Multiple Cerebral Microbleeds in Hyperacute Ischemic Stroke: Impact on Prevalence and Severity of Early Hemorrhagic Transformation After Thrombolytic Treatment

OBJECTIVE. The purpose of our study was to assess whether cerebral microbleeds are related to early hemorrhagic transformation after thrombolytic therapy for hyperacute ischemic stroke.

MATERIALS AND METHODS. The cases of 279 patients with suspected ischemic stroke who underwent MRI including T2*-weighted images were retrospectively evaluated. The inclusion criteria were as follows: imaging performed within 6 hr after symptom onset, presence of territorial infarct of anterior circulation, no history of intracerebral hemorrhage, thrombolytic treatment, and available follow-up MR images. Microbleeds were classified according to number as follows: absent (grade 1, 0 bleeds), mild (grade 2, 1–2 bleeds), moderate (grade 3, 3–10 bleeds), and severe (grade 4, > 10 bleeds). The prevalence and severity of early hemorrhagic transformation after thrombolytic treatment were assessed on follow-up images.

RESULTS. Among 279 patients, 65 patients (37 men, 28 women; mean age, 67 years) met the inclusion criteria. Microbleeds were found in 25 patients. Early hemorrhagic transformation occurred in nine of 40 patients without microbleeds (grade 1) and in eight of 25 patients with microbleeds: two of 12 patients with grade 2, three of eight patients with grade 3, and three of five patients with grade 4 microbleeds. The presence of symptomatic hemorrhage did not correlate with the number of microbleeds. Results of multivariate logistic regression analysis showed that the presence of microbleeds was not associated with hemorrhagic transformation after thrombolytic treatment.

CONCLUSION. Small and large numbers of microbleeds are not independent risk factors for early hemorrhagic transformation and symptomatic hemorrhage after thrombolytic therapy for hyperacute ischemic stroke. Additional studies with large groups of subjects are needed to confirm our conclusion.

Keywords: CNS, ischemic stroke, MRI, MR technique, neuroimaging, thrombolysis

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Materials and Methods

Patients

From March 2001 through October 2004, the cases of 279 patients with suspected hyperacute ischemic stroke who underwent an acute stroke MRI protocol were retrospectively evaluated. The inclusion criteria were clear symptom onset within 6 hr, presence of territorial infarct of anterior circulation regardless of severity, no history of ICH, thrombolytic treatment immediately after initial MRI study, and availability of follow-up MR images obtained 1–3 days after thrombolytic treatment. Stroke onset was defined as the last time the patient was known to be free of deficit. All patients were examined immediately by an attending physician specializing in stroke and by a radiologist using an acute stroke MRI protocol. Clinical assessment included measurement of National Institutes of Health Stroke Scale (NIHSS) score before treatment, 24 hr after treatment, and on day 7 after treatment. We conducted a
Fig. 1—Classification of microbleeds by number.
A, Grade 1, 0 microbleeds in 53-year-old man.
B, Grade 2, 1–2 microbleeds in 62-year-old woman. Normal finding of bilateral low signal intensity (arrows) is present in globus pallidus.
C, Grade 3, 3–10 microbleeds in 59-year-old woman.
D, Grade 4, more than 10 microbleeds in 67-year-old man.
Fig. 2—82-year-old woman with sudden altered mentality 4 hr before examination. A and B, T2*-weighted MR images of two different locations (A, level of frontal horn of lateral ventricle; B, level of anterior commissure) obtained before thrombolysis show grade 4 microbleeds. C and D, Follow-up T2*-weighted MR image (C) and diffusion-weighted image (D) 2 days after intraarterial thrombolytic treatment show no evidence of hemorrhagic transformation in final infarcted area.
detailed computer-assisted review of medical records that included a search for risk factors for ischemic stroke.

**MRI Protocol and Imaging Analysis**

At our institution, an acute stroke MRI protocol has been used routinely since March 2001 to evaluate the condition of patients with suspected ischemic stroke. T2*-weighted gradient-echo imaging has been part of the protocol since September

Fig. 3—61-year-old man with altered mentality 3 hr before examination. A and B, Initial T2*-weighted MR images of two different locations (A, level of frontal operculum; B, level of temporal lobe just below A) show grade 4 microbleeds. C, Follow-up T2*-weighted MR image 1 day after intraarterial thrombolytic treatment shows hemorrhagic transformation in right anterior cerebral artery territory.
of excitations, 1; acquisition time, 3 min 56 sec); matrix, 512 × 512; field of view, 250 mm; number of axial slices, 10; thickness, 5 mm; intersection gap, 2 mm; field of view, 250 mm; acquisition time, 2 min 22 sec); diffusion-weighted imaging (DWI), echo-planar image (EPI), single-shot (number of excitations, 2; field of view, 250 mm; acquisition time, 1 min 32 sec); FLAIR image (TR/TE, 10,002/97; number of axial slices, 20; thickness, 5 mm; intersection gap, 2 mm; matrix, 512 × 512; field of view, 250 mm; number of excitations, 1; acquisition time, 3 min 56 sec); FLAIR image (TR/TE, 6,000/135; flip angle, 90°; number of axial slices, 10; thickness, 5 mm; intersection gap, 2 mm; matrix, 512 × 512; field of view, 250 mm; number of excitations, 1; acquisition time, 1 min 22 sec); 3D contrast-enhanced MR angiogram (TR/TE, 4/1; flip angle, 20°; matrix, 512 × 512; field of view, 250 mm; number of excitations, 1; acquisition time, 5 min 45 sec); FLAIR image (TR/TE, 6,000/135; flip angle, 90°; number of axial slices, 10; thickness, 5 mm; intersection gap, 2 mm; matrix, 512 × 512; field of view, 250 mm; number of excitations, 1; acquisition time, 1 min 22 sec); 3D contrast-enhanced MR angiogram (TR/TE, 6/1; flip angle, 20°; matrix, 512 × 512; field of view, 250 mm; number of excitations, 1; acquisition time, 46 sec). The scanning time for the entire MRI protocol was 11 min 56 sec. This MRI protocol was performed between 8:00 am and 10:00 pm. Between 10:00 pm and 8:00 am, patients with suspected acute ischemic stroke were examined with a CT protocol that included unenhanced CT, perfusion CT, and CT angiography.

Microbleeds were defined as homogeneous rounded areas of signal loss less than 5 mm in diameter without surrounding edema on T2*-weighted images. Symmetric signal loss in the globus pallidus, flow voids, and large ICH foci were excluded. The number and location of microbleeds were assessed on initial T2*-weighted gradient-echo images. Microbleeds were classified as absent (grade 1), mild (grade 2; total number of microbleeds, 1–2), moderate (grade 3; total number of microbleeds, 3–10), and severe (grade 4; total number of microbleeds, >10) according to a grading scale described previously [5] (Fig. 1). Follow-up T2- and T2*-weighted images were obtained 1–3 days after thrombolysis. The hemorrhage was graded as symptomatic hemorrhage if any neurologic deterioration had occurred within the first 48 hr that could be attributed to the presence of such hemorrhage. According to the number and location of microbleeds, we evaluated the prevalence and severity of subsequent hemorrhagic transformation on follow-up MR images. Imaging findings were reviewed by two neuroradiologists without knowledge of clinical information or treatment assignment. Their consensus determined the MRI findings.

**Thrombolytic Treatment**

The MRI-based exclusion criteria before thrombolytic treatment at our institution were as follows: definite parenchymal hemorrhage or hemorrhagic infarct, typical lacunar infarct, no evidence of steno-occlusive lesion on MR angiography, no perfusion-diffusion mismatch, and obvious diffusion abnormality of more than one half of the middle cerebral artery territory. The selected patients were treated for ischemia of the anterior circulation. Twelve of the patients received IV tissue plasminogen activator (tPA) within 3 hr of symptom onset, and 53 patients received intraarterial urokinase within 6 hr of symptom onset. Thrombolysis with IV tPA was administered at a dose of 0.9 mg/kg. Intraarterial urokinase (up to a maximum of 1 million U) was infused at the site of the clot at angiography until recanalization was achieved or the maximum dose was reached.

**Statistical Analysis**

Multivariate logistic regression analysis was used to assess the relation between microbleeds and risk factors for stroke, including age, sex, hypertension, diabetes, hyperlipidemia, smoking, and atrial fibrillation, and the relation between subsequent hemorrhagic transformation and age, sex, baseline NIH-SS score, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, and microbleeds. Fisher’s exact test was used to assess the relation between number of microbleeds and severity of hemorrhagic transformation.

**Results**

Among 279 patients with acute stroke who underwent the MRI protocol at our institution, 65 patients (37 men, 28 women; mean age, 67 years) met the inclusion criteria. Microbleeds were found in 25 patients on initial T2*-weighted images. The rates of early hemorrhagic transformation (Figs. 2 and 3) and symptomatic hemorrhage are shown in Table 1. There was no statistically significant difference between the intraarterial and IV thrombolysis groups in occurrence of hemorrhagic transformation. Multivariate logistic regression analysis showed that hypertension and age were significantly associated with microbleeds (p < 0.05) (Table 2) and that neither a small (≤10) nor large (>10) number of microbleeds was a risk factor for early hemorrhagic transformation. The analysis also showed that baseline NIH-SS score was a significant and independent risk factor for hemorrhagic transformation after thrombolytic treatment of patients with hyperacute ischemic stroke (p < 0.05) (Table 3). Occurrence of symptomatic hemorrhage did not correlate with number of microbleeds.

**Discussion**

Because of the narrow window for management of hyperacute ischemic stroke, only scarce data exist about MRI findings in patients with hyperacute ischemic stroke [6, 7]. Results of several studies of stroke MRI within the first 6 to 12 hr have shown the feasibility and practicality of this method in the setting of acute stroke and thrombolytic therapy [8, 9]. The stroke MRI protocol was useful for defining the ideal candidate for thrombolysis [10], and early recanalization achieved by thrombolysis resulted in significantly smaller infarcts and a better clinical outcome [7, 11, 12]. Results of previous studies also have shown that the performance of MRI before initiation of thrombolytic therapy did not lead to unacceptable delay of therapy and that pretreatment MRI studies may be useful in the selection of candidates for thrombolysis beyond a 3-hr window [9, 13].

**Table 1: Relation Between Number of Cerebral Microbleeds and Frequency and Severity of Early Subsequent Hemorrhagic Transformation After Thrombolysis in Hyperacute Ischemic Stroke**

<table>
<thead>
<tr>
<th>Type of Hemorrhage</th>
<th>Grade 1 (n = 40)</th>
<th>Grade 2 (n = 12)</th>
<th>Grade 3 (n = 6)</th>
<th>Grade 4 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic transformation</td>
<td>9 (23)</td>
<td>2 (17)</td>
<td>3 (38)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Symptomatic hemorrhage</td>
<td>2 (5)</td>
<td>1 (8)</td>
<td>1 (13)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Note—Data are no. (%) of microbleeds.
Hemorrhagic transformation is the most serious and feared complication of acute ischemic stroke. Approximately 20–40% of all stroke patients experience hemorrhagic transformation within the first week after symptom onset [1]. In the National Institute of Neurologic Disorders and Stroke trial of IV tPA, symptomatic hemorrhage occurred at a rate of 6% in patients treated with thrombolysis. In the Prolyse in Acute Cerebral Thromboembolism II trial, major symptomatic hemorrhage occurred in 10% of patients treated with intraarterial prourokinase [15, 16]. In both of these trials, a history of intracranial hemorrhage was an exclusion criterion for thrombolytic treatment. However, the subjects in these trials were screened with head CT only. Because pretreatment MRI was not performed, information regarding the frequency and location of microbleeds among patients enrolled in these pivotal trials was not available.

Microbleeds are frequently detected in patients with cerebral infarction [17] and in patients with ICH [4]. The clinical significance of microbleeds in primary ICH has been reported. Roor et al. [18] proposed that there is a tendency toward a regional association between microbleed location and the site of symptomatic hematoma. However, the risk of ICH after tPA administration in acute ischemic stroke patients with old microbleeds seen on MR images remains a matter of debate. Although it has been suggested that old, clinically silent microbleeds visualized with T2*-weighted MRI may be a marker of increased risk of ICH in patients receiving thrombolytic therapy for acute ischemic stroke [2, 19], data regarding the risk of ICH after thrombolysis in patients with microbleeds are limited because MRI is not commonly performed before thrombolysis. At our institution, evidence of microbleeds on initial acute stroke MR images was not an absolute contraindication to thrombolytic treatment. Previous reports have shown that number of microbleeds correlates with severity of white matter changes and number of lacunar infarcts, which are believed to occur as a result of small-artery disease of the brain [20]. The presence of large numbers of microbleeds may suggest that the microangiopathy has reached an advanced stage in which the blood vessels are prone to bleeding [21, 22]. Results of a 2004 study suggested that stroke patients with a small number of microbleeds on pretreatment MR images can be treated safely with thrombolysis [23]. We believed that large numbers of microbleeds suggesting diffuse bleeding-prone vasculopathy might be associated with hemorrhagic transformation after thrombolysis in hyperacute ischemic stroke. In our study, however, there was no statistically significant difference in occurrence of hemorrhagic transformation between patients with a large number of microbleeds and those without microbleeds. We believe that this result may be due to the small sample size of patients with a large number of microbleeds receiving thrombolytic treatment. In regard to location of microbleeds and hemorrhagic transformation, Kidwell et al. [2] reported hemorrhagic transformation at the site of an old microbleed remote from the acute ischemic field in a patient receiving thrombolytic therapy. In the National Institute of Neurologic Disorders and Stroke IV tPA trial, 20% of all symptomatic hemorrhages occurred outside of the vascular distribution of the ischemic stroke [24]. In our series no patient who received tPA had ICH at the site of an old microbleed. Moreover, we found no ICH outside the acute ischemic or infarcted areas in any patient. This finding emphasizes the crucial role of ischemic injury in the occurrence of thrombolysis-induced ICH. Some authors consider ischemic injury to the microvasculature central to risk of parenchymal hemorrhage after thrombolytic therapy for stroke [25]. Hamann et al. [26] found a correlation between development of hemorrhagic transformation and loss of basal laminar architecture after experimental middle cerebral artery occlusion. Other experimental data have shown increased permeability of the blood–brain barrier related to early ischemia–induced damage to the microvasculature; this increased permeability enhances hemorrhagic transformation after tPA therapy [27].

Limitations of this study were the relatively small populations of patients with a large number (> 10) of microbleeds and of hyperacute ischemic stroke patients treated with thrombolysis. With such a small number of cases as a dependent variable, logistic regression analysis is the only method to separate the confounders may not be possible. Because of these limitations, further studies with larger numbers of patients are needed to confirm our conclusion.

Multiple microbleeds detected with pretreatment T2*-weighted MRI are not an independent risk factor for early hemorrhagic transformation and symptomatic hemorrhage after thrombolytic treatment. Studies are needed with a large number of patients who have a large number of microbleeds, suggesting the presence of advanced small-
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artery vasculopathy with a bleeding-prone state.

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