MRI Detection of New Microbleeds in Patients With Ischemic Stroke

Five-Year Cohort Follow-Up Study

Simone M. Gregoire, MD; Martin M. Brown, FRCP; Constantinos Kallis, PhD; H. Rolf Jäger, FRCR; Tarek A. Yousry, FRCR; David J. Werring, PhD

Background and Purpose—Little is known about the development of cerebral microbleeds in patients with ischemic stroke. We studied the incidence of new microbleeds in a cohort of patients with ischemic stroke or transient ischemic attack screened for microbleeds at baseline.

Methods—Twenty-one surviving patients with ischemic stroke or transient ischemic attack were followed up after a mean interval of 5.5 years with repeat MRI and clinical assessment. Predictors of new microbleeds were tested in logistic regression.

Results—Of patients with microbleeds at baseline, 50% had new microbleeds at follow-up compared with 8% of those without baseline microbleeds (P = 0.047). The presence of microbleeds at baseline predicted new microbleeds (OR, 12; 95% CI, 1.02 to 141.34; P = 0.048), as did mean systolic blood pressure (OR, 1.28 per unit increase; 95% CI, 1.23 to 1.33; P < 0.001). One patient had a stroke (intracerebral hemorrhage) during follow-up.

Conclusions—Patients with ischemic stroke or transient ischemic attack are at risk of developing new microbleeds over 5.5 years, despite most surviving patients remaining clinically stable. Systolic blood pressure is the strongest predictor of microbleed development; better control of hypertension may help prevent new microbleed formation. (Stroke. 2010;41: 00-00.)

Key Words: gradient echo MRI  ■  intracerebral hemorrhage  ■  microbleeds  ■  small vessel disease  ■  stroke

Brain microbleeds seen on gradient-recalled echo T2*-weighted MRI, are increasingly detected in patients with ischemic stroke (IS).1 Microbleeds are a radiological correlate of small hemorrhages adjacent to small vessels affected by cerebral amyloid angiopathy or hypertensive arteriopathy.2 In cerebral amyloid angiopathy, microbleeds accumulate over time and predict clinical decline and larger bleeds.3,4 Little is known about microbleed development over time in patients with IS, although they may have cumulative effects on brain function, including cognition.5 We assessed new microbleeds in patients with IS or transient ischemic attack after 5.5 years of follow-up. We hypothesized that baseline microbleeds and higher blood pressure (BP) increase the risk of developing new microbleeds.

Methods

Consecutive individuals referred to the National Hospital for Neurology and Neurosurgery neurovascular clinic underwent clinical assessment and gradient-recalled echo T2*-weighted MRI. Twenty-five patients with microbleeds and a microbleed-free group (N = 30) matched for clinical and radiological characteristics were selected as described previously.5 Patients with confirmed IS or transient ischemic attack (N = 48) were invited for repeat MRI and clinical assessment. All baseline and follow-up MRIs were carried out on a GE Medical Genesis Signa 1.5-T system using a standardized protocol. Images were assessed by S.M.G. blinded to clinical details using validated rating scales for white matter changes6 and microbleeds.7 Statistical analysis was performed using SPSS Version 16.0 and Stata Version 10.0. The study was approved by our research ethics committee. All participants gave written informed consent.

Results

Of the original cohort (N = 48; N = 21 with microbleeds; N = 27 microbleed-free) 11 patients (23%, N = 7 with microbleeds [33%]; N = 4 microbleed-free [15%]; P = 0.164) died between original study enrollment and follow-up. Of the remaining 37 patients, a final cohort of 21 patients (64%, N = 8 with, N = 13 without microbleeds) underwent repeat MRI and clinical assessment (Table 1). The mean interval between assessments was 5.6 years (SD = 0.44).

At baseline, 8 patients had a total of 62 microhemorrhages (87% lobar, median 4.0, range 1 to 36; Table 2). At

Received September 21, 2009; accepted October 1, 2009.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.568469
follow-up, 5 patients (23%) had developed 56 new microbleeds (all lobar). Among patients with microbleeds at baseline, 4 of 8 (50%) developed new microbleeds compared with one of 13 (8%) microbleed-free patients ($P=0.047$). Examples of new microbleeds are shown in the Figure. The number of new microbleeds in patients with baseline microbleeds was higher than in patients without (54 [range per patient 0 to 34, median 1] versus 2 [range per patient 0 to 2, median 0], $P=0.025$). Microbleed presence at baseline predicted new microbleeds (OR, 12; 95% CI, 1.02 to 141.34; $P=0.048$); microbleed number was weakly predictive (OR, 1.51; 95% CI, 0.99 to 2.30; $P=0.055$). Mean baseline systolic BP predicted new microbleeds (OR, 1.28 per unit increase; 95% CI, 1.23 to 1.33; $P<0.001$) even after adjustment for baseline microbleed presence ($OR, 1.18; 1.01 to 1.38; P=0.002$). All patients who developed new microbleeds had baseline systolic BP >150 mm Hg. Mean systolic BP at follow-up was higher in patients with new microbleeds compared with those without (163 ± 20 mm Hg versus 141 ± 16 mm Hg, $P=0.020$). We found no association between antplatelet use, presence or number of lacunar infarcts, and new microbleeds.

The only vascular events were one intracerebral hemorrhage not at a microbleed site (microbleed group) and one nonfatal myocardial infarction (microbleed-free group).

**Discussion**

In this study, 50% of surviving patients with microbleeds at baseline developed new microbleeds over 5.6 years compared with only 8% of matched microbleed-free patients. The presence of microbleeds at baseline predicted new microbleed development. No similar data are available in IS cohorts, but in patients with cerebral amyloid angiopathy, the development of microbleeds was related to baseline microbleed number* and white matter changes.* Hypertension is an established risk factor for microbleeds in cross-sectional studies,* but we are not aware of longitudinal data on whether hypertension increases the risk of developing new microbleeds. We found that baseline systolic BP predicted the development of new microbleeds and was above 150 mm Hg. Mean systolic BP at follow-up was higher in patients with new microbleeds compared with those without (163 ± 20 mm Hg versus 141 ± 16 mm Hg, $P=0.020$).

**Table 2. No. of Microbleeds at Baseline and Follow-Up and Associated Clinical Events (Patients With ≥1 Microbleed at Baseline, Follow-Up, or Both)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Frontal</th>
<th>Parieto-occipital</th>
<th>Temporal</th>
<th>Basal Ganglia</th>
<th>Infratentorial</th>
<th>Total</th>
<th>Any Clinical Event During Follow-Up</th>
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<td>9 (+9)</td>
<td>1 (+1)</td>
<td>1 (+6)</td>
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<td>1</td>
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<td>0</td>
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</tr>
<tr>
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<td>3 (-3)</td>
<td>1 (+1)</td>
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</tr>
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<td>20 (+2)</td>
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<td>9 (+7)</td>
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<td>0</td>
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<td>8</td>
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<td>1 (+1)</td>
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<td>0</td>
</tr>
<tr>
<td>9*</td>
<td>0 (+1)</td>
<td>0</td>
<td>1 (+1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Nonbolded columns are values at baseline. Bolded columns are follow-up.

(+) indicates no. of additional microbleeds at follow-up compared with baseline for the same region of the brain.

(–) indicates no. of microbleeds less at follow-up compared with baseline for the same region of the brain.

*Patient without microbleeds at baseline.

†One parieto-occipital microbleed could not be seen on follow-up images because of artefacts in that region.
likely because we did not find a significant number of “disappearing” microbleeds at follow-up.

Cerebral microbleeds may be useful for objectively monitoring the progression of small vessel pathology in patients with IS in observational or therapeutic studies. Larger prospective studies are needed to determine whether specific treatments (eg, aggressive hypertension treatment) can reduce microbleed formation and how microbleed accumulation relates to long-term clinical outcomes.

**Acknowledgments**

We are thankful to Helen Green, Susan Wakeling, and Adrienne Wallis of the Department of Radiology for their help with retrieving the MRIs.

The imaging in this study was conducted at the Lysholm Department of Neuroradiology of the National Hospital for Neurology and Neurosurgery and Department of Imaging at University College Hospitals (UCH).

**Sources of Funding**

S.M.G. was supported by a grant from The Stroke Association. D.J.W. is supported by a Department of Health and Higher Educational and Funding Council for England Clinical Senior Lectureship Award. M.M.B.’s Chair in Stroke Medicine is supported by The Reta Lila Weston Trust for Medical Research. This work was undertaken at UCLH/UCL who received a proportion of funding from the UK Department of Health’s National Institute for Health Research Biomedical Research Centers funding scheme (UCLH/UCL Comprehensive Biomedical Research Trust).

**Disclosures**

None.

**References**

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*Stroke*. published online November 5, 2009;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2009/11/05/STROKEAHA.109.568469.citation

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