Clinical and Radiologic Differences Between Primary Intracerebral Hemorrhage With and Without Microbleeds on Gradient-Echo Magnetic Resonance Images

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**Background:** Microbleeds on gradient-echo magnetic resonance (MR) imaging reflect bleeding-prone microangiopathy. The microbleeds are frequently detected in patients with primary intracerebral hemorrhage (PICH). However, some patients do not have microbleeds.

**Objective:** To clarify the risk factors associated with microbleeds in PICH, thus providing insight into the pathogenesis of PICH.

**Design:** Prospective study.

**Setting:** Neurology department of a tertiary referral center.

**Patients:** A consecutive series of 107 patients with PICH.

**Interventions:** Gradient-echo MR imaging to determine distribution patterns and numbers of microbleeds.

**Main Outcome Measures:** Clinical variables and the associated MR imaging abnormalities in patients with PICH with and without microbleeds.

**Results:** Patients with PICH who had microbleeds were significantly older (65.9±10.9 years) than those without microbleeds (53.9±13.0 years; P<.001), and previous stroke, medication with antithrombotics or anticoagulants, lacunes, and leukoaraiosis were more common in patients with microbleeds. However, potential triggering events tending to raise the blood pressure were more common in cases of PICH without microbleeds (18 [56.3%] vs 10 [15.4%]). In logistic regression analysis, age (odds ratio and 95% confidence interval: 1.07, 1.01-1.14), advanced leukoaraiosis (7.79, 1.05-57.74), number of lacunes (1.66, 1.21-2.28), and potential triggering events (0.18, 0.04-0.90) were independent risk factors associated with the presence of microbleeds in patients with PICH.

**Conclusions:** Primary intracerebral hemorrhage without microbleeds was more common in younger patients with precipitating events, whereas PICH with microbleeds was more common in elderly patients with prominent ischemic change and frequent use of antithrombotics or anticoagulants. Our findings might help to determine the pathogenetic type for secondary prevention.

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**RADIENT -ECHO T2*- weighted magnetic resonance imaging (GE-MRI) sensitively detects the paramagnetic effect of blood-breakdown products and can visualize clinically silent microbleeds. This T2* effect occurs by the local magnetic field inhomogeneities caused by hemosiderin. There is pathological confirmation that microbleeds observed on GE-MRIs are hemosiderin deposits. Microbleeds are frequently detected in patients with spontaneous intracerebral hemorrhage and ischemic infarction, as well as in the asymptomatic elderly. Recently, it was documented that the presence of microbleeds on GE-MRIs could identify advanced small-artery disease having a higher tendency for intracerebral bleeding. In patients with primary intracerebral hemorrhage (PICH), the reported frequency of microbleeds on GE-MRI ranges from 17% to 80%. These microbleeds appear to be primarily a consequence of hypertensive microangiopathy or cerebral amyloid angiopathy (CAA). Some patients with PICH have microbleeds, while others do not. This radiologic difference might divide PICH into distinct pathogenetic subgroups. However, few reports have compared the clinical and radiologic patterns for PICH with or without microbleeds.

We made comparative analyses of clinical and radiologic characteristics between PICH with and without microbleeds to clarify the difference in underlying pathogenesis.
PATIENTS
A total of 187 consecutive patients who had PICH and were admitted to the Department of Neurology of our hospital from July 1, 1998, to March 1, 2002, were included in this study. Primary intracerebral hemorrhage was defined as a spontaneous intracerebral hemorrhage without secondary causes, such as vascular malformation, aneurysm, neoplasm, vasculitis, moyamoya disease, coagulation abnormalities, trauma, cerebral infection, and hemorrhagic transformation of an ischemic stroke or sinus thrombosis. Of these 187 patients, 64 were excluded from this study because of the presence of large lesions with a mass effect, previous neurosurgery, movement artifacts, or other considerations that hindered the proper evaluation of microbleeds on GE-MRI, and an additional 16 patients were excluded because of a lack of information about the risk factors or circumstances surrounding the hemorrhage. Thus, the final study population included 107 patients.

VASCULAR RISK FACTORS
The following cerebrovascular risk factors were recorded for all patients. Hypertension was considered to be present if a subject had one or more of the following conditions: (1) repeated blood pressure readings greater than 140/90 mm Hg at intervals of 1 week or more and (2) a history of hypertension and antihypertensive medication. Diabetes mellitus was diagnosed as being present if the fasting serum glucose concentration was 126 mg/dL (6.6 mmol/L) or more, or if the patient was currently undergoing treatment for this disease. Smoking history was coded as present if the subject was a current smoker or an ex-smoker who had quit smoking within 5 years of admission. Serum total cholesterol was examined by enzymatic colorimetric methods. Recent mediation with antithrombotics or anticoagulants was obtained by history. We also investigated information on history of stroke. Cardiac diseases consisted of echocardiographic or electrocardiographic evidence of atrial fibrillation, old myocardial infarction, or congestive heart failure, as determined by the criteria of the Trial of Org 10172 in Acute Stroke Treatment. In addition, data collection included circumstances of onset including the activity at the time, unusual life events (death of relatives, acute disease, emotional stress or upset), and recent alcohol abuse. Potential triggering events were defined as events or activities that may significantly affect blood pressure, eg, sexual intercourse, traumatic events, defecation or micturition, and recent alcohol abuse.

BRAIN MRI
We performed the MRI studies with a 1.5-T superconducting magnet (Signa; GE Medical Systems, Milwaukee, Wis) as described in our previous studies. The standardized MRI protocol consisted of axial T2-weighted spin-echo imaging (repetition time, 2500-4500 milliseconds; echo time, 80-112 milliseconds; flip angle, 20°; section thickness, 5 mm; and gap width, 2 mm), axial T2*-weighted GE sequences (repetition time, 200-300 milliseconds; echo time, 15 milliseconds; flip angle, 20°; field of view, 220 × 170 mm; acquisition matrix size, 256 × 192 pixels; number of signals acquired, 2; section thickness, 1.4 mm; and gap width, 0.7 mm), and axial T1-weighted spin-echo imaging (repetition time/echo time, 380-500/12-15 milliseconds; flip angle, 20°; section thickness, 5 mm; gap width, 2 mm). The GE-MRI was used to count focal areas of homogeneous round signal loss with a diameter of up to 5 mm, unless computed tomographic scanning showed that these areas were calcifications.

We divided the 107 patients into 2 groups according to whether or not they had microbleeds. T2- and T1-weighted MRIs were used to identify leukoaraisis, lacunes, hemorrhage, and infarction. Leukoaraisis was classified as being absent, punctate, or either early confluent or confluent abnormalities, with the former 2 groups referred to as no or mild leukoaraisis and the latter 2 groups as advanced leukoaraisis. This dichotomization was performed on the basis of previous study findings that showed that more extensive abnormalities reflect a true ischemic process. Lacunes were defined as small lesions of ischemic on a T2-weighted image and a corresponding distinctive low-intensity area on a T1-weighted image. All radiographic scans were reviewed by 2 neurologists whose consensus determined the MRI findings. The investigators were blinded to the classical and demographic data at the time of magnetic resonance analysis.

STATISTICS
We used the Pearson χ² test or Fisher exact test, as appropriate, to compare the frequency distribution of categorical variables between groups. Continuous variables were compared with the unpaired t test or Mann-Whitney test, as appropriate, after normality distribution testing. Multivariate logistic regression analysis was used to determine the independent clinical and radiologic characteristics associated with microbleeds in PICH. The SPSS Version 11.0 software (SPSS Inc, Chicago, Ill) was used for data analysis. Statistical significance was set at P<.05.

RESULTS
The age range of patients was 17 to 91 years (mean ± SD, 62.4 ± 12.8 years; 63 men and 44 women). The locations of PICH were the basal ganglia in 32.7% of patients, lobar area in 27.1%, thalamus in 23.4%, cerebellum in 12.2%, and pons in 4.6%. Primary intracerebral hemorrhage involving multiple areas was seen only in 1 patient, who had 3 lobar hemorrhages. Of 107 patients with PICH, microbleeds were observed in 75 (70.1%) and ranged in number from 1 to 198 (mean ± SD, 11.6 ± 30.6; median, 3). Representative MRIs are shown in the Figure. The patients with PICH who had microbleeds were significantly older than those without microbleeds (Table 1). Previous stroke, current medication with antithrombotics or anticoagulants, numbers of lacunes, and advanced leukoaraisis were found to be more common in patients with PICH with microbleeds, while the frequency of hypertension was not statistically different between the 2 groups. The patients without microbleeds showed a higher incidence of potential triggering events just before stroke. Potential triggering events were spouse death (n = 2), severe somatic pain (n = 3), asthmatic attack (n = 1), exhaustive exercise (n = 7), dispute (n = 3), recent alcohol abuse (n = 9), micturition after awakening (n = 2), and heavy work (n = 6).

Multivariate logistic regression analysis indicated that age (odds ratio and 95% confidence interval: 1.07, 1.01-1.14), advanced leukoaraisis (7.79, 1.05-57.74), and number of lacunes (1.66, 1.21-2.28) were independent risk factors associated with the presence of microbleeds in patients with PICH (Table 2), while potential triggering events (0.18, 0.04-0.90) had the inverse relationship with microbleeds.
We were also able to identify 5 nonhypertensive patients with lobar hemorrhage with numerous microbleeds exclusively in the lobar area, strongly suggestive of CAA (Figure, F). The ages of these 5 patients ranged from 71 to 91 years (mean, 78.2 years; 3 men and 2 women), and 3 of these patients had a history of recurrent lobar intracerebral hemorrhage.

COMMENT

Primary intracerebral hemorrhage with and without microbleeds had clinical or radiologic characteristics different from each other. Whereas PICH with microbleeds was more common in elderly patients with prominent ischemic change and frequent use of antithrombotics or anticoagulants, PICH without microbleeds was more common in younger patients with precipitating events. We speculate that PICH with and without microbleeds forms pathogenetically distinct subgroups, and that the subgroups might need distinct strategies for secondary prevention.

In our study, microbleeds were observed in 70.1% of patients on GE-MRI. Two earlier investigations using conventional MRI sequences documented that microbleeds were detected in 17% and 33% of patients with ICH. Greenberg et al observed microbleeds in 12 (80%) of 15 patients with lobar hemorrhage. Except for these 3 studies, the reported frequency of microbleeds in PICH on GE-MRI ranged from 54% to 71%. Our frequency corresponds to those of the previous studies. The clinical and radiologic differences between patients with PICH with and without microbleeds have rarely been studied; to the best of our knowledge, only 1 study has been published. In that study involving 109 patients with PICH, hypertension, previous stroke, lacunes, and white-matter hyperintensity were more common in patients with PICH with microbleeds, but age showed no significant difference. Our study showed that patients with PICH who had microbleeds were older than patients without microbleeds, while the frequency of hypertension did not show any statistically significant difference between the 2 groups. This disparity might be related to ethnic differences or different definitions of hypertension, as the previous authors diagnosed hypertension in the presence of a 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 PICH. Our results suggest that PICH without microbleeds may be the result of a pathomechanism other than chronic hypertensive microangiopathy.

Remarkably, patients with PICH without microbleeds showed a higher incidence of potential triggering events. The relationship between increasing age and the declining impact of potential triggering events might be explained by the vascular thickening that accompanies aging. Ultrastructural study has shown that the small arteries observed in elderly patients are accompanied by medial hypertrophy, even in the absence of elevated blood pressure. Recently, one report was published that indicated that there was a decreasing risk of intracerebral hemorrhage resulting from hypertension with increasing age. Accordingly, potential triggering events might constitute an important risk factor among younger people without microbleeds. Caplan documented that 2 mechanisms leading to PICH—(1) an acute increase in blood flow in areas of normal or ischemic arterioles and capillaries and (2) damage to penetrating blood vessels caused by chronic arterial hypertension—probably could explain most PICH. Whereas the importance of the second mechanism, ie, lipohyalinosis and microaneurysm, has been somewhat exaggerated, the studies about intracerebral hemorrhage following episodes of acutely elevated blood pressure have been restricted to case reports. Depending on those reports, PICHs can develop under the medical conditions characterized by acute hypertension, such as acute glomerulonephritis, eclampsia, and pheochromocytoma, and under the autonomic hyperactive conditions such as acute stress, dental pain, and sexual intercourse. In addition, strenuous physical activity, sudden postural changes, defecation or micturition, alcohol consumption, and emotional stress have been considered as the potential triggering factors.
of multiple lobar hemorrhages in the patients older than 60 years. To clarify the pattern of microbleeds in either hypertensive microangiopathy or CAA, further studies are needed.

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REFERENCES


