Magnetic Resonance Imaging Detection of Microbleeds Before Thrombolysis
An Emerging Application

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Background—Hemorrhagic transformation (HT) is a major complication of thrombolytic treatment for acute ischemic stroke. Although a history of prior intracerebral hemorrhage diagnosed by head CT is a contraindication to thrombolysis, there are no guidelines or data regarding evidence of prior asymptomatic microbleeds visualized with T2*-weighted magnetic resonance imaging (MRI).

Methods—Pretreatment T2*-weighted MRI sequences were retrospectively analyzed in all patients receiving intra-arterial thrombolytic therapy and undergoing a pretreatment MRI at our institution. The frequency and location of prior microbleeds was determined and compared with the frequency and location of secondary HT after therapy.

Results—Five of 41 patients undergoing MRI before receiving intra-arterial thrombolytic therapy demonstrated evidence of prior microbleeds on the pretreatment MRI studies. Major symptomatic hemorrhage occurred in 1 of 5 patients with microbleeds compared with 4 of 36 patients without. Only 1 patient in the entire 41-patient cohort experienced any HT outside the acute ischemic field. In this patient, the symptomatic hemorrhage occurred directly at the site of a prior microbleed, contralateral to the acute ischemic event.

Conclusions—Old silent microbleeds, visualized with T2*-weighted MRI sequences, may be a marker of increased risk of HT in patients receiving thrombolytic therapy for acute ischemic stroke. Pretreatment screening of thrombolytic candidates with these MRI sequences may be useful in the future to identify these patients. (Stroke. 2002;33:95-98.)

Key Words: hemorrhage ■ magnetic resonance imaging ■ stroke, acute ■ stroke, ischemic ■ thrombolysis
Characteristics of 5 Patients With Microbleeds

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>No. of Microbleeds</th>
<th>Location of Microbleed(s)</th>
<th>Location of Acute Infarction</th>
<th>HT at Site of Microbleed(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90/F</td>
<td>1</td>
<td>R temporal lobe</td>
<td>L parietal and temporal lobes</td>
<td>No</td>
</tr>
<tr>
<td>78/F</td>
<td>1</td>
<td>R thalamus</td>
<td>R frontal lobe</td>
<td>No</td>
</tr>
<tr>
<td>74/F</td>
<td>12</td>
<td>Bilateral thalami and cerebellum</td>
<td>R frontal lobe</td>
<td>No</td>
</tr>
<tr>
<td>74/M</td>
<td>1</td>
<td>R frontal lobe</td>
<td>L frontal, parietal, and temporal lobes</td>
<td>No</td>
</tr>
<tr>
<td>96/F</td>
<td>2</td>
<td>L periventricular white matter and cerebellum</td>
<td>R frontal, parietal, and temporal lobes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

R, right; and L, left.

(deoxyhemoglobin, ferritin, and hemosiderin), which lead to a loss of signal on T2*-weighted sequences. We present a case of HT at the site of an old microbleed that was remote from the acute ischemic field in a patient receiving thrombolytic therapy, and analyze the prevalence of microbleeds in our series of patients undergoing pretreatment MR imaging and receiving intra-arterial thrombolysis.

Methods

Patients

The current analysis was performed as part of an ongoing prospective study of MRI changes in patients receiving intra-arterial thrombolytic therapy for acute ischemic stroke. Patients from this larger study were included in the current analysis if (1) they presented with symptoms of acute cerebral ischemia with a large-vessel occlusion demonstrated at angiography; (2) were treated with either combined intravenous/intra-arterial tissue plasminogen activator (tPA) within 3 hours of symptom onset, or with only intra-arterial thrombolytics within 6 hours from symptom onset for patients with anterior circulation ischemia or 12 hours from symptom onset for patients with posterior circulation ischemia; and (3) had a pretreatment EPI-SWI or GRE sequence performed.

Thrombolytic Procedure

Combined intravenous/intra-arterial tPA was administered at a dose of 0.6 mg/kg IV, 10% bolus over 1 minute, remaining dose infused over 30 minutes, followed by a 10 mg/h intra-arterial infusion until recanalization was achieved or a maximum intra-arterial dose of 22 mg was reached.7 Pure intra-arterial thrombolysis was administered with either urokinase (up to a maximum of 1 000 000 U) or tPA (generally up to a maximum dose of 22 mg) infused at the site of the clot at the time of angiography until recanalization was achieved or until maximum dose was reached. Gentle mechanical clot disruption was also allowed at the time of the intra-arterial thrombolysis infusion.

Clinical assessment included NIH Stroke Scale (NIHSS) score measurements before treatment, at 24 hours, and at day 7.8

Imaging Methods

Head CT imaging was performed before thrombolysis, immediately after thrombolysis, and at 24 hours. Scans were obtained with 5-mm contiguous slices, no gap (General Electric High Speed Advantage scanner). MRIs were performed on a 1.5-T Siemens Visions scanner (Siemens Medical Solutions). GRE sequences were obtained using 7-mm slice thickness, no gap, field of view 220 mm, TR 800 ms, TE 15 ms, and flip angle 30°. EPI-SWI sequences were obtained using 5- to 7-mm slice thickness, no gap, field of view 240 mm, TR 2000 ms, and TE 60 ms.

The pretreatment EPI-SWI sequences and GRE sequences were reviewed for evidence of old clinically silent microbleeds. Microbleeds were defined as punctate, homogenous, rounded, hypointense lesions <0.5 cm in size visualized on GRE or SWI sequences. Scan interpretation was performed independently by 2 separate readers (a neuroradiologist [J.P.V.] and a neurologist [C.S.K.]) blinded to later scan results and clinical outcome. On the 1 patient in whom there was a discrepancy, the 2 raters reviewed the scans together and came to a consensus view.

Regions of HT were identified on head CTs performed immediately after treatment and at 24 hours. HT was categorized as occurring within the acute ischemic field if it was in the same vascular territory of the primary target vessel or outside the acute ischemic field if remote from the territory of the primary target vessel. Symptomatic hemorrhage was defined as HT associated with a worsening of 4 or more points on the NIHSS score or a worsening of 1 or more points in the level-of-consciousness item (this was the definition of symptomatic hemorrhage used in the Prolyse in Acute Cerebral Thromboembolism [PROACT] II trial). The study was approved by the UCLA Institutional Review Board.

Statistical Methods

Dichotomous variable group differences between patients with and without old microbleeds were analyzed using the Fisher exact test. Group differences for continuous variables between patients with and without old microbleeds were analyzed using the Wilcoxon rank-sum test.

Results

A total of 41 patients were studied with GRE (7 patients) or EPI-SWI MRI (all 41 patients) sequences before receiving intra-arterial thrombolitics. Pretreatment MRIs revealed evidence of old silent microbleeds in 5 cases (12%). Of the 5 cases with microbleeds, 3 patients had evidence of only 1 microbleed, 1 patient had evidence of 2 microbleeds, and 1 patient had evidence of 12 microbleeds (Table 1). There was no difference in microbleed detection rate between GRE and SWI sequences in the 7 patients who underwent both types of scans. There was no difference in baseline characteristics between patients with old microbleeds versus those without, including age, history of hypertension, diabetes, hypercholesterolemia, tobacco use, and severity of pretreatment neurologic deficit. One patient with a prior microbleed evident on the pretreatment MRI sequences but not on the pretreatment head CT scan experienced a symptomatic hemorrhage at the site of the microbleed and remote from the acute ischemic field (see Case Report, below).

Among all 41 patients in the cohort, combined symptomatic and asymptomatic HT occurred in 15 (37%). Major symptomatic HT occurred in 5 patients (12%). HT occurred within the acute ischemic field in all patients except in the 1 case reported below. Major symptomatic hemorrhage occurred in 1 of 5 patients with prior microbleeds versus 4 of 36 patients without (P = NS). Any HT occurred in 2 of 6 patients
with prior microbleeds versus 13 of 35 without ($P=\text{NS}$). Any HT outside the acute ischemic field occurred in 1 of 5 patients with prior microbleeds versus 0 of 36 without ($P=0.12$). Any HT outside the acute ischemic field occurred in 1 of 2 patients with multiple prior microbleeds versus 0 of 39 patients with none or only 1 prior microbleed ($P=0.049$).

Intra-arterial urokinase was the thrombolytic agent in 11 patients, of whom 2 experienced any HT and 1 experienced major HT; combined intravenous/intra-arterial tPA was the thrombolytic agent in 12 patients, of whom 3 experienced any HT and 1 experienced major HT; pure intra-arterial tPA was the thrombolytic agent in 18 patients, of whom 9 experienced any HT and 3 experienced major HT.

**Case Report**

A 96-year-old left-handed female with a history of hypertension, atrial fibrillation, and remote prior occipital and cerebellar strokes presented to our institution 44 minutes after sudden onset of aphasia and left hemiparesis. Her NIHSS score on admission was 17. Baseline head CT (Figure 1a), performed 1 hour and 50 minutes after symptom onset, showed loss of gray-white differentiation and early sulcal effacement but no hypodensity in the left middle cerebral artery (MCA) territory. No region of acute or old hemorrhage was apparent on the head CT.

Pretreatment MRI, performed 1 hour and 36 minutes after symptom onset, demonstrated acute ischemic changes on diffusion-weighted imaging (DWI) (Figure 1b) in the right MCA territory. During cerebral angiography, a right M1 MCA occlusion was visualized and the patient was treated with 20 mg of tPA administered intra-arterially. Recanalization was achieved at 3 hours and 10 minutes from symptom onset. After the procedure, a repeat head CT and MRI demonstrated an evolving ischemic infarct in the right MCA territory and an acute 1-cm hematoma in the left frontal lobe (Figures 1c and 1g, respectively). The patient had persistent hemiparesis on the left and new hemiparesis on the right with altered mental status associated with an increase in her NIHSS score from 17 to 24. Over the next few days, there was no improvement in her neurologic status and she was transferred to another facility on hospital day 7.

Review of the pretreatment imaging studies revealed evidence of an old, clinically silent microbleed in the left periventricular region visualized on both GRE and SWI sequences (Figures 1c and 1d) at the site of the subsequent hemorrhage.

**Discussion**

We found that 5 of 41 patients (12%) undergoing MR imaging before receiving intra-arterial or combined intravenous/intra-arterial thrombolytics had evidence of old microbleeds on pretreatment MR studies but not head CTs. In 1 case, major symptomatic HT occurred at the site of an old microbleed, contralateral to the acute infarct field, representing the only remote hemorrhage in this cohort.

GRE MRI sequences detect the paramagnetic effect of blood-breakdown products, allowing visualization of clinically silent microbleeds that, often, cannot be detected with head CT. Fazekas et al. performed a histopathologic analysis of small regions of signal loss visualized on GRE MRI sequences and confirmed that these regions indicate previous extravasation of blood and are related to bleeding-prone microangiopathy. This study demonstrated that cerebral microbleeds represent collections of hemosiderin-laden macrophages that occur adjacent to small vessels.

These microbleeds are most commonly associated with microangiopathy due to hypertension, cerebral amyloid angiopathy, or prior ischemic injury, and are presumably due to weakening of the vessel walls. In hypertension, progressive lipohyalinosis and fibrinoid degeneration occur, often associated with microaneurysm formation. In cerebral amyloid angiopathy, progressive deposition of amyloid within the vessel wall leads to fibrinoid necrosis.

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 microbleeds in various populations. These studies have demonstrated that MRI evidence of microbleeds is seen in 38% to 66% 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. In their study of patients with a history of atherosclerosis, Kwa et al found that hemosiderin deposits visualized with MRI were significantly associated with cerebral white matter lesions.

Intracranial hemorrhage is the most serious and feared complication of both anticoagulant and, now, thrombolytic therapy administered to acute ischemic stroke patients. HT occurs at a rate of 1% per year in patients on oral anticoagulants. Prior studies have demonstrated that patients with small-vessel disease are at higher risk of HT with oral anticoagulation.

However, to our knowledge, no reported study has determined whether MRI evidence of old microbleeds, visualized with MRI sequences, is a significant marker of increased risk of hemorrhage with use of antithrombotic therapies.

In the National Institute of Neurological Disorders and Stroke (NINDS) trial of intravenous tPA, symptomatic hemorrhage occurred at a rate of 6% in treated patients, and in the PROACT II trial, major symptomatic hemorrhage occurred in 10% of patients treated with intra-arterial prourokinase. In both of these trials, previous history of intracranial hemorrhage was an exclusion criterion. However, patients were screened with head CT scans only. Because pretreatment MRIs were not performed, no information is available regarding the frequency and location of old microbleeds among patients enrolled in these pivotal trials.

In the NINDS intravenous tPA trial, 20% of all symptomatic hemorrhages occurred outside of the vascular distribution of the presenting ischemic stroke. In the large Global Utilization of Streptokinase and Tissue Plasminogen Activator for Ocluded Coronary Arteries (GUSTO-1) trial of thrombolytic therapy for the treatment of acute myocardial infarction, intracerebral hemorrhage rates ranged from 0.47% to 0.94% based on the various treatment regimens, and presumably occurred in regions not experiencing acute cerebral ischemia. It is therefore interesting to speculate that these hemorrhages may have occurred at sites of old small-vessel injury or prior microbleeds. Although the majority of cases of HT after thrombolytic therapy are likely due to disruption of the blood-brain barrier in acutely injured tissue, a significant minority, particularly those located in regions remote from the acute ischemic field, may be associated with old microbleeds.

There are several limitations to our study. We do not have pathological verification that the MRI lesions represent old blood-breakdown products. Other potential etiologies for small focal hypointensities on GRE and SWI sequences include calcifications, cavernous angiomas, and shearing injury. In addition, although all patients did have EPI-SWI studies performed, not all patients had GRE sequences, precluding a direct comparison of the 2 sequences. The small sample size may have limited our ability to find a statistically significant difference in the rate of symptomatic and asymptomatic hemorrhages in patients with and without old microbleeds. A prospective study with a larger number of patients will be required to more accurately determine the relationship between old microbleeds and HT after thrombolytic therapy. If these lesions do represent markers of bleeding-prone angiopathy and increased risk of HT after thrombolytic therapy, then MRI GRE and EPI-SWI sequences may provide a useful means of pretreatment screening.

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References

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