Microbleeds Are Associated With Subsequent Hemorrhagic and Ischemic Stroke in Healthy Elderly Individuals

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Background and Purpose—Cerebral microbleeds (MBs) are frequently detected in patients with stroke, especially those who experience intracerebral hemorrhage. However, the clinical significance of MBs in subjects without cerebrovascular disease is still unclear. We performed a prospective study to determine whether the presence of MBs provides useful prognostic information in healthy elderly individuals.

Methods—We tracked 2102 subjects (mean age, 62.1 years) over a mean interval of 3.6 years after they voluntarily participated in the brain checkup system at the Shimane Institute of Health Science. An initial assessment was performed to document the presence of MBs and silent ischemic brain lesions and to map the location of the MBs. During the follow-up period, we obtained information about stroke events that occurred in each subject.

Results—MBs were detected in 93 of the 2102 subjects (4.4%). Strokes occurred in 44 subjects (2.1%) during the follow-up period. They were significantly more common among subjects with MBs. Age and hypertension were independent risk factors for MBs. The presence of MBs was more strongly associated with a deep brain hemorrhage (hazard ratio, 50.2; 95% CI, 16.7 to 150.9) than ischemic stroke (hazard ratio, 4.48; 95% CI, 2.20 to 12.2). All hemorrhagic strokes occurred in deep brain regions, and they were associated with MBs located in the deep brain region.

Conclusions—This longitudinal study demonstrated that the presence of MBs can be used to predict hemorrhagic and ischemic stroke, even in healthy elderly individuals. **(*Stroke*. 2011;42:1867-1871.)**

Key Words: hypertension ■ intracerebral hemorrhage ■ magnetic resonance imaging ■ microbleeds ■ prevention ■ risk factor

Cerebral microbleeds (MBs) are represented on T2*-weighted MRI scans as spotty, low-intensity lesions and are frequently detected in patients with stroke. In patients with intracerebral hemorrhage (ICH) or ischemic cerebrovascular disease, the presence of MBs has a strong predictive value for future recurrent hemorrhagic and ischemic strokes.[1,2] A recent meta-analysis revealed that MBs were present in 44% of patients with recurrent ischemic stroke and 83% with recurrent ICH.[3] On the other hand, MBs only occur in approximately 5% to 6% of subjects without cerebrovascular disease or neurological symptoms.[4,5] The occurrence of MBs in healthy elderly subjects is associated with advanced age or chronic hypertension.[6] Although a variety of research has investigated the clinical significance of MBs in patients with stroke, only 1 study to date has examined the long-term prognosis of healthy subjects with MBs.[7]

Even in healthy elderly individuals, silent brain infarctions and subcortical white matter lesions are generally thought to be strong risk factors for subsequent stroke.[8,9] These asymptomatic ischemic lesions often coexist with MBs in patients with stroke[10]; thus, it is important to understand the individual contributions of these conditions to stroke onset. We performed a prospective study to examine whether MBs and silent ischemic brain lesions are independently associated with subsequent stroke in healthy elderly individuals. Furthermore, the distribution of MBs has lately attracted attention because it may represent distinct underlying vascular pathology; lobar and deep brain MBs are associated with cerebral amyloid angiopathy and hypertensive vasculopathy, respectively.[11] Thus, we further examined the relationship between MB distribution and future stroke events in the same cohort.

Materials and Methods

Subjects

We studied prospectively a total of 2238 consecutive subjects who voluntarily participated in the brain checkup system at the Shimane Institute of Health Science between 2001 and 2007. The screening system entailed collection of medical, neurological, and psychiatric history; family history of stroke; formal neurological examinations

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Table 1. Risk Factors for Asymptomatic MRI Lesions

	MBs		SBI		PVH		SWML	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age per 1 y	1.08 (1.04–1.12)	<0.0001	1.09 (1.07–1.11)	<0.0001	1.11 (1.07–1.15)	<0.0001	1.10 (1.08–1.13)	<0.0001
Sex, male	1.46 (0.77–2.78)	0.25	1.61 (1.06–2.46)	0.03	0.80 (0.41–1.56)	0.51	0.86 (0.58–1.25)	0.42
Hypertension	4.21 (2.20–8.08)	<0.0001	2.27 (1.62–3.19)	<0.0001	1.54 (0.91–2.61)	0.10	2.03 (1.50–2.74)	<0.0001
Diabetes mellitus	1.14 (0.52–2.51)	0.75	1.52 (0.96–2.41)	0.07	1.66 (0.82–3.36)	0.16	0.76 (0.46–1.26)	0.29
Family history of stroke	0.93 (0.55–1.57)	0.79	1.09 (0.79–1.52)	0.59	2.04 (1.17–3.54)	0.01	1.31 (0.97–1.77)	0.08
Ischemic heart disease	1.96 (0.91–4.22)	0.08	1.09 (0.62–1.94)	0.76	1.39 (0.63–3.11)	0.42	1.51 (0.91–2.50)	0.11
Smoking	0.55 (0.28–1.06)	0.07	1.03 (0.69–1.54)	0.87	1.07 (0.55–2.10)	0.84	1.11 (0.75–1.64)	0.61
Alcohol habit	1.45 (0.68–3.07)	0.34	1.18 (0.75–1.86)	0.47	1.32 (0.63–2.80)	0.47	1.07 (0.69–1.69)	0.76

Results were analyzed by use of a logistic regression analysis.

MBs indicates microbleeds; SBI, silent brain infarction; PVH, periventricular hyperintensity; SWML, subcortical white matter lesion.

by an experienced neurologist; neuropsychological testing; MRI of the head; electrocardiogram; chest radiography; and blood tests. The inclusion criteria for this prospective study were as follows: no history of neurological or psychiatric disorders, no abnormalities on neurological examination, no severe medical illness (ie, renal failure, liver dysfunction, or heart failure), and informed consent to this study. The study design including information acquisition from other sources was approved by the institutional ethics committee.

To obtain follow-up information about health conditions, we mailed questionnaires to all subjects on an annual basis. When medical events were reported, we conducted telephone interviews with the subjects and their family members. When vascular events were suspected, we obtained information on all subjects by questioning neurologists in the hospitals they attended about details of the events, including brain imaging results. On the basis of the information obtained from these sources, we determined the stroke type, that is, cerebral infarction, transient ischemic attack, ICH, or subarachnoid hemorrhage. Cerebral infarction was further classified using the Trial of ORG 10172 in Acute Stroke Treatment criteria.[12] The final analysis included only those subjects with whom we could follow-up for at least 1 year after the initial examination; we were able to obtain a follow-up ratio of 93.9% with a total of 2102 subjects (1126 men and 976 women) with a mean age of 62.1 (8.0) years (range, 31 to 87 years).

See http://stroke.ahajournals.org for the methods of acquiring demographic and laboratory data and MRI data.

Statistical Analysis

To make comparisons between groups, we used Student *t* test (parametric data) and Mann-Whitney *U* test or the χ^2 test (nonparametric data). Probability values were 2-tailed, and significance was defined as $P<0.05$. A logistic regression analysis was performed to examine risk factors for asymptomatic brain lesions; the variables included age, sex, family history of stroke, hypertension, diabetes mellitus, ischemic heart disease, smoking, and alcohol consumption. Cumulative stroke-free rates were estimated by the Kaplan-Meier product-limit method, and the curves of the different groups were compared using the log-rank test. To assess the impact of MBs on the incidence of ischemic and hemorrhagic strokes, the hazard ratio and 95% CI of symptomatic stroke events during the follow-up period were calculated using the Cox proportional hazards model with a stepwise variable selection with adjustments for age and sex. Variables with $P>0.10$ were removed from the stepwise model.

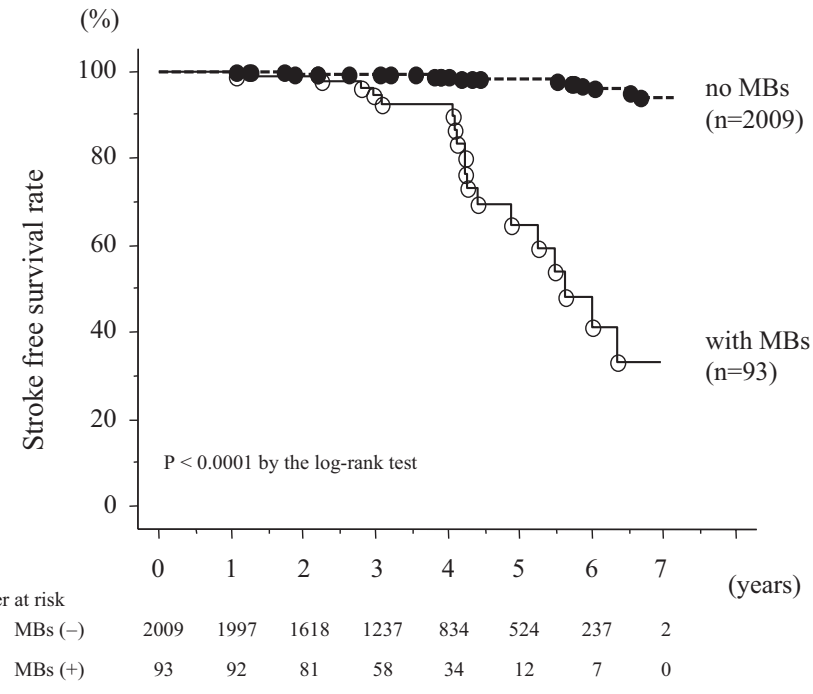

Figure. Kaplan-Meier curves of the stroke-free survival rate stratified by presence or absence of microbleeds (MBs).

Table 2. Significant Independent Predictors for Subsequent Ischemic Stroke and ICH

	Ischemic Stroke		ICH	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
MBs, yes	4.48 (2.20–12.2)	<0.0001	50.2 (16.7–150.9)	<0.0001
SBI, yes	2.94 (1.26–6.82)	0.012	. . .	. . .

Results were analyzed by use of a stepwise Cox regression with adjustments for age and sex.

ICH indicates intracerebral hemorrhage; HR, hazard ratio.

Results

MBs were detected in 93 of 2102 subjects (4.4%). They were located in the deep brain regions of 56 subjects (52.7%), in the lobar region of 10 subjects (12.9%), and in both regions of 27 subjects (34.4%). Other silent lesions were also fairly common: silent brain infarction was found in 262 subjects (12.5%); periventricular hyperintensity (+) in 105 subjects (5.0%); and subcortical white matter lesion (+) in 358 subjects (17.5%). Results of the logistic regression analysis indicated that age and hypertension were independent risk factors for all asymptomatic brain lesions (Table 1).

The average follow-up period was 3.6 (1.7) years, during which 12 subjects died from critical illness, including cancer and ischemic heart disease, and 1 subject died from ICH. Stroke occurred in 44 subjects (2.1%), including 22 subjects with cerebral infarctions, 10 with ICH, 4 with subarachnoid hemorrhages, and 8 with transient ischemic attack. We classified 22 cases with cerebral infarction according to the Trial of ORG 10172 in Acute Stroke Treatment criteria: 5 subjects had large-artery atherosclerosis; 3, cardioembolism; 12, small-vessel occlusion; and 2, stroke of incomplete evaluation. Strokes were significantly more common in subjects with MBs (18 subjects [19.4%]) than in those without MBs (26 subjects [1.3%]; $P<0.0001$). Stroke-free rate curves were generated using the Kaplan-Meier method together with the log-rank test (Figure). Clinical strokes were significantly more common among subjects with MBs than among those without MBs ($P<0.0001$).

Results of Cox proportional hazards model investigating associations of risk factors with stroke onset are presented in Table 2. We included MBs, silent brain infarction, periventricular hyperintensity, subcortical white matter lesion, family history of stroke, hypertension, diabetes mellitus, ischemic heart disease, smoking, and alcohol consumption as predictor variables in the stepwise regression model. The presence of MBs (hazard ratio, 4.48; 95% CI, 2.20 to 12.2; $P<0.0001$) and silent brain infarction (hazard ratio, 2.94; 95% CI, 1.26 to 6.82; $P=0.012$) were significant risk factors for ischemic stroke, although MBs were a much stronger predictor. However, the presence of MBs was an even more potent risk factor for ICH (hazard ratio, 50.2; 95% CI, 16.7 to 150.9, $P<0.0001$). Other factors were not associated with future stroke events.

Among 18 subjects with MBs followed by strokes, 9 were associated with hemorrhagic strokes and 9 others with ischemic strokes. No subjects with MBs restricted to the lobar region experienced strokes for either ischemic or hemorrhagic types during the follow-up period. On the other hand, all 18 subjects who had strokes had MBs in the deep brain region; in 50% of these cases, subjects also had MBs in the lobar region. Location of MBs (eg, deep brain region only or both deep brain and lobar regions) did not have a significant influence on whether patients had ICH or ischemic strokes. ICH occurred in 4 subjects with MBs in the deep brain region and in 5 subjects with MBs in both deep brain and lobar regions. Similarly, ischemic strokes also occurred in 5 subjects with MBs in the deep brain region and in 4 subjects with MBs in both deep brain and lobar regions.

Table 3 presents the clinical characteristics and MRI findings of subjects (n=10) who had ICH during the follow-up period. In the initial assessment, 9 of these patients were found to have MBs. A hemorrhage occurred in the putamen in 5 subjects, in the thalamus in 4 subjects, and in the cerebellum in 1 subject. All these individuals had hypertension, except for 1 who had diabetes mellitus.

We failed to obtain follow-up data from 136 subjects, among whom 5 (3.7%) had MBs at the initial examination. The demographic data and all MRI findings, including MBs,

Table 3. Clinical Characteristics and Radiological Findings of the Subjects With ICH During the Follow-Up

Case No.	Age, y	Sex	Location of ICH	Hypertension	DM	MBs	SBI	PVH	SWML
1	61	Female	Putamen	+	−	−	−	−	+
2	67	Female	Thalamus	+	−	+	−	−	+
3	76	Female	Putamen	+	−	+	+	+	+
4	69	Male	Cerebellum	+	−	+	−	−	−
5	64	Male	Thalamus	+	−	+	+	−	−
6	63	Male	Putamen	+	+	+	+	−	−
7	65	Male	Thalamus	+	−	+	+	−	+
8	67	Male	Putamen	+	−	+	+	+	−
9	53	Male	Putamen	+	−	+	−	−	+
10	66	Male	Thalamus	+	−	+	+	+	+

ICH indicates intracerebral hemorrhage; DM, diabetes mellitus; MBs, microbleeds; SBI, silent brain infarction; PVH, periventricular hyperintensity; SWML, subcortical white matter lesion.

in these subjects lost to follow-up were not statistically different from those in subjects included in the analysis.

Discussion

In the current study, subjects who had MBs were 5 and 50 times as likely to experience ischemic stroke and ICH, respectively, than those who did not have MBs. Thus, the presence of MBs is a strong independent risk factor for subsequent strokes, even in subjects without a history of cerebrovascular disease. These results are much more dramatic than those of a previous study, which found that patients with MBs were 7 times more likely to develop ICH than those without MBs.[13] Follow-up studies were conducted to investigate whether MBs have a higher association with hemorrhagic or ischemic future stroke. However, most of these studies were hospital-based and included subjects who had already experienced symptomatic hemorrhage or infarction. Furthermore, the results of these studies were conflicting; 2 that focused on a small group of patients with stroke demonstrated a significant association between MBs and subsequent ICH,[14,15] whereas the third study found that MBs were associated with future ischemic but not hemorrhagic stroke.[2]

A recent longitudinal study demonstrated for the first time that the presence of MBs was a predictor for first-ever symptomatic cerebrovascular events in subjects without a history of symptomatic stroke.[7] Subjects from that study had a much higher prevalence of MBs (17%) than was recorded in the focal group of the present study (4.4%) and a correspondingly higher overall stroke incidence rate (34.0 versus 20.9 per 1000 person-years, respectively). This is likely because the previous study group included individuals who were at a high risk of stroke, whereas we examined relatively healthy patients. Regardless, 1 commonality between the previous and current research was the finding that MBs strongly predicted the occurrence of future cerebral infarctions in subjects without cerebrovascular disease. However, in the previous study, this relationship did not persist after adjustment for age, sex, and hypertension. Because we obtained a larger sample size, and therefore had higher statistical power, our results offer more persuasive evidence of an association between the presence of MBs and the occurrence of future ICH, even after adjustment for clinical variables.

The distribution of MBs seems to be an important factor influencing the risk of ICH. Generally, MBs in the basal ganglia or thalamus are thought to be related to hypertensive or arteriosclerotic microangiopathy. Wardraw et al reported that MBs were observed more frequently in lacunar stroke than in cortical stroke and were associated with a higher incidence of white matter lesions.[16] Cumulatively, these findings support the notion that MBs and lacunar stroke have a common pathological background such as small-vessel diseases.[17] In agreement with this view, 9 of 10 subjects with MB-associated ICH experienced a hemorrhage in the putamen, thalamus, or cerebellum in the present study (Table 3).

It is important to note that MBs were found in the lobar region in some subjects and that this type of MB has a distinct pathogenesis from that in the deep brain region.[18] Lobar MBs may be related to cerebral amyloid angiopathy,[19] which is a major cause of lobar ICH in elderly persons. None of our subjects experienced a lobar hemorrhage due to CCA, probably because there were very few elderly subjects who were ≥80 years old in our study (3.6% of all patients). Moreover, MBs are often found in patients with dementia such as Alzheimer disease[20] or cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[21,22] Further longitudinal studies are needed to investigate whether the presence of lobar MBs is related to the occurrence of ICH in lobar regions.

We observed MBs in 4.4% of the study subjects. This rate is lower than that reported in the Rotterdam Scan Study (23.5%).[23] However, the prevalence of MBs in the present study was similar to that documented by the Framingham study (4.7%)[5] and Roob's report (6.4%).[4] The prevalence of MBs depended on the characteristics of the cohort, particularly clinical status and age distribution. Thus, the discrepancy between our statistics and those reported in the Rotterdam Scan Study probably stems from the fact that the latter included subjects with a history of cerebrovascular disease and examined patients who were older (mean age, 69.6 years) than those studied here (mean age, 62.1 years). Furthermore, detection of MBs may be more important in Japan than in Western countries, because the proportion of ICH in population-based studies accounted for approximately 20% of all stroke cases in Japan[24] and was different from the incidence (<10% of ICH) in Western countries.[25] Deep brain hemorrhage is more common than lobar hemorrhage, and it has been reported that the former accounted for 83% of all ICH cases in Japan.[26]

There are several limitations to the present study. First, we were unable to obtain information about medical treatment during the follow-up period. Specifically, we were unable to investigate the potential importance of antithrombotic medication, which may increase the risk of hemorrhagic events in patients with MBs.[27,28] Second, because the primary follow-up method relied on mailed questionnaires, we were also unable to collect data on the control state of blood pressure and glucose level. Third, we did could not obtain follow-up data from 136 subjects who were lost to follow-up at a constant rate, although their demographic data, including MRI findings at the initial examination, were comparable to those of other subjects. Finally, our subject selection may have been biased, because all subjects were recruited from a group of individuals who voluntarily participated in the brain checkup system. These individuals may have had different demographic characteristics (eg, motivation to seek health care and economic level) than subjects included in other population-based cohort studies.

Conclusions

The presence of MBs is a strong risk factor for subsequent ischemic stroke and ICH, even in healthy elderly individuals. To prevent stroke, subjects with MBs should carefully manage risk factors. Specifically, because all subjects who experienced stroke after presenting with MBs also had hypertension, patients with MBs should be treated with intensive antihypertensive medication to prevent subsequent ischemic or hemorrhagic stroke.

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Disclosures

None.

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