Microbleeds in Patients with Primary Intracerebral Hemorrhages

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Objective: We investigate risk factors of cerebral microbleeds (MBs) and their relation to concomitant magnetic resonance (MR) findings in intracerebral hemorrhage (ICH) patients.

Methods: We studied 100 consecutive patients with primary ICH over a 1-year period. These patients underwent brain MR images using 3.0-T scanners within the first week of the hemorrhage. MBs and old hematomas were located and counted by using T2*-weighted gradient-echo MR imaging. We also counted lacunes and graded white matter and periventricular hyperintensity on T1- and T2-weighted spin-echo sequences. The association between MBs and vascular risk factors and MR abnormalities were analyzed.

Results: MBs were seen in 77 of ICH patients, and their number ranged from 1 to 65 lesions (mean 11, median 6). The locations of MBs were subcortex-cortex (40.6%), basal ganglia (26.7%), thalamus (16.1%), brain stem (12.5%), and cerebellum (9.1%). Analysis of clinical data revealed that age, hypertension, history of stroke, and duration of hypertension were frequently associated with MBs. The incidence of lacunes, old hematomas, and advanced leukoaraiosis was significantly higher in the MBs group, compared with the patients without MBs.

Conclusion: MBs are frequently observed in ICH patients with advancing age, chronic hypertension, and previous hemorrhagic stroke, and are also closely related with morphological signs of occlusive type microangiopathy, such as lacunar infarct and severe leukoaraiosis.

KEY WORDS: Intracerebral hemorrhage · Magnetic resonance image · Microbleed · Hypertension · Microangiopathy.

Introduction

Intracerebral hemorrhage (ICH) is associated with a high mortality and morbidity1-9, and the control of risk factors is major in preventing the occurrence of hemorrhagic stroke. It could be of clinical importance to estimate a person's individual risk for suffering from a primary ICH by using neuroradiologic tools. The advent of gradient-echo(GE) T2*-weighted magnetic resonance(MR) imaging has generated recent interest in cerebral microbleeds(MBs), which are detected as small areas of signal loss, indicative of a bleeding-prone microangiopathy or vascular vulnerability.2,3,20 Our major goals were to clarify whether their presence was associated with vascular risk factors and MR abnormalities concomitant with primary ICHs.

Materials and Methods

Patients population

We examined consecutive series of symptomatic ICH patients from January 2004 to December 2004 at our hospital, and selected 100 who underwent brain MRI, including T2*-weighted GE sequences. These patients consisted of 53 women and 47 men with a mean age 58.9 ± 11.5 years (range, 34 to 85 years). Patients with a known cause of hemorrhage such as trauma, cerebral tumors, cerebral amyloid angiopathy, coagulopathy, or vascular malformation were excluded. The locations of the spontaneous ICHs were as follows: basal ganglia in 46 patients, cortex-subcortex in 25, thalamus in 22, cerebellum in five, and brain stem in two. Fresh hematomas were grouped by cerebral regions as lobar lesions (involving cerebral white
matter and cortex) and deep lesions (involving basal ganglia, thalamus, cerebellum, or brain stem). Thirty-three patients had suffered from a previous stroke, which was reportedly hemorrhagic in 28 patients.

Risk factors

Major cerebrovascular risk factors were identified on the basis of medical history and laboratory findings. Patients were considered to have systemic hypertension if their blood pressure repeatedly exceeded 140/90mmHg or if they were taking antihypertension medications beyond the second week after the ICH. Diabetes mellitus was diagnosed either by a fasting serum glucose above 140mg/dl or by previous or intercurrent treatment. Each patient's cigarette smoking history was categorized as either smoking or nonsmoking on admission. The latter category included former regular smokers who had quit more than 1 year earlier. Alcohol intake was considered habitual if a patient's alcohol consumption exceeded 100gm of ethanol per week. Risk factors included hypertension (66%), diabetes (15%), hyperlipidemia (16%), smoking (35%), and alcohol use (34%).

MRI studies

All patients underwent computed tomography (CT) and MRI examinations of the brain with the same protocol. MR images of the brain were obtained on 3.0-T system (Signa; GE Medical Systems, Milwaukee, WI, USA) within the first week of the hemorrhage. A GE sequence optimized to maximize the susceptibility effect of hemosiderin was employed for axial examination of the brain (repetition time 425 msec, echo time 20 msec, flip angle 15°, field of view 230 x 17.25 mm, matrix 512 or 256 x 160 pixels, number of excitations 1, axial slices 20, section thickness 5mm, and gap 2mm), in addition to the standard spin echo(SE) T1- and fast spin echo(FSE) T2-weighted sequences. The MR findings were reviewed in a blind-ed fashion by the staff neuroradiologist.

MBs were defined as small (< 5mm), well-margined, rounded foci of signal loss on GE T2*-weighted MRI and were located and counted throughout the entire brain (Fig. 1). The corresponding areas were checked on CT, and areas with calcifications were disregarded. The severities of MBs were graded as being mild (total number of MBs, 1-2), moderate (3-9), or severe (≥ 10) [9]. Irregularly shaped areas (linear, curvilinear, cystic, starlike, and so forth) of signal loss on T2*-weighted GE with a diameter of more than 7mm due to a known prior symptomatic episode of hemorrhage were separately counted as old hematomas [9]. A black ring around a cystlike lesion was also regarded as the scars from previous ICH. White matter hyperintensities, defined as focal areas of increased signal intensity on fluid-attenuated inversions recovery MR images, were graded into absent (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3). Periventricular hyperintensities were specified as caps or lining (grade 1), bands (grade 2), or irregular extending into the deep white matter (grade 3) [9]. The grade 2 or 3 white matter hyperintensity and grade 3 periventricular hyperintensity were considered advanced. Areas of ischemic parenchymal destruc- tions lesions exhibiting both hyperintensity on T2-weighted FSE images and corresponding hypointensity on T1-weighted SE images were diagnosed as either lacunes (≤ 15mm in diameter) or cortical infarcts.

Data analysis

We divided the 100 subjects into 2 groups, depending on whether or not they had MBs. Various variables (demographic,
MRI, and risk factors) were compared between the MBs group and the non-MBs group. Statistical analyses were performed by the SPSS (Chicago, IL) version 10.0 software. We used the Pearson chi-square test and Student’s T test to compare the frequency distribution of categorical or continuous variables between both groups. P<0.05 was considered to represent a statistically significant finding.

**Results**

MBs were seen in 77 of ICH patients, and their number ranged from 1 to 65 lesions (mean ± SD, 11.2 ± 13.0). The degree of MBs was mild in 13 patients (16.9%), moderate in 38 patients (49.3%), and severe in 26 patients (33.8%). Among the 863 MBs, 350 (40.6%) were located in the subcortex/cortex, 203 (26.7%) in the basal ganglia, 122 (14.1%) in the thalamus, 109 (12.5%) in the brain stem (predominantly in pons), and 79 (9.1%) in the cerebellum (mostly in the dentate nucleus) (Table 1).

The patients with MBs were not only older but also were more often hypertensive and more frequently had a previous stroke history, compared with the patients without MBs (Table 2). A statistically significant difference was also found in the duration of hypertension between the two groups (P=0.001). The percentage of other risk factors was similar between MBs and non-MBs groups.

Table 3 shows the frequency of concomitant MR findings for the both groups. Subcortical and deep white matter hypertensity was found in 80 patients; 44 had punctate, 19 had early confluent, and 17 had confluent abnormalities. Eighty-five patients showed abnormal periventricular hypertenstities; 51 had caps, 8 had bands, and 26 had irregular types. The silent lacunes were found in 47 of 77 patients (61.0%) with MBs and 8 of 23 patients (34.8%) without MBs. MBs group showed a mean of 3.7 (range 1-12) lacunes and the other group had 1.8 lesions (range 1-3). Total 44 old hematoma were observed in twenty-seven patients with MBs, 11 of them demonstrated ≥2 old hematomas at different sites. They involved the basal ganglia (n=24), thalamus (n=6), brain stem (n=2), cerebral cortex-subcortex (n=11), and cerebellum (n=1). Patients with MBs had significantly higher grades of white matter and periventricular hypertensive lesions, and they more commonly showed lacunes and areas of hemosiderin deposition from old hemorrhages. However, locations for ICHs, number of lacuna, and territorial infarct did not differ significantly between the both groups.
Discussion

MRI of the brain using GE sequence has greatly enhanced our ability to detect small micro- or petechial hemorrhages. Recently, Roob et al. reported that cerebral MBs could be found in 6.4% of otherwise healthy elderly and may therefore be a means of detecting early diseases. The frequency of MBs was varyingly reported in different subject groups; however, since the introduction of GE MRI, MBs have been shown to occur in about 50% of cases of primary ICH. The rates in our study are higher than those in the earlier investigations that used conventional MRI sequences or lower Tesla MR scanner in all or most of their patients. This difference can be easily explained by much higher sensitivity of 3.0 Tesla MR imaging in the detection of small hemosiderin deposits. The incidence of hypertension in this series was also somewhat high as compared with previous studies. Because hypertension is a well-established cause of small vessel disease, this would also influence the higher detection rate of MBs in present study. The dotlike hemosiderin spots on GE MRI were found in 84.9% of 5666 patients with hypertension, whereas they were found only in 61.8% of 2134 patients without hypertension.

Some reports suggested that regions with the greatest number of MBs could be the sites of future bleeding in a given patient. The overall number of MBs in individual patients in our series was quite variable and ranged from 1 to 65 lesions. With regard to its location, MBs were most frequently seen in cortical-subcortical and thalamoencephalonic regions, where symptomatic hematoma are commonly observed, and the cerebellum was relatively spared in our cases. Although, we did not compare the anatomic distributions of symptomatic ICHs and asymptomatic MBs, prior analyses reported that topographic correspondence between large and small pontine hemorrhages may provide evidence that the two lesions share some etiological basis. Further investigation may determine whether deep-seated MBs associated with hypertension portend future symptomatic primary angiobasal hemorrhages.

The prolonged degeneration of arterioles predispose patients to the development of cerebral hemorrhages, which could be justified by the longer history of hypertension and higher incidence of former stroke. The present study confirmed that patients with MBs were significantly older and had a higher frequency of chronic hypertension. Additionally, our results clearly showed that MBs occurred more frequently in patients with histories of brain stroke, particularly those with histories of hemorrhagic stroke, compared with those without previous stroke. Twenty-seven (35.1%) of 77 patients with MBs had previous ICHs at the time of presentation. Based on the GE MR images acquired with the a 3-tesla unit of better resolution, the scars from previous symptomatic ICH, a ill-defined and larger signal loss lesions, were sharply demonstrated and differentiated from the dotlike MBs. These hypointense hemorrhagic scars from old clots provide further evidence of severe microangiopathy with a subsequent increased vascular vulnerability. Support regarding prediction of the probability of further bleeding after a first ICH may be another contribution of detection of MBs by GE MRI. From the preliminary experiences, it might be speculated that individuals with a large number of MBs might be at greater risk for rebleeding. Imazum et al. indicated that the small vessel disease recurrence rate was significantly higher in patients with greater numbers of subcortical hemosiderin spots in their study with small sample size.

Although the characteristic neuroradiologic findings of patients who are prone to cerebral hemorrhage have not been elucidated, earlier studies have reported the coexistence of ICH, lacunar infarction, and leukoaraiosis in hypertensive patients. 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. In most cases, the distribution of microhemorrhage lesions on GE MRI overlap the same areas known to be involved by lacunar infarction, cerebral hemorrhage, and leukoaraiosis. A strong correlation between the white matter hyperintensity and the number of MBs was also observed. This is probably because of the simultaneous negative effects of hypertension. That assumption was confirmed in this study; of 66 hypertensive patients, 62 patients (93.9%) had white matter hyperintensity, and 60 patients (90.9%) had periventricular hypertense lesion, and lacunes were found in 45 patients (68.2%). The authors propose that ICH always requires an underlying ischemic lesion to set in motion the chain of events that ultimately shatters the surrounding brain, destroying the blood vessels that rupture and bleed. With further prospective study on the patients of hemorrhagic stroke, the diagnostic and prognostic significance of the MBs on T2*-weighted GE MRI will be determined in the near future.

Conclusion

More than three quarters of patients with primary ICH showed focal areas of signal loss on GE T2*-weighted MRI that was indicative of old cerebral MBs. Clinically silent MBs could be viewed as direct evidence for bleed-prone microangiopathy in comparison with the indirect evidence from leukoaraiosis and lacunes, which frequently coexist, and seem to be a potential predictor for major intracerebral hemorrhages.
The diagnostic potential of these abnormal MR findings to identify individuals at risk of spontaneous ICHs may require further investigation.

References

Commentary

Dotlike low-density spots on T2*-weighted gradient echo (GE) MR images, which is especially sensitive in detecting hemosiderin have been histologically diagnosed as MBs related to bleeding-prone microangiopathies including lipo-hyalinosis, amyloid angiopathy, or other microangiopathies. Although the clinical and diagnostic significance of MBs is not yet fully understood, many recent reports presented that MBs were potential risk factor for early cerebral bleeding after ischemic stroke and they had highly significant association with other morphological signs of cerebral microangiopathy, such as lacunes and extensive periventricular and deep white matter damage. In this carefully designed study the authors observe that age, hypertension, history of stroke, and duration of hypertension are frequently associated with MBs and confirm that MBs have highly significant association with other morphological signs of cerebral microangiopathy such as lacunar infarction and leukoaraiosis. Although hypertensive microangiopathy appears to be the prevailing cause of MBs, cerebral amyloid angiopathy has also been associated with MBs located in subcortex-cortex region. In this paper authors excluded the patients with cerebral amyloid angiopathy, but still subcortex-cortex region appeared to be a predilection site for MBs. This result suggests that hypertensive microangiopathy is the prevailing cause of MBs in subcortex-cortex region also. To clarify the significance of MBs in the development of hemorrhagic or ischemic stroke prospectus long term follow-up study will be needed in patients with MBs on T2*-weighted GE MR images.

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