Frequency and Location of Microbleeds in Patients With Primary Intracerebral Hemorrhage

Gudrun Roob, MD; Anita Lechner, MD; Reinhold Schmidt, MD; Erich Flooh, MSc; Hans-Peter Hartung, MD; Franz Fazekas, MD

Background and Purpose—MRI is known to detect clinically silent microbleeds (MBs) in patients with primary intracerebral hemorrhage (pICH), but the frequency and diagnostic and clinical significance of this finding are still debated. Therefore, we investigated a consecutive series of pICH patients and analyzed the patterns of MB distribution in the context of clinical variables and location of the symptomatic hematoma.

Methods—The study population consisted of 109 patients with pICH. There were 59 women and 50 men aged 22 to 91 years (mean 64.6 years). MRI was obtained on a 1.5-T system with use of a gradient-echo T2*-weighted sequence. A cohort of 280 community-dwelling asymptomatic elderly individuals who underwent the same imaging protocol served for comparison.

Results—MBs were seen in 59 (54%) patients and ranged in number from 1 to 90 lesions (mean 14, median 6). In the majority of patients, MBs were located simultaneously in various parts of the brain, with a preference for cortical-subcortical regions (39%) and the basal ganglia/thalami (38%). There was some tendency toward a regional association between MB location and the site of the symptomatic hematoma, but we could not discern specific patterns of MB distribution. Logistic regression analysis identified MBs, periventricular hyperintensity grades, and lacunes but not risk factors as independent variables contributing to a correct classification of pICH and control individuals.

Conclusions—MBs can be detected in more than half of the patients with pICH and appear to be quite general markers of various types of bleeding-prone microangiopathy. (Stroke. 2000;31:2665-2669.)

Key Words: etiology ■ hemosiderin ■ intracerebral hemorrhage ■ magnetic resonance imaging ■ microcirculation

Magnetic resonance imaging (MRI) has the potential to reveal residues of intracerebral bleeding throughout life because of its high sensitivity for iron-containing compounds. At the site of intracerebral hemorrhage (ICH), hemosiderin remains stored in macrophages and leads to focal dephasing of the MRI signal. This causes areas of past bleeding to appear dark on T2-weighted images. Gradient-echo techniques with high sensitivity for differences in magnetic susceptibility enhance these effects of hemosiderin. Previous studies have called attention to the frequent observation of small areas of signal loss in patients with primary ICH (pICH), which were suggested to represent residues of earlier clinically silent microbleeds (MBs). Subsequently, this assumption was supported by correlative histopathologic data, which confirmed perivascular hemosiderin deposition around angiopathic arterioles as the predominant cause for such a finding. The association with small-vessel diseases explains that MBs were also reported in patients with cerebral ischemic damage and even in a small proportion of asymptomatic elderly individuals. However, the clinical and diagnostic significance of this finding is not yet fully understood.

In patients with pICH, the reported frequency of earlier MBs ranges from 17% to 80%. These large differences are probably a consequence of small patient groups examined, differences in patient selection, and the inconsistent use of either conventional spin-echo or gradient-echo MR techniques or both. Although hypertensive microangiopathy appears to be their prevailing cause, MBs have also been strongly associated with the presence of cerebral amyloid angiopathy. In this context, a cortical-subcortical appearance of MBs has been suggested to be an almost pathognomonic finding. On the basis of this assumption, it could be speculated that certain patterns in the distribution of MBs may serve to indicate different types of microangiopathy. The amount of predictive information contained in the detection of MBs and possible concerns regarding the use of anticoagulants in such patients have also been debated.

We attempted to provide further information on these aspects by performing a detailed analysis of the frequency and distribution patterns of MBs in the context of clinical variables and hematoma location in a large consecutive series of patients with pICH. We also performed a comparison with
findings in a community-dwelling cohort of asymptomatic elderly individuals, and a logistic regression analysis was carried out to define the contribution of MBs to the correct identification of pICH patients.

Subjects and Methods

The study population consisted of 109 patients with a final diagnosis of pICH from consecutive referrals to MRI by the neurology department of a university hospital. This included all patients admitted with intracerebral bleeding who were able to undergo such an examination. pICH was defined as spontaneous nontraumatic intracerebral bleeding without evidence of any kind of vascular malformation or a brain tumor as the source of the hematoma. The patients’ ages ranged from 22 to 91 years (mean 64.9 years); there were 59 women and 50 men. Other demographic and clinical variables are shown in Table 1. Hypertension was diagnosed in the case of a past history of increased blood pressure or if the blood pressure recordings continued to repeatedly exceed 160/95 mm Hg past the second week after the ICH. Diabetes mellitus was defined by fasting blood sugar >140 mg% or previous treatment. Twenty-four patients had suffered from a previous stroke, which was reportedly hemorrhagic in 9 patients.

MRI was performed on a 1.5-T superconducting magnet. The imaging protocol consisted of conventional spin-echo mixed intensity and T2-weighted (repetition time [TR]/echo time [TE] 2300 to 2600/20 to 90 ms) or fast spin-echo T2-weighted (TR 29 900 ms, TE 120 ms) and cerebrospinal fluid–suppressed T2-weighted (fluid-attenuated inversion recovery; TE 130 ms, TR 6000 ms, and inversion time 1900 ms) scans, a T1-weighted (TR/TE 600/15 ms) sequence, and a gradient-echo T2*-weighted images (TR/TE 600/16 ms, flip angle 20°) imaging series. Slice thickness was uniformly 5 mm, and the interslice gap was 10%. All scans were reviewed by an experienced investigator who recorded the size and location of the clinically symptomatic hematoma and the presence of additional parenchymal abnormalities unaware of the patients’ clinical data. Symptomatic hematomas were grouped as (1) lobar, involving the cortex and/or deep white matter regions, (2) basal ganglionic/thalamic, or (3) infratentorial, involving the brain stem and/or the cerebellum. In accordance with previous studies, MBs were defined on gradient-echo T2*-weighted images as homogeneous rounded lesions with a diameter of 2 to 5 mm, and their location and number in specific regions of the brain was recorded (Figures 1 and 2). Larger areas of signal loss were considered to represent old hematomas. Hyperintensities of the deep and subcortical white matter were specified and graded into absent, punctate, early confluent, and confluent. Periventricular hyperintensities were described as caps or lining, bands, or irregular extending into the

Table 1. Demographic, Clinical, and Morphological Variables for Patients With pICH and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>pICH (N=109)</th>
<th>Controls (N=280)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>64.9±12.3</td>
<td>59.9±6.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>50 (45.8)</td>
<td>149 (53.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>67 (61.5)</td>
<td>89 (31.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>15 (13.8)</td>
<td>13 (4.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>White matter hyperintensity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punctate</td>
<td>33 (30.3)</td>
<td>149 (53.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early confluent</td>
<td>27 (24.8)</td>
<td>28 (10)</td>
<td></td>
</tr>
<tr>
<td>Confluent</td>
<td>31 (28.4)</td>
<td>11 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Periventricular hyperintensity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caps/lining</td>
<td>54 (49.5)</td>
<td>109 (38.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bands</td>
<td>15 (13.8)</td>
<td>11 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>27 (24.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lacunae, n (%)</td>
<td>57 (52.3)</td>
<td>23 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarcts, n (%)</td>
<td>11 (10.1)</td>
<td>6 (2.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>MBs, n (%)</td>
<td>59 (54.1)</td>
<td>18 (6.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pearson $\chi^2$ test was used for frequency comparisons. *Student t test.

Figure 1. Patient (aged 78 years) with pICH in left thalamus extending into basal ganglia. a and b, Fluid-attenuated inversion recovery (TE 130 ms, TR 6000 ms, and inversion time 1900 ms) images show site of bleeding, irregular periventricular hyperintensity, and cribriform state of basal ganglia. c and d, Gradient-echo T2*-weighted images (TR/TE 600/16 ms, flip angle 20°) reveal multiple foci of signal loss suggestive of old MBs within the basal ganglia and less numerous foci in cortical-subcortical regions (arrows).

Figure 2. Patient (aged 63 years) with subacute bleeding in right parietal lobe. a, T1-weighted (TR/TE 600/15 ms) scan is shown. b and c, Gradient-echo T2*-weighted images (TR/TE 600/16 ms, flip angle 20°) show multiple cortical-subcortical foci of signal loss around the hematoma (arrows). d, Two MBs are also seen in basal ganglia (arrows).
Areas of ischemic parenchymal destruction, i.e., lesions exhibiting signal isointensity with cerebrospinal fluid in their centers, were diagnosed as lacunes (<10 mm in diameter) or infarcts.

A cohort of 280 asymptomatic elderly participants of the Austrian Stroke Prevention Study (ASPS) who underwent the same imaging protocol while our study group of pICH patients was being selected served as a comparison. The rationale and design of the ASPS and the MRI findings of this cohort have been published previously.7,11

In short, MRI examinations with a gradient-echo T2*-weighted sequence revealed that MBs may be found even in neurologically normal elderly individuals. The clinical and imaging data of the ASPS cohort that are relevant to the present study are summarized in Table 1.

Statistical analysis was performed with the Statistical Package of Social Sciences (SPSS, Inc). We used the Pearson χ² test to compare the frequency distribution of categorical variables between groups. Continuous variables were compared with the Student t test. A logistic regression analysis was used to define those demographic, clinical, and morphological variables that independently contributed to a correct classification of individuals as pICH patients or controls.

### Results

The clinically symptomatic hematoma was lobar in 43 (39%) patients, it was located in the basal ganglia/thalami in 50 (46%) patients, and it involved the brain stem/cerebellum in 14 (13%) patients. Two patients had >1 acute bleeding at different sites. MBs were seen in 59 (54%) of pICH patients, and their number ranged from 1 to 90 lesions (mean 14, median 6). Patients with MBs were significantly more often hypertensive and more frequently had a previous stroke than patients without MBs. Also, the majority of patients with MBs exhibited multiple lesions, which were noted simultaneously in various parts of the brain (Figures 1 and 2).

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### Discussion

We found evidence of old MBs in 54% of patients with pICH by using gradient-echo T2*-weighted MRI. This frequency corresponds closely to that of 57% recently reported by Tanaka et al5 in a smaller series of 30 patients. Earlier investigations that have reported a smaller rate of MBs in association with ICH have used conventional MRI sequences in all or most of their patients.2,12 Therefore, these lower numbers most likely resulted from the inferior sensitivity of conventional T2-weighted scans in the detection of small hemosiderin deposits. A much higher detection rate of MBs has recently been documented with the use of a gradient-echo technique compared with conventional T2 sequences in a direct comparison.6 Greenberg et al6 observed MBs in 80% of patients with pICH exhibiting a significantly greater mean number of MBs in the basal ganglia (3.1±5.9 versus 0.95±1.9, P<0.02) and in the cerebellum (1.0±2.1 versus 0.02±0.15, P<0.02) than did individuals with a lobar pICH (Figures 1 and 2). No significant differences between pICH subgroups were noted in regard to the presence and number of MBs in cortical-subcortical regions. We also did not find significant differences in the distribution of MBs related to the presence or absence of hypertension. Among the 15 patients with MBs and normal blood pressure, 12 (80%) showed MBs in cortical-subcortical regions, and 8 (53%) had MBs in the basal ganglia/thalami. MBs were seen in a cortical-subcortical location in 31 (70%) of 44 patients with hypertension and in the basal ganglia/thalami in 33 (75%) hypertensive patients with MBs.

Comparison of the pICH study group with the cohort of neurologically asymptomatic elderly individuals showed highly significant differences in regard to almost all clinical and morphological variables assessed (Table 1). Therefore, we used logistic regression analysis to define those variables that would best allow us to correctly separate pICH patients and control subjects. Three variables emerged that independently contributed to such classification. These variables were the presence of MBs, the grade of periventricular hyperintensity, and the number of lacunes (Table 4). No clinical or demographic variable entered this model.
their patients, but this sample was small and was composed only of patients with lobar hemorrhage.

The overall number of MBs in individual patients in our series was quite variable and ranged from 1 to 90 lesions. Most frequently, MBs were seen in cortical-subcortical regions or in the basal ganglia including the thalami. MBs in the brain stem and cerebellum were less frequent, and the white matter was relatively spared. Typically multiple MBs were found scattered throughout the brain. Therefore, a separation of patient subgroups based on a specific location of MBs was impossible, and a grading of regional preferences from the absolute number of MBs appeared problematic because of differences in the size of the regions to compare (eg, cortical-subcortical versus brain stem). Therefore, we decided to compare the distribution of MBs between patients on the basis of the site of the symptomatic hematoma. This analysis revealed some correspondence between pICH location and MB topography, as illustrated in Figure 3; ie, frequency and number of MBs in the basal ganglia/thalami and the infratentorial region were greater in patients with a pICH at these sites than in patients with a lobar hematoma. However, concerning cortical-subcortical MBs, no clear differences emerged between pICH subgroups. Thus, we were unable to confirm a specific pattern of MBs strongly suggestive of cerebral amyloid angiopathy in this unselected series. In this context, the probably rather small number of patients with cerebral amyloid angiopathy in our sample has to be considered. Moreover, histopathologic findings suggest a combination of cerebral amyloid angiopathy with hypertensive microangiopathy as the cause of a more widespread distribution of MBs in some patients. Interestingly, however, a preferential cortical-subcortical location of MBs was not even found in the normotensive pICH patients of our study population.

In line with previous studies, we found highly significant associations between the presence of MBs and other morphological signs of cerebral microangiopathy, such as lacunes and extensive periventricular and deep white matter damage, and we confirmed hypertension as the single most important clinical risk factor for the occurrence of MBs. A significantly higher frequency of a preceding stroke in patients with MBs can be viewed as further clinical evidence of a globally more pronounced vasculopathy of these patients. Comparison with a cohort of normal elderly control subjects showed the expected differences regarding a significantly higher rate of hypertension and also of diabetes mellitus in pICH patients. However, only MRI findings emerged as independent discriminating variables in a logistic regression model. These morphological variables were the presence of MBs and the grade of periventricular hyperintensity and the number of lacunes. CT studies have already associated lacunes and leukoaraiosis with a higher risk of intracerebral bleeding either spontaneously or after anticoagulant therapy. This analysis supports MBs as a further important marker of bleeding-prone small-vessel diseases. In this context, Greenberg et al have recently shown the accumulation of MBs over time on repeated MRI examination of a small group of patients with intracerebral bleeding. Large-scale prospective studies using gradient-echo T2*-weighted MRI in elderly individuals are now needed to substantiate these assumptions.

### Table 4. Logistic Regression Analysis: Significant and Independent Discriminators Between pICH Patients and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient B</th>
<th>Standard Error</th>
<th>Wald</th>
<th>P</th>
<th>Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBs</td>
<td>1.634</td>
<td>0.371</td>
<td>19.384</td>
<td>0.000</td>
<td>5.124</td>
</tr>
<tr>
<td>PVH grade</td>
<td>1.275</td>
<td>0.231</td>
<td>30.389</td>
<td>0.000</td>
<td>3.580</td>
</tr>
<tr>
<td>No. of lacunes</td>
<td>0.958</td>
<td>0.314</td>
<td>9.322</td>
<td>0.002</td>
<td>2.608</td>
</tr>
</tbody>
</table>

PVH indicates periventricular hyperintensity grade.
References


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