Silent Cerebral Microbleeds on T2*-Weighted MRI
Correlation with Stroke Subtype, Stroke Recurrence, and Leukoaraiosis

Hiroyuki Kato, MD, PhD; Masahiro Izumiyama, MD, PhD; Kimiaki Izumiyama, MD, PhD; Akira Takahashi, MD, PhD; Yasuto Itoyama, MD, PhD

Background and Purpose—Gradient-echo T2*-weighted MRI is uniquely sensitive to detect silent, old hemosiderin deposits, but the clinical significance of such “microbleeds” remains to be determined. Therefore, we investigated the incidence and the number of microbleeds among different stroke subtypes and the correlation with stroke recurrence and the severity of leukoaraiosis.

Methods—This study consisted of 213 patients (73.5±9.1 years old, 104 men and 109 women), who were classified according to stroke subtypes into atherothrombotic infarction (24 patients), cardioembolic infarction (23 patients), lacunar infarction (66 patients), intracerebral hemorrhage (35 patients), and control (65 patients) groups. Gradient-echo T2*-weighted MRI was performed with a 1.5 T system, and asymptomatic microbleeds were located and counted.

Results—The incidence and the number of microbleeds were significantly greater in patients with intracerebral hemorrhage (71.4% and 9.1±13.8, respectively) and lacunar infarction (62.1% and 7.4±16.1) compared with patients with cardioembolic infarction (30.4% and 2.5±5.6), atherothrombotic infarction (20.8% and 0.63±1.53), and controls (7.7% and 0.09±0.34). There was a correlation between the number of microbleeds and the severity of periventricular hyperintensity (r=0.626, P<0.0001). There was also a correlation between the number of microbleeds and the number of intracerebral hemorrhages (r=0.689, P<0.0001) or lacunar infarctions (r=0.514, P<0.0001). The locations of microbleeds were subcortical white matter (31.8%), thalamus (24.8%), basal ganglia (19.8%), brain stem (12.0%), and cerebellum (11.7%).

Conclusions—The findings suggest that microbleeds on T2*-weighted MRI are an indicator of advanced small artery disease of the brain with an increased risk for bleeding. This result should be taken into consideration when treating patients with stroke, and further studies are required. (Stroke. 2002;33:1536-1540.)

Key Words angioathy ■ cerebral infarction ■ hemosiderin ■ intracerebral hemorrhage ■ magnetic resonance imaging

Recent studies have revealed that gradient-echo T2*-weighted MRI is extremely sensitive for detecting small areas of signal loss, which represent remnants of previous silent microbleeds.1-4 This T2* effect occurs through the local magnetic field inhomogeneities caused by hemosiderin deposit. There is pathological confirmation that the microbleeds on T2*-weighted MRI represent hemosiderin deposits.5,6 The deposits may be a result of minor blood leakage through damaged blood vessels in addition to frank minor hemorrhage. Whatever the source, they may remain detectable for years. The microbleeds are barely detectable with T2-weighted spin-echo MRI and are not visualized with other conventional scans. Of particular interest is that the microbleeds are frequently detected in patients with cerebral infarction2,4 as well as in patients with intracerebral hemorrhage4,7,8 and even in a small number of healthy individuals without stroke episodes.1,9

Recognizing bleeding-prone microangiopathy in stroke patients is of extreme clinical significance when treating hypertensive patients with or without episodes of intracerebral hemorrhage. Furthermore, the risk of intracerebral hemorrhage after prophylactic treatment with oral anticoagulants is larger in patients with ischemic stroke than in patients with myocardial infarction, atrial fibrillation, or peripheral arterial disease.9 However, the diagnostic and prognostic significance of the microbleeds on T2*-weighted MRI is still debated and remains to be determined. Therefore, to further clarify the significance of microbleeds in stroke patients, we compared the incidence and the number of microbleeds among different stroke subtypes and examined the association with the recurrence of ischemic and hemorrhagic stroke and the severity of white matter disease (leukoaraiosis).

Subjects and Methods
We routinely examined our stroke patients with T2*-weighted MRI, in addition to conventional MRI scans, during a 1-year period from May 2000 to April 2001 in a community-based hospital. The stroke
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patients undertook the MRI study because of acute stroke, recurrent stroke, or follow-up at chronic stages, and included both inpatients and outpatients. Two experienced neurologists (M.I., K.I.) studied the clinical history and neurological examination. MRI reports were made by one of them. The third, consulting neurologist (H.K.) reviewed the MRI records and recruited stroke patients consecutively. Then he reviewed the medical records and the MR images and made an additional neurological examination when necessary.

MRI was performed on a 1.5 T superconducting magnet system (Siemens Magnetom Symphony), and the whole brain was scanned with a 5-mm slice thickness of 5 mm and a 1.5-mm interslice gap, producing 19 axial images. The imaging protocol consisted of T2*-weighted gradient echo (repetition time [TR]/echo time [TE]=800/26 ms, flip angle 30°), T1-weighted spin echo (TR/TE=530/15 ms), T2-weighted fast-spin echo (TR/TE=5000/120 ms), fluid-attenuated inversion recovery (FLAIR) (TR/TE=9000/105 ms, inversion time 2500 ms) and diffusion-weighted echo planar (TR/TE=5000/135 ms) imaging series, and intracranial and extracranial MR angiography.

Stroke subtypes were classified by the use of the criteria of the National Institute of Neurological Disorders and Stroke (10) into (1) atherothrombotic infarction (24 patients, male [M]/female [F]=15/9), (2) cardioembolic infarction (23 patients, M/F=13/10), (3) lacunar infarction (66 patients, M/F=37/29; 22 patients had 1 to 2 infarcts, 21 had 3 to 4 infarcts, and 23 had >5 infarcts), and (4) intracerebral hemorrhage (35 patients, M/F=15/20; 21 patients had 1 hemorrhage, 10 had 2 hemorrhages, and 4 had 3 hemorrhages). Stroke of undetermined cause and infarction of mixed categories were excluded from this study. Patients with intracerebral hemorrhage were classified regardless of the presence or absence of concomitant small infarctions on MRI. Consecutive patients who undertook MRI for the scrutiny of headache or dizziness without neurological deficits and abnormal MRI findings and were older than 60 years to match ages, served as controls (65 patients, M/F=24/41). Thus, this study consisted of a total of 213 patients (M/F=104/109).

Microbleeds were defined as small, silent foci of signal loss on T2*-weighted MRI other than the principal lesion(s) responsible for stroke episodes and were located and counted through the entire brain. Symmetric signal loss in the globus pallidum, most likely calcification, void artifact of the pial blood vessels, and intracerebral lesions with a hemorrhagic component were ruled out. Periventricular hyperintensities (PVHs) on T2-weighted images (leukoaraiosis) were classified into 4 grades using a scoring system (11) in which grade 0=no white matter lesions except for small triangular foci around the frontal horns, grade 1=PVHs surrounding both anterior and posterior horns and/or discrete patchy white matter lesions, grade 2=extensive patchy white matter lesions and their early confluent stages, and grade 3=PVHs reaching confluence completely surrounding the lateral ventricle. Lacunar infarction was defined as a small deep lesion (usually <15 mm in diameter) with high signal intensity on T2-weighted images, low signal intensity on T1-weighted, and FLAIR images with perilesional halo on FLAIR images, ruling out enlarged perivascular spaces and patchy leukoaraiosis.

All the data were expressed as mean values±SD. Statistical analysis was performed with the ANOVA followed by the Bonferroni/Dunn test for parametric analysis, and the Kruskal-Wallis test followed by the Mann-Whitney U test with Bonferroni correction for nonparametric analysis. Correlation study was performed with the Spearman rank correlation test. P<0.05 was considered statistically significant.

Results

The background of the patients is summarized in Table 1. There were no statistical differences in age or male/female ratio among the groups. Hypertension was more frequently seen in the lacunar infarction and intracerebral hemorrhage groups than in the control group (Table 1). Atrial fibrillation was observed in all the patients of the cardioembolic group but was rare in other groups. Diabetes mellitus was uniformly distributed among the groups.

The incidence and the number of microbleeds are summarized in Table 2. One or two microbleeds were observed in 5 (7.7%) of 65 control subjects. Microbleeds were observed in all stroke subtypes, and the incidence was particularly high in intracerebral hemorrhage (71.4%, P<0.001) and lacunar infarction (62.1%, P<0.001). The incidence in cardioembolic infarction (30.4%, P=0.0264) was also higher than that of controls, but the incidence in atherothrombotic infarction (20.8%) was not statistically different from controls. The numbers of microbleeds in intracerebral hemorrhage (9.1±13.8 [mean±SD], P=0.0001) and lacunar infarction (7.4±16.1, P=0.0001) were significantly greater than that of controls (0.09±0.34); but those in cardioembolic infarction (2.5±5.6) and atherothrombotic infarction (0.63±1.53) were not statistically different from controls. Representative MR images are shown in Figure 1.

All the stroke subgroups, particularly lacunar infarction and intracerebral hemorrhage, exhibited more severe grades of PVH than the control group (Table 2). There was a significant correlation between the severity of PVH and the number of microbleeds when the 213 patients were examined all together (r=0.626, P<0.0001; Figure 2). Among patients with intracerebral hemorrhage, there was a significant correlation between the number of hemorrhages and the number of microbleeds (r=0.689, P<0.0001) or the grades of PVH (r=0.429, P=0.0125; Figure 3). Among the patients with lacunar infarction, there was also a significant correlation between the number of infarcts and the number of microbleeds.

### Table 1. Background of the Patients

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Patients (M/F), n</th>
<th>Age, y</th>
<th>HT, %</th>
<th>AF, %</th>
<th>DM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>24 (15/9)</td>
<td>73.6±10.2</td>
<td>45.8</td>
<td>4.2</td>
<td>12.5</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>23 (13/10)</td>
<td>77.4±6.2</td>
<td>39.1</td>
<td>100*</td>
<td>4.3</td>
</tr>
<tr>
<td>Lacunar</td>
<td>66 (37/29)</td>
<td>74.2±9.3</td>
<td>71.2*</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>35 (15/20)</td>
<td>72.3±10.6</td>
<td>62.9*</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Control</td>
<td>65 (24/41)</td>
<td>72.2±8.2</td>
<td>30.8</td>
<td>3.1</td>
<td>6.2</td>
</tr>
</tbody>
</table>

HT indicates hypertension; AF, atrial fibrillation; and DM, diabetes mellitus. Values are mean±SD. *P<0.01 vs control.

### Table 2. Prevalence of Silent Microbleeds on T2*-Weighted MRI in Different Subtypes of Stroke

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Microbleeds</th>
<th>n</th>
<th>Range</th>
<th>PVH Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>20.8</td>
<td>0.63±1.53</td>
<td>0–6</td>
<td>1.3±0.90**</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>30.4*</td>
<td>2.5±5.6</td>
<td>0–21</td>
<td>1.3±0.82**</td>
</tr>
<tr>
<td>Lacunar</td>
<td>62.1**</td>
<td>7.4±16.1**</td>
<td>0–119</td>
<td>1.7±0.99**</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>71.4**</td>
<td>9.1±13.8**</td>
<td>0–61</td>
<td>1.6±0.98**</td>
</tr>
<tr>
<td>Control</td>
<td>7.7</td>
<td>0.09±0.34</td>
<td>0–2</td>
<td>0.62±0.68</td>
</tr>
</tbody>
</table>

Values are mean±SD. PVHs are graded 0 (normal) through 3 (severe). *P<0.05, **P<0.01 vs control.
bleeds ($r=0.514$, $P<0.0001$) or the grades of PVH ($r=0.301$, $P=0.0154$; Figure 4).

The locations of microbleeds analyzed from 31 patients who had more than 10 microbleeds (a total of 743) were subcortical white matter (31.8%), thalamus (24.8%), basal ganglia (19.8%), brain stem (predominantly in the pons, 12.0%), and cerebellum (mostly in the dentate nucleus, 11.7%).

Discussion

Although an interest in ischemic and hemorrhagic stroke categories has been reported in the literature, this is the first study to examine the incidence and the number of microbleeds according to 4 subtypes of stroke. The findings of the present study were summarized as follows. (1) The microbleeds were most frequently seen in patients with intracerebral hemorrhage and lacunar infarction, among the various stroke subtypes. (2) The number of microbleeds correlated with the severity of leukoaraiosis. (3) There was a correlation between the number of microbleeds and the number of intracerebral hemorrhages or lacunar infarctions.

Since intracerebral hemorrhage and lacunar infarction have been thought to occur as a result of small artery disease of the brain, the findings of this study suggest a strong connection between microbleeds and small artery disease. The pathology of small artery disease typically exhibits lipohyalinosis of the arterioles associated with lacunar infarcts and white matter lesions (leukoaraiosis). Hypertension is the major cause of the lipohyalinosis and microaneurysms, which may cause intracerebral hemorrhage as well. Earlier studies have reported the coexistence of intracerebral hemorrhage, lacunar infarction, and leukoaraiosis in hypertensive patients. The present study also showed that hypertension was frequent in intracerebral hemorrhage and lacunar infarction. Therefore, the presence of multiple microbleeds suggests that the microangiopathy has reached an advanced stage, in which the blood vessels are prone to bleeding.

Another explanation may be cerebral amyloid angiopathy, which is also a small artery disease in the nonhypertensive state.
elderly, presenting lobar hemorrhage with the coexistence of lacunar infarcts and white matter lesions.16,17 Our patients were old enough to consider amyloid angiopathy in some patients with intracerebral hemorrhage. Patients with cerebral amyloid angiopathy also exhibit microbleeds on T2*-weighted MRI, and the detection of microbleeds may be a potential tool to assess the disease progression.18 In any event, multiple microbleeds on T2*-weighted MRI may be a risk factor for intracerebral hemorrhage and its recurrence. This assumption may be supported by the findings on the location and frequency of microbleeds obtained in this study, which were quite similar to those of symptomatic hypertensive intracerebral hemorrhage.

The incidence and the number of microbleeds were relatively low, although higher than in controls, in patients with cardioembolic infarction and atherothrombotic infarction. Only the incidence in cardioembolic infarction was statistically significant. This result seems reasonable because strokes of these subtypes (cardioembolic and atherothrombotic) do not occur on the basis of small artery disease. However, moderate leukoaraiosis as well as the greater number of microbleeds, although statistically not significant, suggests that there was coexistence of small artery disease of a limited extent in the patients of these subgroups. Furthermore, microbleeds are found even in healthy elderly subjects. Roob et al9 found 1 to 5 microbleeds in 18 (6.4%) of 280 healthy individuals (mean age 60 years) in Austria, and Kinoshita et al detected 1 to 3 microbleeds in 3 (5%) of 66 normal individuals (mean age 62.1 years) in Japan. In our study, we detected 1 to 2 microbleeds in 5 (7.7%) of 65 control subjects. The incidence of microbleeds in control individuals is similar among these studies, although our rate is slightly higher. The reason may be that (1) the age of our control subjects was higher (mean age 72.2 years), and (2) our control subjects were not completely healthy, undertaking MRI for the scrutiny of headache or dizziness, which could be caused by undetectable cerebrovascular disorders. In the series by Roob et al,9 hypertension and aging were considered to be the variables related to the microbleed detection, suggesting a contribution of mild small artery disease even in healthy elderly subjects.

Of interest is the clinical significance of microbleeds in patients with ischemic stroke. Cerebral hemorrhage is one of the major complications of anticoagulation and antiplatelet therapies instituted for prevention of ischemic stroke. In the recent Stroke Prevention in Reversible Ischemia Trial (SPRINT), the efficacy of secondary prevention after cerebral ischemia was compared between aspirin (30 mg daily) and oral anticoagulation (international normalized ratio [INR], 3.0 to 4.5), and the trial was stopped because of high bleeding complications after anticoagulation.19 The anticoagulant-related risk factors for cerebral bleeding were leukoaraiosis and age older than 65 years, in addition to the intensity of anticoagulation.20 Another trial of warfarin therapy for secondary prevention of ischemic stroke in elderly patients with atrial fibrillation conducted in Japan resulted in higher bleeding complications in the conventional INR (2.2 to 3.5) group compared with the low INR (1.5 to 2.1) group.21 Thus, anticoagulation in patients with small-vessel cerebrovascular disease carries a higher risk of intracerebral hemorrhage. This is in remarkable contrast to the results of primary stroke prevention in atrial fibrillation, which resulted in negligible anticoagulant-induced bleeding complications.20,22 Aspirin therapy also increases the risk of hemorrhagic stroke, although the overall benefit may outweigh its adverse effects.23 Therefore, it is of particular importance to extract such patients who are prone to bleeding complications after anticoagulant or antiplatelet therapy. The detection of microbleeds on T2*-weighted MRI might be a direct indicator for such a risk.

A question arises whether patients who have multiple lacunar infarction and a number of microbleeds cause intracerebral hemorrhage in the long term. Whether the patients with cardioembolic infarction and atherothrombotic infarction who exhibited microbleeds have a higher risk of cerebral hemorrhage is another question to be answered. Of interest is a disease termed cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a hereditary small-vessel disease.24 Clinically, CADASIL is characterized by recurrent cerebral infarcts and dementia, but intracerebral hemorrhage is rare. Patients with CADASIL are prone to microbleeds, but the patients taking antiplatelet drugs did not show higher incidence of microbleeds.25 Therefore, whether our hypothesis is correct should be tested in subsequent prospective studies.

In conclusion, the clinical significance of the detection of microbleeds is 2-fold. First, patients with multiple microbleeds may be at an increased risk for intracerebral hemorrhage or rebleeding. Second, we may be able to identify patients who suffer from bleeding complications after long-term anticoagulation or antiplatelet therapy for secondary prevention of ischemic stroke. Therefore, we suggest that stroke patients should be routinely examined with T2*-weighted MRI. This information may help in evaluating the presence of advanced, bleeding-prone microangiopathy that may be critically related to prognosis and the selection of therapy.

References
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