Blood–Brain Barrier Permeability and Long-Term Clinical and Imaging Outcomes in Cerebral Small Vessel Disease

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**Background and Purpose**—Increased blood–brain barrier (BBB) permeability occurs in cerebral small vessel disease. It is not known if BBB changes predate progression of small vessel disease.

**Methods**—We followed-up patients with nondisabling lacunar or cortical stroke and BBB permeability magnetic resonance imaging after their original stroke. Approximately 3 years later, we assessed functional outcome (Oxford Handicap Score, poor outcome defined as 3–6), recurrent neurological events, and white matter hyperintensity (WMH) progression on magnetic resonance imaging.

**Results**—Among 70 patients with mean age of 68 (SD±11) years, median time to clinical follow-up was 39 months (interquartile range, 30–45) and median Oxford Handicap Score was 2 (interquartile range, 1–3); poor functional outcome was associated with higher baseline WMH score (P<0.001) and increased basal ganglia BBB permeability (P=0.046). Among 48 patients with follow-up magnetic resonance imaging, WMH progression at follow-up was associated with baseline WMH (ANOVA P<0.0001) and age (ANOVA P=0.032).

**Conclusions**—Further long-term studies to evaluate the role of BBB dysfunction in progression of small vessel disease are required in studies that are large enough to account for key prognostic influences such as baseline WMH and age. (Stroke. 2013;00:000-000.)

**Key Words:** blood–brain barrier ■ lacunar stroke ■ leukoaraiosis ■ stroke

The blood–brain barrier (BBB) becomes increasingly permeable with normal advancing age, particularly in patients with vascular dementia1 and small vessel disease (SVD; Figure).2–4 Cross-sectional studies do not determine whether increased BBB permeability predate progression of SVD and therefore might be causative. We followed-up patients previously recruited in our cross-sectional study of BBB permeability changes in lacunar stroke2 to see if increased BBB permeability predate progression of SVD.

**Methods**

We originally recruited 97 previously independent patients with nondisabling ischemic stroke: half were lacunar and half were cortical (controls). We assessed stroke severity (National Institutes of Health Stroke Scale [NIHSS] score) and performed diagnostic magnetic resonance (MR) imaging (MRI), with diffusion-weighted imaging, T1, T2, fluid-attenuated inversion recovery, and T2*, to confirm stroke subtype and to quantify white matter hyperintensities (WMH). We assessed BBB permeability in basal ganglia, cortex, white matter, and lateral ventricular cerebrospinal fluid 1 to 3 months after the index stroke with sequential MR T1 imaging before and after intravenous gadolinium (described previously).2,5 The study was approved by the Lothian Research Ethics Committee (2002/W/RA/03); all participants gave written informed consent.

Approximately 3 years later, we followed-up all patients to determine functional status (Oxford Handicap Score [OHS]),6 similar to the modified Rankin Score; poor functional outcome=OHS 3–6; dead=OHS 6) and recurrent strokes, and to assess SVD progression on structural MRI. We cross-checked the history of patients with hospital records. Follow-up MRI was performed on the same 1.5-T MR scanner (22 mTm-1 maximum strength gradients GE Signa LX; Milwaukee, WI) using the same diagnostic sequences (T1, T2, fluid-attenuated inversion recovery, T2*, diffusion-weighted imaging) described previously.2 We analyzed imaging features blindly, noting new infarcts or hemorrhages, WMH (Fazekas score),7 and change in WMH (Prins score).8 The intraclass correlation coefficient for WMH rating by the neuroradiologist was 0.964. We registered follow-up to baseline scans and measured intracranial, whole brain, and WMH volumes using a validated multispectral image analysis tool.9 We masked infarcts to avoid confounding WMH volume,10 normalized brain and WMH volumes to intracranial volume, and determined WMH volume change.

We performed univariate and multivariate analysis (binary logistic regression) to identify variables associated with functional status and WMH change at follow-up adjusted for duration of follow-up. We performed univariate and multivariate linear regression to examine associations among BBB permeability at baseline, WMH progression, and functional outcome. We analyzed factors associated with WMH volume change by ANCOVA. All analyses were performed in Minitab (version 15; State College, PA) or SAS 9.1 (www.sas.com).
Results
We obtained clinical follow-up for 70 of 97 patients (78%) and MRI for 48 of 97 (49%) of the original study patients. The 70 patients with clinical follow-up did not differ from the 27 without clinical follow-up in baseline age (mean at original presentation 68±11 vs 63±12; P=not significant), median NIHSS (both 2; interquartile range [IQR], 1–3), hypertension (both 66%), or lacunar stroke (50% vs 43%). The median baseline Fazekas deep and periventricular WMH scores were each 1; periventricular and deep Fazekas scores were >2 in 20 and 9 patients, respectively.

At clinical follow-up with median of 39 months (IQR, 30–48), 25% had poor outcome (12 with OHS 3–5; 6 dead). Twenty-five had clinical or imaging evidence of recurrent neurological events (36%) as follows: 2 had clinically diagnosed recurrent stroke; 23 had new focal weakness; and 4 had new infarct on follow-up imaging. In univariate analyses, poor functional outcome was associated with increasing age, higher baseline WMH score, and basal ganglia BBB permeability, but not baseline NIHSS, hypertension, diabetes, or stroke subtype (Table). On multivariate logistic regression (adjusted for baseline age, WMH score, BBB permeability), predictors of poor outcome were baseline total WMH score (odds ratio, 4.8; IQR, 4.8–11.4; P<0.001) and basal ganglia BBB permeability (odds ratio, 2.2; IQR, 1.0–4.6; P=0.046).

Forty-eight patients had follow-up MRI at a median of 39 months (IQR, 30–45) months after index stroke; baseline age (67±10), median NIHSS (2; IQR, 2–3), proportion hypertensive (65%), lacunar index stroke (48%), and WMH score were the same for the 70 as for all with clinical follow-up. Six of 48 patients (13%) had OHS of 3 to 5. WMH score had increased in 33 of 48 and remained unchanged in 15 of 48 patients according to Prins and Fazekas scores (Figure B). On univariate analyses, baseline WMH score, but not age, time, or stroke, strongly predicted progression of WMH (odds ratio, 8.7; 95% confidence interval [CI], 2.1–25.3; P<0.001). Median WMH volume at baseline was 8.5 mL (95% CI, 5.9–15.2), at follow-up it was 12.2 mL (95% CI, 8.6–19.7), and median increase was 3.2 mL (95% CI, 1.2–7.5; P<0.0001). The strongest predictors of increasing WMH volume at follow-up were baseline WMH volume (ANCOVA P<0.0001) and age (ANCOVA P=0.032). WMH volume at follow-up increased by 1.80-times (95% CI, 1.56–2.08) per unit (mm3) of WMH volume and 1.01-times (95% CI, 1.00–1.02) per additional year of age at baseline.

Discussion
Poor functional outcome, 3 years after lacunar or mild cortical ischemic stroke, was associated with having more WMH, being older, and having increased BBB permeability in the basal ganglia. Worsening of WMH was dominated by having more WMH at baseline and older age. One-third had clinical/imaging evidence of recurrent neurological events, although only 2 had recurrent stroke formally diagnosed, consistent with recent recognition of WMH-associated subtle neurological symptoms.11 Long-term poor functional outcome and WMH progression

Figure. A 72-year-old patient with right hemisphere lacunar stroke. A, Two days after stroke magnetic resonance, diffusion-weighted imaging (DWI) shows the acute right centrum semiovale lacunar infarct, T2* shows a few microbleeds, and fluid-attenuated inversion recovery (FLAIR) shows numerous white matter hyperintensities (WMHs). Blood–brain barrier imaging 6 weeks later: FLAIR 30 minutes after intravenous gadolinium (Gd) shows gadolinium in cortical sulci and perivascular spaces (arrows). B, FLAIR and T2* images 2 years later show increased WMHs and microbleeds (baseline FLAIR and T2* shown for comparison).
were not associated with vascular risk factors, baseline NIHSS score, or stroke subtype, possibly because the study was small, NIHSS score was very mild, or because of secondary prevention, although this does not control risk factors perfectly.

WMH increased in most patients at follow-up. Similar change in WMH scores (27%–74% increase)\(^6\) or volume (1.1–2.4 mL)\(^6\) have been noted previously, but the magnitude of effect of WMH or age on WMH progression, and the association with BBB permeability, are novel.\(^7\) These data on WMH progression, particularly the 95% confidence intervals (increase over 3 years of 1.56–2.08 times per additional mm\(^3\) of baseline WMH volume and 1.00–1.02 times per additional year of age at baseline), provide useful data for sample size calculations for studies wishing to use WMH change as a surrogate outcome measure.

The study strengths include testing clinical and imaging predictors of SVD progression, use of qualitative and quantitative WMH measures, careful blinding, and validated imaging methods.\(^5,9,10\) Weaknesses include small sample size, quantitative WMH measures, careful blinding, and validated imaging predictors of SVD progression, use of qualitative and quantitative WMH measures, careful blinding, and validated imaging methods.

Future studies assessing BBB permeability in SVD should assess recurrent stroke, covert neurological symptoms, accumulating SVD features, and vascular risk factors, should track BBB permeability to new lesion formation,\(^4\) and should be powered to adjust for multiple overlapping covariates, particularly WMH load.

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### Table. Predictors of Poor Outcome (OHS 3–6) 3 Years After Lacunar or Mild Cortical Stroke

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<tr>
<th>Variable</th>
<th>Univariate</th>
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<tr>
<td></td>
<td>OR/Unit Increase</td>
<td>95% CI</td>
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<td>OR (95% CI)/ Unit Increase</td>
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<td>Age (per year)</td>
<td>1.09</td>
<td>1.03–1.17</td>
<td>0.007</td>
<td>1.37 (0.61–3.10)(^†)</td>
<td>0.40</td>
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<tr>
<td>Male</td>
<td>1.50</td>
<td>0.4–6.2</td>
<td>0.5</td>
<td>2.15 (1.01–4.57)(^*)</td>
<td>0.046</td>
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<td>Hypertension, yes or no</td>
<td>1.00</td>
<td>0.3–3.1</td>
<td>1.0</td>
<td>1.5 (0.19–11.9)(^*)</td>
<td>0.7</td>
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<td>Diabetes, yes or no</td>
<td>1.50</td>
<td>0.3–6.7</td>
<td>0.6</td>
<td>0.8 (0.6–1.1)(^*)</td>
<td>0.2</td>
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<td>Cortical vs lacunar stroke</td>
<td>1.67</td>
<td>0.55–5.05</td>
<td>0.364</td>
<td>3.3 (1.4–7.5)(^†)</td>
<td>0.005</td>
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<td>Basal ganglia permeability</td>
<td>2.10</td>
<td>1.1–4.3</td>
<td>0.027</td>
<td>3.5 (1.4–8.6)(^†)</td>
<td>0.006</td>
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<tr>
<td>White matter permeability</td>
<td>0.9</td>
<td>0.2–5.5</td>
<td>0.9</td>
<td>4.8 (2.0–11.4)(^†)</td>
<td>&lt;0.001</td>
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<td>CSF permeability</td>
<td>0.8</td>
<td>0.6–1.0</td>
<td>0.06</td>
<td>4.1 (1.6–10.3)(^†)</td>
<td>&lt;0.001</td>
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<tr>
<td>Fazekas DWMH score (0–3)</td>
<td>3.91</td>
<td>1.82–8.39</td>
<td>&lt;0.001</td>
<td>3.5 (1.4–8.6)(^†)</td>
<td>0.006</td>
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<td>Fazekas PVWMH score (0–3)</td>
<td>4.09</td>
<td>1.90–8.78</td>
<td>&lt;0.001</td>
<td>4.8 (2.0–11.4)(^†)</td>
<td>&lt;0.001</td>
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<tr>
<td>Fazekas WMH combined score (0–6)</td>
<td>4.50</td>
<td>2.0–10.0</td>
<td>&lt;0.001</td>
<td>4.1 (1.6–10.3)(^†)</td>
<td>&lt;0.001</td>
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OHS indicates Oxford Handicap Score; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; DWMH, deep white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; and WMH, white matter hyperintensity.

*Corrected for baseline WMH. †Corrected for age. ‡Per unit increase in WMH.

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### References

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