complex. Causal hypotheses for lobar ICH include arteriovenous malformations (in younger patients), amyloid angiopathy (in older patients), bleeding diatheses (eg, oral anticoagulation), and hemorrhagic transformation of nonlacunar cerebral infarction. However, uncertainty remains as to whether some patients with lobar ICH may have a distinct underlying vasculopathy that predisposes them to arterial rupture in the cortical-subcortical region of the cerebral hemispheres.

The retinal vasculature offers a means for noninvasively studying cerebrovascular pathologic abnormalities because the retinal and cerebral small vessels are developmentally of similar size and share physiologic characteristics. Also, the blood-retinal barrier is analogous to the blood-brain barrier. Retinal microvascular signs were previously shown to predict clinical stroke events and stroke mortality and to vary according to different ischemic stroke subtypes. We reported that patients with small deep ICH and lacunar infarcts, presumably caused by intracranial small vessel disease, were more likely than patients with nonlacunar cerebral infarction to have retinal arteriolar wall signs (ie, severe focal arteriolar narrowing and...
arteriovenous nicking) that are suggestive of small vessel disease in the retina. Consistent with another study,\textsuperscript{10} in other reports from the Multi-Centre Retinal Stroke Study, we did not find that patients with deep ICH or lacunar stroke had a higher prevalence of retinopathy lesions (microaneurysms, retinal hemorrhages, cotton-wool spots, and hard exudates).\textsuperscript{11,12}

Although deep (lacunar) ICH is known to be associated with retinal arteriolar wall signs due to hypertension, we hypothesized that patients with lobar ICH may have a distinct spectrum of retinal microvascular signs that differ from those seen in deep ICH and cerebral infarction, possibly due to amyloid angiopathy. In this study, we tested this hypothesis by examining the frequency of retinal microvascular signs in patients with lobar ICH, comparing this with the frequency in patients with deep ICH, lacunar infarction, or nonlacunar cerebral infarction.

**METHODS**

**STUDY POPULATION**

The study sample consisted of participants from the Multi-Centre Retinal Stroke Study, a hospital-based study of patients with acute stroke, between February 1, 2005, and December 31, 2007. Detailed methods have been described elsewhere.\textsuperscript{13} In brief, only patients with acute stroke (n=842) from the Australian arms of the Multi-Centre Retinal Stroke Study (Sydney and Melbourne) were included in this study (the Singapore site did not recruit patients with ICH). Written informed consent was obtained from patients or their next of kin. The study was approved by the human research ethics committees of the respective hospitals.

Patients were admitted to the hospital generally within 1 to 2 days after the stroke event. All the patients underwent a standardized questionnaire interview, a neurological examination, brain imaging, and an extensive assessment of atherosclerotic diseases and their risk factors. Blood pressure was measured on admission, and if it was elevated, antihypertensive medication was commenced. Hypertension, diabetes mellitus, and hypercholesterolemia were diagnosed according to self-reported history of these conditions, including the use of relevant medications (antihypertensive medications, oral hypoglycemic agents and insulin, and lipid-lowering medications, respectively). Cigarette smoking status was also self-reported. In the present study, we included 655 patients after excluding 43 cases classified as stroke mimics, 93 as transient ischemic attacks, 29 as secondary ICH, and 22 as having ungradable retinal images.

**ASSESSMENT OF STROKE**

A final consensus diagnosis of acute stroke was made for each patient by a panel of stroke experts with access to the clinical information and neuroimaging. All the patients underwent computed tomography (CT), and a subset underwent magnetic resonance imaging.\textsuperscript{11} The finding of a hyperdense intraparenchymal or intraventricular lesion on CT (that was not determined to be calcium) led to a diagnosis of ICH (lobar or deep ICH differentiated by location); hemorrhagic transformation of an infarction was coded as a cerebral infarct, and ICH due to secondary causes, such as trauma, neoplasm, or arteriovenous malformation, was excluded. Cerebral infarction was subclassified using a pragmatic modification of the Trial of Org 10172 in Acute Stroke Treatment classification, as adopted by the Greater Metropolitan Clinical Taskforce for Stroke in New South Wales, Australia.\textsuperscript{14} Ischemic stroke subtypes were classified into 5 core etiologic groups: large vessel atherosclerosis, small vessel (lacunar) atherosclerosis, cardioembolic infarction, stroke of other etiology, and stroke of undetermined etiology. Nonlacunar cerebral infarction included large vessel atherosclerosis and cardioembolic infarction.

**RETINAL PHOTOGRAPHY AND GRADING**

Retinal photography was performed within the first week of admission to the hospital. Retinal photography procedures are described elsewhere.\textsuperscript{13} All the study participants had up to 6 retinal photographic fields taken of each eye, mimicking fields 1 to 6 of the Diabetic Retinopathy Study,\textsuperscript{15} using a nonmydriatic digital camera (Canon D60; Canon, Tokyo, Japan), after pharmacologic pupil dilation in most patients. Deidentified images were graded centrally at the Centre for Vision Research, University of Sydney. Retinal arteriolar wall signs were graded as absent, mild, or severe for focal arteriolar narrowing (Figure 1), arteriovenous nicking (Figure 2, arrow), and enhanced arteriolar light reflex (Figure 2). Isolated retinopathy lesions (microaneurysms, retinal hemorrhages, cotton-wool spots, and hard exudates [Figure 3]) in patients with or with-
out diabetes were graded as either present or absent. The grading was performed by comparing with a standard set of images for various retinal microvascular signs, as previously described. All retinal lesions detected were adjudicated by a senior researcher (J.J.W.) and a retinal specialist (P.M.).

STATISTICAL METHODS

Acute stroke subtypes (including lobar ICH) were independent variables, and retinal microvascular signs were dependent variables. We constructed logistic regression models to assess the associations of lobar ICH with various retinal vascular signs compared with deep ICH, lacunar infarction, and nonlacunar cerebral infarction in separate models. Models were adjusted for age, sex, hypertension, hypercholesterolemia, diabetes, and cigarette smoking status. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

RESULTS

Of the 655 patients (77.8% of 842 patients recruited from the Melbourne and Sydney centers), 25 were classified as lobar ICH, 51 as deep ICH, 93 as lacunar infarction, and 486 as nonlacunar cerebral infarction. Of the 25 lobar ICH cases, 24 (96.0%) were white, and the remaining patient was Chinese. Two patients had diabetes. Hematoma location was recorded in 16 of these patients with lobar ICH: 3 in the right hemisphere, 13 in the left hemisphere, and 0 in the brainstem. For most patients with lobar ICH, the mean (SD) hematoma size was 35.3 (14.9) mm (range, 10-70 mm). Only 3 patients with lobar ICH were recorded as using anticoagulant medications on hospital admission.

Patient characteristics and vascular risk factors by acute stroke subtypes are given in Table 1. Patients with lobar ICH were more likely to be older (73.0 vs 64.9 years) and white (96.0% vs 76.5%) than those with deep ICH. Patients with lobar ICH were less likely than those with lacunar infarction and nonlacunar cerebral infarction to have hypertension (40.0% vs 65.6% and 64.6%) or to be prescribed an antplatelet agent (20.8% vs 42.9% and 44.1%). However, patients with lobar ICH were more likely than those with lacunar infarction to have atrial fibrillation (23.8% vs 2.3%) and dementia (29.2%) compared with deep ICH (7.8%), lacunar infarction (2.2%), or nonlacunar cerebral infarction (5.4%).

Retinopathy and severe arteriovenous nicking were more frequently present in patients with lobar ICH (48.0% and 36.0%, respectively) and deep ICH (42.0% and 40.4%) than in those with lacunar infarction (35.5% and 22.5%) and nonlacunar cerebral infarction (31.9% and 21.2%). In contrast, severe focal arteriolar narrowing and severe enhanced arteriolar light wall reflex were less frequently present in patients with lobar ICH (12.0% and 17.4%) or nonlacunar cerebral infarction (13.2% and 19.9%) than in those with deep ICH (31.9% and 31.9%) and lacunar infarction (19.8% and 24.7%). After multivariable adjustment, lobar ICH was significantly associated with the presence of any retinopathy lesions (OR, 3.0; 95% CI, 1.3-6.9) compared with nonlacunar cerebral infarction (Table 2). Lobar ICH did not differ significantly from deep ICH and lacunar cerebral infarction in its associations with retinopathy lesions or retinal arteriolar wall signs except for focal narrowing, which was less frequent in lobar ICH compared with deep ICH.

After excluding the 2 patients with lobar ICH (8.0%) who had diabetes, retinopathy lesions were present in 11 of the 23 patients with lobar ICH without diabetes. Retinopathy lesions were more frequent in patients with lobar ICH than in those with either nonlacunar cerebral infarction (47.8% vs 24.6%; adjusted OR, 3.3; 95% CI, 1.4-8.1) or lacunar infarction (47.8% vs 30.4%; adjusted OR, 3.5; 95% CI, 1.1-10.9) (Table 3).

Of the different retinopathy lesions in patients with acute stroke without diabetes, microaneurysms and retinal hemorrhages were more frequent in patients with lobar ICH (47.8%) than in patients with deep ICH (36.6%), lacunar infarction (26.1%), or nonlacunar cerebral infarction (22.0%). Cotton-wool spots were also more frequent in patients with lobar ICH (17.4%) than in other stroke subtypes. Hard exudates were not found in any patients with lobar ICH.

The proportion of patients with various retinal vascular signs did not differ significantly between patients with lobar ICH and hypertension and those without hypertension (focal arteriolar narrowing: 0% vs 20.0%, P = .13; arteriovenous nicking: 30.0% vs 40.0%, P = .61; enhanced arteriolar wall light reflex: 11.1% vs 21.4%, P = .52; and retinopathy lesions: 50.0% vs 46.7%, P = .87).

COMMENT

We previously compared patients with acute stroke and deep ICH and those with lacunar and nonlacunar cerebral infarction in terms of their association with retinal vascular signs and reported that patients with deep ICH were more likely to have retinal arteriolar wall signs similar to lacunar infarction. In contrast to patients with deep ICH, in this study, we found that after excluding patients with diabetes compared with patients with lacunar or nonlacunar cerebral infarction, those with lobar...
ICH were more likely to have retinopathy lesions, reflecting a breakdown of the blood-retina barrier and indicating the breakdown of the blood-brain barrier. Patients with lobar ICH were less likely to have focal arteriolar narrowing compared with those with deep ICH. These findings lend support to a distinct vasculopathy underlying lobar ICH compared with other stroke subtypes.

At least 5 distinct pathologic entities leading to small vessel damage in the brain have been proposed: (1) an intrinsic arteriolar wall abnormality termed lipohyalinosis (a destructive wall lesion containing mural foam cells and fibrinoid necrosis in some acute lesions), (2) a degenerative “atherosclerotic” type termed hyaline arteriosclerosis (a concentric thickening of the hyaline wall seen commonly in old age), (3) amyloid angiopathy (caused by neuron-derived /H9252-H9253-amyloid infiltration into the vessel wall), (4) insidious endothelial (blood-brain barrier) dysfunction, and (5) other rare causes. Retinal arteriolar wall signs, often related to hypertension, are also proposed to be caused by an intrinsic arteriolar abnormality, such as lipohyalinosis or arteriosclerosis.

### Table 1. Patient Characteristics and Vascular Risk Factors by Acute Stroke Subtypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lobar ICH (n=25)</th>
<th>Deep ICH (n=51)</th>
<th>P Value</th>
<th>Lacunar Infarction (n=93)</th>
<th>P Value</th>
<th>Nonlacunar Cerebral Infarction (n=486)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>73.0 (10.4)</td>
<td>64.9 (14.9)</td>
<td>.02</td>
<td>67.8 (13.3)</td>
<td>.07</td>
<td>69.3 (14.1)</td>
<td>.19</td>
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<td>Male sex, %</td>
<td>56.0</td>
<td>68.6</td>
<td>.28</td>
<td>63.4</td>
<td>.50</td>
<td>55.8</td>
<td>.98</td>
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<td>White race, %</td>
<td>96.0</td>
<td>76.5</td>
<td>.03</td>
<td>83.9</td>
<td>.12</td>
<td>88.8</td>
<td>.26</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>40.0</td>
<td>60.8</td>
<td>.09</td>
<td>63.6</td>
<td>.02</td>
<td>64.6</td>
<td>.01</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>8.0</td>
<td>17.7</td>
<td>.26</td>
<td>23.8</td>
<td>.06</td>
<td>22.5</td>
<td>.09</td>
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<td>Hypercholesterolemia, %</td>
<td>24.0</td>
<td>25.5</td>
<td>.89</td>
<td>44.1</td>
<td>.07</td>
<td>37.8</td>
<td>.16</td>
</tr>
<tr>
<td>Admission SBP, mean (SD), mm Hg</td>
<td>166 (38)</td>
<td>174 (34)</td>
<td>.38</td>
<td>161 (28)</td>
<td>.54</td>
<td>154 (27)</td>
<td>.13</td>
</tr>
<tr>
<td>Admission DBP, mean (SD), mm Hg</td>
<td>87 (23)</td>
<td>92 (17)</td>
<td>.33</td>
<td>82 (16)</td>
<td>.28</td>
<td>79 (16)</td>
<td>.08</td>
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<td>Smoking history, %</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Past</td>
<td>28.0</td>
<td>29.4</td>
<td>.90</td>
<td>27.2</td>
<td>.93</td>
<td>35.6</td>
<td>.43</td>
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<tr>
<td>Current</td>
<td>16.0</td>
<td>23.5</td>
<td>.45</td>
<td>33.7</td>
<td>.09</td>
<td>21.9</td>
<td>.49</td>
</tr>
<tr>
<td>Cardiovascular history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>4.0</td>
<td>2.0</td>
<td>.60</td>
<td>8.6</td>
<td>.44</td>
<td>13.0</td>
<td>.18</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12.0</td>
<td>11.8</td>
<td>.98</td>
<td>10.8</td>
<td>.86</td>
<td>19.8</td>
<td>.34</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>12.0</td>
<td>3.9</td>
<td>.18</td>
<td>8.6</td>
<td>.60</td>
<td>16.1</td>
<td>.59</td>
</tr>
<tr>
<td>Atrial fibrillation on ECG</td>
<td>23.8</td>
<td>12.2</td>
<td>.29</td>
<td>2.3</td>
<td>&lt;.001</td>
<td>20.5</td>
<td>.71</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8.3</td>
<td>7.8</td>
<td>.94</td>
<td>8.6</td>
<td>.97</td>
<td>12.0</td>
<td>.59</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>28.0</td>
<td>23.5</td>
<td>.67</td>
<td>20.4</td>
<td>.42</td>
<td>18.3</td>
<td>.22</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>4.0</td>
<td>11.8</td>
<td>.27</td>
<td>8.6</td>
<td>.44</td>
<td>16.4</td>
<td>.10</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>16.0</td>
<td>35.3</td>
<td>.08</td>
<td>21.5</td>
<td>.54</td>
<td>26.5</td>
<td>.24</td>
</tr>
<tr>
<td>Dementia</td>
<td>29.2</td>
<td>7.8</td>
<td>.01</td>
<td>2.2</td>
<td>&lt;.001</td>
<td>5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>12.5</td>
<td>15.7</td>
<td>.72</td>
<td>7.5</td>
<td>.44</td>
<td>10.6</td>
<td>.77</td>
</tr>
<tr>
<td>NIHSS score, mean (SD)</td>
<td>5.5 (5.8)</td>
<td>5.6 (5.7)</td>
<td>.94</td>
<td>2.6 (2.4)</td>
<td>.07</td>
<td>3.3 (4.0)</td>
<td>.16</td>
</tr>
<tr>
<td>Antiplatelet drug therapy, %</td>
<td>20.8</td>
<td>24.0</td>
<td>.76</td>
<td>42.9</td>
<td>.05</td>
<td>44.1</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; ECG, echocardiography; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TIA, transient ischemic attack.

The P values are for comparison with lobar ICH.

### Table 2. Association Between Lobar ICH and Retinal Microvascular Signs Compared With Deep ICH, Lacunar Infarction, and Nonlacunar Cerebral Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Focal Arteriolar Narrowing</th>
<th>Arteriovenous Nicking</th>
<th>Enhanced Arteriolar Light Reflex</th>
<th>Any Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, No. (%)</td>
<td>OR (95% CI)</td>
<td>Patients, No. (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>15 (31.9)</td>
<td>1 [Reference]</td>
<td>19 (40.4)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>3 (12.0)</td>
<td>0.22 (0.04-0.96)</td>
<td>9 (36.0)</td>
<td>0.73 (0.24-2.29)</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>18 (19.8)</td>
<td>1 [Reference]</td>
<td>20 (22.5)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>3 (12.0)</td>
<td>0.34 (1.0-1.5)</td>
<td>9 (36.0)</td>
<td>2.0 (0.7-5.8)</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarctiona</td>
<td>59 (13.2)</td>
<td>1 [Reference]</td>
<td>94 (21.2)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>3 (12.0)</td>
<td>0.9 (0.2-3.1)</td>
<td>9 (36.0)</td>
<td>2.0 (0.8-4.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio.

a Including diabetes and nondiabetes.

b Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes, and cigarette smoking.
Cotton-Wool Spots

In the general, nondiabetic older population, retinopathy lesions have been reported to be associated with clinical stroke, subclinical cerebral infarction, white matter lesions, cerebral atrophy, and cognitive decline. Retinopathy lesions, such as microaneurysms and hemorrhages, have been linked to disruption of the blood-retina barrier leading to neuronal and glial damage. Cotton-wool spots are signs of ischemic infarction in the retinal nerve fiber layer.

The present study did not find a difference in the frequency of retinopathy lesions between lobar and deep ICH but rather found a difference between lobar ICH and ischemic stroke (lacunar and nonlacunar cerebral infarction). This may be due to small numbers and, thus, lack of power. However, the finding that focal arteriolar narrowing was significantly less frequent in lobar ICH compared with deep ICH lends additional support to the hypothesis that a different vasculopathy may occur in lobar ICH. This is also in keeping with current knowledge that hypertension is a major risk factor for deep ICH but not for lobar ICH. In population-based studies, focal arteriolar narrowing was associated with acute hypertension and current elevated blood pressure levels. Focal arteriolar narrowing is proposed to occur when blood pressure rises above the upper limit of autoregulation, ranging from 130 to 160 mm Hg.

The present study also demonstrated that dementia was more common in patients with lobar ICH (29.2%) than in those with deep ICH (7.8%) or lacunar (2.2%) or nonlacunar cerebral infarction (5.4%) infarction (Table 1). This finding is consistent with findings from other studies and supports the hypothesis that some lobar ICH cases may be due to amyloid angiopathy caused by neuron-derived β-amyloid infiltration into the vessel wall, as seen in Alzheimer disease. In the Atherosclerosis Risk in Communities Study population (8374 participants aged 51-70 years), participants with retinopathy lesions had poorer cognitive function across 3 neuropsychological tests. However, the Atherosclerosis Risk in Communities Study did not demonstrate any association of retinal arteriolar wall signs with poorer cognitive function. One proposed mechanism for the association of retinopathy lesions with lobar ICH and dementia may involve diffuse degeneration of the endothelial wall with β-amyloid infiltration, leading to rupture or breakdown of the blood-brain barrier, and manifest in parallel with the breakdown of the blood-retina barrier indicated by retinopathy lesions.

The strengths of the present study include its prospective recruitment of a relatively large sample of patients, including all ages (aged 19-94 years) and a wide spectrum of stroke severity, standardized masked evaluation of retinal photographs by graders, and the use of validated diagnostic criteria for stroke subtypes by stroke physicians. There are 4 important limitations of this study. First, the few patients with lobar ICH (n=25) may not be a representative sample for lobar ICH cases and could have limited the study power to detect weak associations of lobar ICH with retinal arteriolar wall signs. The high prevalence of atrial fibrillation in patients with lobar ICH and the low National Institutes of Health Stroke Scale scores in the overall study sample indicate selection bias. This was unavoidable in this study owing to the requirement to obtain high-quality retinal images, for which a precondition for recruitment was that the patients could tolerate 15 to 20 minutes in a sitting position for the photography to be performed. Second, the brain CTs were assessed without masking to a patient’s hypertension status, and this may have affected hemorrhage location detection and, hence, introduced nondifferential misclassification, particularly for large hemorrhages. However, because focal arteriolar narrowing was significantly less frequent in lobar compared with deep ICH (focal arteriolar narrowing and deep ICH are known to be related to hypertension), such misclassification, if any, may be minimal. Third, some lobar ICH cases may have been misdiagnosed as cases that were early, severe hemorrhagic transformation of nonlacunar cerebral infarction. Spontaneous hemorrhagic transformation of nonlacunar cerebral infarction occurs in up to 15% of ischemic strokes within the first few days of the events, and the possibility of misclassification with ICH is greatest in patients with minor stroke undergoing brain CT 24 hours or longer after the stroke event. Supporting this possibility is the high frequency of atrial fibrillation in patients with lobar ICH (24%), higher than any other acute stroke subgroup but similar to the frequency observed in nonlacunar cerebral infarction (21%), a condition com-

### Table 3. Association Between Lobar ICH and Retinopathy Lesion Types Compared With Deep ICH, Lacunar Infarction, and Nonlacunar Cerebral Infarction in Patients Without Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Retinopathy (No Diabetes)</th>
<th>Microaneurysms or Hemorrhages</th>
<th>Cotton-Wool Spots</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, No. (%) OR (95% CI)</td>
<td>Patients, No. (%) OR (95% CI)</td>
<td>Patients, No. (%) OR (95% CI)</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>16 (39.0) 1 [Reference]</td>
<td>15 (36.6) 1 [Reference]</td>
<td>5 (12.2) 1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>11 (47.8) 2.3 (0.7-7.7)</td>
<td>11 (47.8) 2.0 (0.7-8.5)</td>
<td>4 (17.4) 1.8 (0.3-10.5)</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>21 (30.4) 1 [Reference]</td>
<td>18 (26.1) 1 [Reference]</td>
<td>2 (3.0) 1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>11 (47.8) 3.5 (1.1-10.9)</td>
<td>11 (47.8) 3.5 (1.2-10.7)</td>
<td>4 (17.4) 26.1 (1.6-423.3)</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarction</td>
<td>90 (24.6) 1 [Reference]</td>
<td>80 (22.0) 1 [Reference]</td>
<td>13 (3.6) 1 [Reference]</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>11 (47.8) 3.3 (1.4-8.1)</td>
<td>11 (47.8) 3.0 (1.6-9.8)</td>
<td>4 (17.4) 5.7 (1.5-21.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio.

*Adjusted for age, sex, hypertension, hypercholesterolemia, and cigarette smoking.*
commonly caused by thromboembolism from atrial fibrillation. We did not collect data on the timing of brain CT in relation to the onset of stroke symptoms, and neither did we routinely record information on gradient-echo sequences to assess the frequency of amyloid angiopathy at the 2 Australian sites. Fourth, because this study was cross-sectional, we do not know whether retinopathy lesions predispose to lobar ICH or are secondary to lobar ICH. Longitudinal studies are needed to confirm the link between retinopathy and lobar ICH.

The Multi-Centre Retinal Stroke Study sample size was calculated primarily for comparison of retinal microvascular signs in lacunar vs nonlacunar cases, and the present findings from hemorrhagic stroke are primarily hypothesis generating. Despite the statistical power issues, the finding of an association between lobar ICH and retinopathy lesions is novel, supporting the hypothesis that lobar ICH has a different specific underlying microvascular disease associated with the breakdown of the blood-brain barrier.

In summary, in this study of patients with acute stroke, those with lobar ICH were more likely to have retinopathy signs compared with patients with either lacunar or nonlacunar cerebral infarction. Other retinal arteriolar signs were less frequent in patients with lobar ICH than in those with other stroke subtypes. This pattern of association (retinopathy associated with lobar ICH and retinal arteriolar wall signs associated with deep ICH and lacunar infarction) supports the hypothesis of a distinct vasculopathy underlying lobar ICH, possibly cerebral amyloid angiopathy, leading to disruption and breakdown of the blood-brain barrier.

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REFERENCES


