Cerebral Microbleeds as a Risk Factor for Subsequent Intracerebral Hemorrhages Among Patients With Acute Ischemic Stroke

Yu Hua Fan, MD; Lei Zhang, MD; Wynnie W.M. Lam, MD; Vincent C.T. Mok, MD; Ka Sing Wong, MD

Background and Purpose—Cerebral microbleeds (MBs) detected by gradient-echo MRI are considered evidence of advanced microangiopathy with potential for further bleeding. The goal of this study was to determine whether the presence of MBs is a risk factor for subsequent intracerebral hemorrhage among patients with acute ischemic stroke.

Methods—We prospectively examined patients hospitalized with acute cerebral infarction with gradient-echo T2*-weighted MRI for the presence of MBs. We recorded demographics, medical history, and stroke severity. Patients were then followed up for the development of stroke, other vascular events, and death.

Results—One hundred twenty-one consecutive patients with a mean age of 67.96 ± 10.97 years were recruited. MBs were present in 43 patients (35.5%). During follow-up of 27.15 ± 11.68 months, 16 patients had recurrent stroke. There was no difference between patients with or without MB for the development of ischemic stroke (5 and 6 respectively, P = 0.841). However, 4 patients (9.3%) with MBs and 1 patient (1.3%) without an MB had intracerebral hemorrhage during follow-up (P = 0.053). Of the 5 patients who developed subsequent intracerebral hemorrhages, 3 were treated with aspirin and 2 with anticoagulation. Two of the intracerebral hemorrhages occurred in the site where asymptomatic MBs were found at baseline.

Conclusions—MBs appear to be a risk factor for subsequent intracerebral hemorrhage among patients with ischemic stroke in this small cohort of Chinese stroke patients. A large cohort study is required to confirm this observation. (Stroke. 2003;34:2459-2462.)

Key Words: intracerebral hemorrhage ■ magnetic resonance imaging, gradient-echo

Cerebral microbleeds (MBs) detected by gradient-echo MRI are considered evidence of advanced microangiopathy with potential for further bleeding.1,2 MBs have been found not only in patients with intracerebral hemorrhages1-3,5 but also in patients with ischemic stroke.4 The frequency and incidence of MBs in ischemic stroke have been reported in several previous studies,6,7 but the long-term clinical significance of MBs in these patients remains unknown. Recent studies suggested that the presence of MBs in patients with acute ischemic stroke was a risk factor for cerebral bleeding after thrombolysis and hemorrhagic transformation in the acute stage.8,9 Our goal was to determine whether the presence of MBs is a risk factor for subsequent intracerebral hemorrhage among patients with ischemic stroke.

Methods

We recruited consecutive acute stroke patients admitted through the accident and emergency department of a general regional hospital. All patients in our study were hospitalized because of acute cerebral infarction within 7 days of symptom onset. In addition to routine investigations, all recruited patients underwent MRI examination with gradient-echo T2*-weighted MRI, in addition to conventional T1- and T2-weighted MRI scans. Patients with intracranial hemorrhage, those in unstable condition, and those who could not have an MRI examination for various reasons (such as claustrophobia and pacemaker insertion) were excluded. We recorded the demographics, medical history, and stroke severity in detail. Blood pressure was measured after admission to the stroke unit or a medical ward. The clinical management of the patients during hospitalization and after hospital discharge was left to the attending physicians, who were not involved in this study.

Patients were followed up by telephone interview for the development of stroke, including ischemic or hemorrhagic; other vascular events such as ischemic heart disease; and death. We interviewed the patients with further vascular events or their relatives and examined the discharge summary, results of investigations such as CT scan, and hospital records. We defined stroke as acute onset of focal neurological deficit lasting > 24 hours presumably of vascular origin after investigation to exclude other causes. The diagnosis of intracerebral hemorrhage required the presence of hyperintense signals on the CT scan on admission. All case ascertainment was done without knowledge of the MRI results.

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2459
MRI Studies
MRI was performed on a 1.5-T scanner (Gyroscan ACS NT, Philips Medical Systems) using a standard head coil. The whole brain was scanned with a 5-mm slice thickness and 0.5-mm interslice gap. A gradient-echo sequence optimized to maximize the susceptibility effect of hemosiderin was used for axial examination of the brain (repetition time, 300 ms; echo time, 30 ms; flip angle, 30°; field of view, 230 mm; matrix, 256×256; 70% rectangular field of view; acquisitions, 2), in addition to the standard spin-echo T1- and T2-weighted sequences.

MBs were defined as small, silent foci of signal loss or hypointensity on the gradient recall-echo images.10 Symmetric signal loss or hypointensity in the globus pallidum, most likely calcification, was ruled out. Flow void artifacts of the pial blood vessel based on morphology and correlation with T1- and T2-weighted and CT images were not regarded as MBs.

Statistical Analysis
All data were analyzed with SPSS 10.0 for Windows. Dichotomous variable group differences between patients with and without MBs were analyzed with Pearson’s χ² test. For data having an expected count of >5, Pearson’s χ² test was used. For those data with cells containing expected values of <5, Fisher’s exact test was used. Group differences for continuous variables between patients with and without MBs were analyzed with Student’s t test. We used P<0.05 as the level of significance.

Results
We examined 147 acute stroke patients with MRI from January 1999 to November 2000. Twenty-six patients were excluded for the following reasons: intracerebral hemorrhages (20 patients), intracranial tumors (4 patients), and epilepsy (2 patients). Thus, a total of 121 consecutive patients with acute cerebral infarction were studied with gradient-echo T2* MRI sequence. The characteristics of the patients are summarized in Table 1. Forty-three patients (35.5%) were found to have MBs. An example of MBs is shown in Figure 1. MBs usually involved multiple locations. MBs were found in the lobes in 31 patients, in the basal ganglia in 24 patients, in the thalamus in 17 patients, in the pons in 14 patients, and in the cerebellum in 11 patients. The mean diastolic blood pressure was higher in the patients with MBs than those without (90.33 and 84.65 mm Hg, respectively; P=0.042).

History of previous intracerebral hemorrhages was more common in the group with MBs than those without (5 of 43 and 0 of 78, respectively; P=0.005). The mean follow-up time was 27.51±11.68 months. Four patients were lost to follow-up, 2 in each group of patients. During follow-up, 16 patients developed stroke, including 11 ischemic strokes and 5 intracerebral hemorrhages. Five patients developed ischemic heart diseases, and 14 patients died. There were no differences between patients with or without MBs for the development of ischemic stroke (5 and 6, respectively; P=0.747), ischemic heart diseases (1 and 4; P=0.654), and death (5 and 9; P=1.0). However, 4 patients (9.3%) with MBs

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of 121 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=121)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Systolic BP, mean±SD, mm Hg</td>
</tr>
<tr>
<td>Diastolic BP, mean±SD, mm Hg</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Drinking, n (%)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

*Patients with MBs have higher blood pressure and higher frequency of previous stroke and intracerebral hemorrhages than patients without MBs.
†Fisher’s exact test.

Figure 1. Gradient-echo MRI (A) showed an asymptomatic MB in the occipital lobe (arrow). Same patient developed a symptomatic intracerebral hematoma at the same site as shown in the CT scan (B).
and 1 patient (1.3%) without an MB had intracerebral hemorrhage during follow-up \( (P=0.053) \). None of the 5 patients who had subsequent intracerebral hemorrhage had a history of symptomatic intracranial hemorrhage. In the 4 patients with MBs who had subsequent intracerebral hemorrhages, 2 of the intracerebral hemorrhages occurred at the site where asymptomatic MBs were found at baseline (Figures 1 and 2).

Long-term antithrombotic therapy, including antiplatelet and anticoagulation, was used in 32 patients (74%) with MBs and in 72 patients (92%) without MBs \( (P=0.007) \). Antiplatelet drugs were used in 28 patients (65%) with MBs and in 69 patients (89%) without MBs. Four patients (9.3%) with MBs and 3 patients (4.4%) without MBs received anticoagulation therapy. Eleven patients (25.6%) with MBs and 6 patients (7.7%) without MBs received no antiplatelet or anticoagulation therapy, mainly because of contraindication such as gastrointestinal bleeding, allergy, and history of symptomatic intracerebral hemorrhage. Of the 4 patients with MBs who developed subsequent intracerebral hemorrhages, 3 were treated with aspirin and 1 with anticoagulation. The 1 patient without a MB who developed subsequent intracerebral hemorrhage was treated with anticoagulation.

**Discussion**

The development of MRI sequences that are highly sensitive to the detection of blood-breakdown products has led to a growing number of studies characterizing the occurrence of MBs in various populations. These studies have demonstrated that MRI evidence of MBs is seen in 33% to 80% of patients with primary intracerebral hemorrhages, in 21% to 26% of patients with ischemic stroke, and in 5% to 6% of asymptomatic or healthy elderly individuals.\(^1\)\(^-\)\(^6\),\(^11\)

Earlier studies have reported the coexistence of MBs and intracerebral hemorrhage, lacunar infarcts, and leukoariosis in hypertensive patients. The number of MBs correlated with the severity of white matter changes and the number of lacunar infarcts. Because lacunar infarcts and white matter changes have been thought to occur as a result of small-artery disease of the brain, these studies suggested a strong connection between MBs and small-artery disease. Moreover, the presence of multiple MBs may suggest that the microangiopathy has reached an advanced stage in which the blood vessels are prone to bleeding.\(^1\)\(^,\)^\(^2\)\(^,\)^\(^6\)\(^,\)^\(^7\) Therefore, several researchers proposed the hypothesis that the presence of MBs may indicate higher risk of ICH, both spontaneously and after antithrombotic therapy.\(^2\)\(^,\)^\(^11\)\(^,\)^\(^12\) Several studies have suggested that the presence of MBs could be considered a risk factor for cerebral bleeding in patients with ischemic stroke.\(^8\)\(^,\)^\(^9\)\(^,\)^\(^11\) Nighoghossian et al\(^8\) found that old MBs were involved in the group of known risk factors favoring cerebral bleeding within 1 week after brain ischemia. Kidwell et al\(^8\) suggested that old silent MBs might be a marker of increased
risk of hemorrhagic transformation after thrombolysis. In patients with aspirin-associated intracerebral hemorrhages, old silent MBs were found to be more frequent and more extensive than in the control patients. Thus, MBs may be also a risk factor for aspirin-associated intracerebral hemorrhages. However, these studies are all cross-sectional, case-control, or short-term cohort study. To the best of our knowledge, there is no long-term study of the risk of subsequent ICH among patients with MBs. In our study, 121 patients were followed up for an average of 27.15 months. Four patients with MBs and 1 without an MB developed intracerebral hemorrhages during follow-up. Our data suggest that MBs might be an important risk factor for subsequent intracerebral hemorrhage, although the differences were just borderline significant. For the other types of vascular events, including cerebral infarction and ischemic heart disease, there was no difference between patients with and without MBs. Furthermore, the hematomas in 2 patients were found at the site of the old MBs. Kidwell et al also found that in patients undergoing thrombolysis, old silent MBs were visualized at the site of the subsequent hemorrhage. Thus, MBs may be a risk factor for subsequent intracerebral hemorrhage but not for ischemic events among patients with ischemic stroke. Nevertheless, an MB is not always visible at the site of subsequent hemorrhage, as shown in the other 3 patients.

In our patients, antithrombotic therapy was used less frequently in the patients with MBs than in those without MBs. The reason might be that there were more previous intracerebral hemorrhages in patients with MBs than those without MBs. All 5 patients who developed subsequent intracerebral hemorrhages received antithrombotic therapy. As a whole, because of the high risk of ICH in patients with MBs, whether antithrombotic treatments are beneficial in this specific group of patients remains unclear. A prospective study to assess the risk-to-benefit ratio of antithrombotic treatment in this group of patients is needed. The problem of intracerebral hemorrhage is especially relevant for Chinese patients, who have a higher frequency of intracerebral hemorrhage than whites.

Several considerations must be given to our study. First, although consecutively collected, the hospital-based stroke cases may not be representative of the community-based population. Furthermore, the relatively small number of patients in this study, especially the low frequency of ICH, may affect the robustness of the results. Third, there was an imbalance regarding blood pressure and prior hemorrhagic stroke between those with and those without MB. It is likely that the imbalance was related to the somewhat higher blood pressure among patients with MBs. With such a small number of intracranial hemorrhages as a dependent variable, logistic regression analysis to separate the confounders may not be possible. Thus, because of these limitations, further studies with larger numbers of patients are needed to confirm our conclusion.

Acknowledgment
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References

TABLE 2. Vascular Events During Follow-Up of 121 Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=121, n (%))</th>
<th>MBs(+) (n=43, n (%))</th>
<th>MBs(−) (n=78, n (%))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke</td>
<td>16 (13.2)</td>
<td>9 (20.9)</td>
<td>7 (9.0)</td>
<td>0.157</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>5 (4.13)</td>
<td>4 (9.3)</td>
<td>1 (1.28)</td>
<td>0.053*</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>11 (9.01)</td>
<td>5 (11.6)</td>
<td>6 (7.7)</td>
<td>0.747*</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5 (4.13)</td>
<td>1 (2.33)</td>
<td>4 (5.13)</td>
<td>0.654*</td>
</tr>
<tr>
<td>Death</td>
<td>14 (11.6)</td>
<td>5 (11.6)</td>
<td>9 (11.5)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.
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