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

Hirokazu Bokura, MD, PhD; Reiko Saika, MD; Takuya Yamaguchi, MD; Atsushi Nagai, MD, PhD; Hiroaki Oguro, MD, PhD; Shotai Kobayashi, MD, PhD; Shuhei Yamaguchi, MD, PhD

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 stroke10; 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...
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 χ² 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.

### Table 1. Risk Factors for Asymptomatic MRI Lesions

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

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.

Figure. Kaplan-Meier curves of the stroke-free survival rate stratified by presence or absence of microbleeds (MBs).
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,
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. 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, whereas the third study found that MBs were associated with future ischemic but not hemorrhagic stroke. 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. 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. Cumulatively, these findings support the notion that MBs and lacunar stroke have a common pathological background such as small-vessel diseases. 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. Lobar MBs may be related to cerebral amyloid angiopathy, 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 or cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. 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%). However, the prevalence of MBs in the present study was similar to that documented by the Framingham study (4.7%) and Roob’s report (6.4%). 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 and was different from the incidence (<10% of ICH) in Western countries. 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.

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. 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.
Sources of Funding
Part of this study was supported by Mitsubishi Pharma Research Foundation and a Grant-in-Aid for scientific research from JSPS.

Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

Title: Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals

Supplemental Methods

Acquisition of demographic and laboratory data
At the initial examination, blood samples were taken after an overnight fast to measure glucose levels and HbA1c. Blood pressure was measured three times after a 15-min resting period, and the mean of these values was used in all further analyses. Hypertension was defined as a systolic blood pressure $\geq 140$ mm Hg, a diastolic blood pressure $\geq 90$ mm Hg, and/or a history of hypertension with anti-hypertension therapy. Diabetes mellitus was defined as a fasting serum glucose level $\geq 126$ mg/dl, hemoglobin A1c level $\geq 6.5\%$, or a medical history of diabetes mellitus. A smoker was defined as any subject whose smoking index exceeded 200. Regular alcohol consumption was defined as more than 58 ml of alcohol consumed per day.

MRI
MRI examinations were performed during the first visit, using a 1.5-Tesla MRI (Symphony Ultra Gradient, Siemens). The entire head of each patient was scanned using a T2-weighted image (T2WI) pulse sequence ($TR = 4500$ ms, $TE = 86$ ms), T1-weighted image (T1WI; $TR = 2500$ ms, $TE = 3.9$ ms), FLAIR images ($TR = 8000$ ms, $TE = 92$ ms), and gradient-echo T2*-weighted images (T2*WI; $TR = 670$ ms, $TE = 25$ ms, flip angle = $20^\circ$) in the transverse plane, and T1WI in the coronal plane, with a slice thickness of 7 mm.

MBs and other asymptomatic ischemic brain lesions
In T2*WI, MBs were defined as 2- to 10-mm in diameter homogenous round foci of signal loss that were 2- to 10-mm in diameter. MB distribution was classified as occurring in either the deep brain region (including the basal ganglia, thalamus, brain stem, and cerebellum), or the lobar region (including the cerebral cortex and subcortical white matter). SBI was defined as a focally hyperintenseity lesion larger than 3 mm in diameter in the T2WI, corresponding to a hypointenseity lesion in the T1WI. FLAIR images were used to differentiate infarcts from enlarged perivascular spaces. These were distinguished from SBI based on the basis of their size and location: enlarged perivascular spaces are often observed around the perforating or medullary arteries in
the lower third of the basal ganglia\(^1\). Periventricular hyperintensity (PVH) was graded on a scale of 0 to 4, where 0 = very little or unclear PVH, 1 = thin but apparent PVH restricted to the frontal horn, 2 = smooth PVH surrounding the entire lateral ventricle or horn, 3 = thick, irregular PVH surrounding the lateral ventricle and horn, and 4 = marked diffuse PVH\(^2\). SWML was graded on a scale of 0 to 3 according to the Fazekas’ grading scheme\(^3\), where 0 = absent, 1 = punctate, 2 = beginning of confluencet, and 3 = confluencet. PVH and SWML were evaluated separately because PVH is found adjacent to the ventricles, while SWML is found separate from them. We defined PVH grades 0–2 as “PVH (−)” and grades 3–4 as “PVH (+)”; similarly, SWML grades 0–1 were defined as “SWML (−)”, and grades 2–3 were termed “SWML (+)”. All MRI findings were read and determined separately by an experienced neurologist and neuroradiologist who were blind to patients’ profiles. When their opinions were inconsistent, a second neurologist was brought in for consultation.

Supplemental Reference


健常高齢者の微小出血はその後の出血性・虚血性脳卒中と関連がある

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被験者

2001～2007年に島根県病院などで自主的に脳検診を受けた、2年間の随時観察群を対象に前向き研究を実施した。検診には、内科的、神経学的、精神医学的病歴および脳卒中の家族歴の収集、経験豊富な神経内科医による正規の神経学的検査、神経心理学的検査、頭部MRI、心電図、胸部X線検査、血液検査が含まれていた。この前向き研究の組入れ基準は以下の通りである：神経疾患および精
表１ 無症候性のMRI病変の危険因子

<table>
<thead>
<tr>
<th>変数</th>
<th>MB OR(95% CI)</th>
<th>p 値</th>
<th>SBI OR(95% CI)</th>
<th>p 値</th>
<th>PVH OR(95% CI)</th>
<th>p 値</th>
<th>SWML OR(95% CI)</th>
<th>p 値</th>
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</thead>
<tbody>
<tr>
<td>年齢（1歳あたり）</td>
<td>1.06(1.04~1.12)</td>
<td>&lt;0.0001</td>
<td>1.09(1.07~1.11)</td>
<td>&lt;0.0001</td>
<td>1.11(1.07~1.15)</td>
<td>&lt;0.0001</td>
<td>1.10(1.08~1.13)</td>
<td>&lt;0.0001</td>
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<td>男性</td>
<td>1.46(0.77~2.78)</td>
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<td>1.61(1.06~2.46)</td>
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<td>0.80(0.41~1.56)</td>
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<td>0.86(0.58~1.25)</td>
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<td>高血圧</td>
<td>4.21(2.20~8.08)</td>
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<td>2.27(1.62~3.19)</td>
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<td>1.52(0.96~2.41)</td>
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<td>脳卒中の家族歴</td>
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<td>眼発作</td>
<td>0.55(0.28~1.06)</td>
<td>0.07</td>
<td>1.03(0.69~1.54)</td>
<td>0.87</td>
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<td>酒精</td>
<td>1.45(0.68~3.07)</td>
<td>0.34</td>
<td>1.18(0.75~1.86)</td>
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<td>0.47</td>
<td>1.07(0.69~1.69)</td>
<td>0.76</td>
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</tbody>
</table>

結果の分析にはロジスティック回帰分析を用いた。
MB：微小出血、SBI：無症候性脳梗塞、PVH：脳室周囲高信号域、SWML：皮質下白質変化。

神経疾患の既往がないこと、神経学的検査で異常が認められること、重度の内科的疾患（胃不全、肝機能障害、心不全）がないこと、本研究参加の同意が得られていること、他の情報源からの情報収集を含め、本研究デザインは研究実施施設の倫理委員会の承認を得た。

追跡調査時の健康状態に関する情報を収集するために、被験者全員に年1回の割合で質問票を郵送した。医学的事象が報告された場合は、被験者とその家族に電話で面接を行った。血管性イベントが疑われる場合は、被験者が受診した病院の神経内科医に脳画像検査結果を含む事象の詳細を尋ねることによって、すべての被験者の情報収集した。これらの情報源から得られた情報に基づき、脳卒中の種類（脳梗塞、一過性脳虚血発作、ICH、脳下出血）を判断した。脳梗塞については、Trial of ORG 10172 in Acute Stroke Treatment（TOAST）基準12）を用いてさらに細かく分類した。最終解析には、初回評価から1年以上追跡調査が可能であった被験者のみを含めた。

追跡調査率は93.9％で、被験者は合計2,102例（男性1,126例、女性976例）、平均年齢は62.1（8.0）歳（範囲：31～87歳）であった。

人口統計学的データ、臨床検査データ、MRIデータの収集方法については、http://stroke.ahajournals.orgを参照のこと。

統計解析

群間比較を行うために、Studentのt検定（パラメトリックデータ）、Mann-WhitneyのU検定またはχ^2検定（ノンパラメトリックデータ）を用いた。両側検定による確率（p）値を算出し、p < 0.05を有意差ありとみなした。ロジスティック回帰分析により、無症候性脳病変の危険因子を検討した。変数には、年齢、性別、脳卒中の家族歴、高血圧、糖尿病、虚血性心疾患、喫煙、飲酒を含めた。

Kaplan-Meier法により累積無脳卒中率を推定し、ログランク検定を用いて各群の曲線を比較した。虚血性脳卒中および出血性脳卒中発症率に対するMBの影響を検討するために、ステップワイズ変数選択によるCox比例ハザードモデルを用い、年齢および性別について補正を行い、追跡調査期間中の症候性脳卒中イベントのハザード比と95％CIを算出した。p > 0.10の変数はステップワイズモデルから除外した。

図

微小出血（MB）の有無によって層別化した無脳卒中生存率のKaplan-Meier曲線

結果

2,102例中93例（4.4％）にMBが認められた。56例（52.7％）は脳深部領域に、10例（12.9％）は脳葉領域に、27例（34.4％）は両方の領域にMBが存在した。その他の無症候性脳病変もかなり高率にみられ、262例（25.3％）に無症候性脳梗塞が、105例（5.0％）に脳室周囲高信号域（+）が、358例（17.5％）に皮質下白質変化（+）が認められた。ロジスティック回帰分析の結果、年齢および高血圧が、
あらゆる無症候性脳変性的独立した危険因子であることが示された（表1）。
平均追跡調査期間は3.6（1.7）年で、この間に発症および虚血性心疾患を含む重複疾患により12例が死亡し、1例がICHにより死亡した。44例（2.1％）が脳卒中を発症し、このうち22例は脳梗塞、10例はICH、4例は脳出血で各1例、8例は過性脳性脳発作であった。TOAST基準に従って脑梗塞症例22例を分類した結果、5例は大血管アテローム性硬化、3例は心原性脳塞栓症、12例は小血管閉塞、2例は評価不十分な脳中であった。MBのある被験者[18例（19.4％）]をMBのない被験者[26例（13.0％）]に比べて、脳卒中発症頻度は有意に高かった（p＜0.0001）。Kaplan-Meier法とログランク検定を用いて各危険因子を統計学的に有意に評価した（図）。臨床的脳卒中の頻度は、MBのない被験者よりもMBのある被験者の方が有意に高かった（p＜0.0001）。

危険因子と脳卒中発症との関連を調べたCox比例ハザードモデルの結果を表2に示す。予測因子変数として、MB、無症候性脳梗塞、脳室周囲高信号域、皮質下白質変性、脳卒中の家族歴、高血圧、糖尿病、虚血性心疾患、喫煙、飲酒をステップワイズ回帰モデルに含めた。MBの存在（ハザード比=4.48、95％CI：2.20～12.2、p＜0.0001）と無症候性脳梗塞（ハザード比=2.94、95％CI：1.26～6.82、p=0.012）およびMBは脳卒中の有意な危険因子であったが、MBの存在はICHのさらに強力な危険因子であった（ハザード比=50.2、95％CI：16.7～150.9、p＜0.0001）。他の因子と脳卒中イベントとの間の関連はみられなかった。

MBを有し、脳卒中をきたした被験者18例のうち、9例は出血性脳卒中、残る9例は虚血性脳卒中であった。追跡調査期間中、MBが脳性脳卒中のみに限定されていた被験者には虚血性脳卒中出血性脳卒中も生じなかった。これに対し、脳卒中をきたした18例はいずれも脳卒中にMBが存在しており、このうち50％は脳卒中にもMBが認められた。MBの位置（深部脳卒中のみ、深部脳卒中と脳梗塞の両方など）は、ICHが虚血性脳卒中からの違いに有意な影響を及ぼしていなかった。深部脳卒中

<table>
<thead>
<tr>
<th>表2</th>
<th>将来的な虚血性脳卒中およびICHの有意な独立した予測因子</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>虚血性脳卒中</td>
</tr>
<tr>
<td>変数</td>
<td>HR(95%CI)</td>
</tr>
<tr>
<td>MBあり</td>
<td>4.48(2.20～12.2)</td>
</tr>
<tr>
<td>SBIあり</td>
<td>2.94(1.26～6.82)</td>
</tr>
</tbody>
</table>

結果の分析には、年齢および性別について補正したステップワイズCox回帰を用いた。

ICH：脳内出血、HR：ハザード比。

考 察

本研究では、MBを有する被験者はMBのない被験者に比べて、虚血性脳卒中発症リスクが5倍、ICH発症リスクが50倍高かった。このように、脳血管疾患の既往のない人々においても、MBの存在は将来の脳卒中の有力な独立した危険因子である。本研究結果は過去の研究結果に比べてはるかに柳林であり、過去の研究では、MBのある患者的ICH発症リスクはMBのない患者の7倍であった1）。将来の出血性脳卒中または虚血性脳卒中どちらがMBとより強く関連しているかについては、複数の追跡調査研究が行われているが、ほとんどの研究は病院をベースにしており、被験者はすでに症候性の出血や梗塞をきたした患者であった。さらに研究結果にも不一致がみられる。2件の研究では、少数の脳卒中患者群においてMBと将来のICHとの間有意な関連が認められた14,15が、もう1件の研究では、MBと将来の虚血性脳卒中との間には関連がみられなかったものの、出血性脳卒中の関連は認められなかった2）。

最近実施された縄断研究において、症候性脳卒中の既往のない人々にみられるMBが、症候性脳血管イベント初発の予測因子であることが初めて示された3）。この研究
表 3 造詣調査期間中に ICH をきたした被験者の臨床特性および画像検査所見

<table>
<thead>
<tr>
<th>症例番号</th>
<th>年齢（歳）</th>
<th>性別</th>
<th>ICH の部位</th>
<th>高血圧</th>
<th>DM</th>
<th>MB</th>
<th>SBI</th>
<th>PVH</th>
<th>SWML</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>女性</td>
<td>被殻</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>女性</td>
<td>視床</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>女性</td>
<td>被殻</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>男性</td>
<td>小脳</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>男性</td>
<td>視床</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>男性</td>
<td>被殻</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>男性</td>
<td>視床</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>男性</td>
<td>被殻</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>男性</td>
<td>被殻</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>男性</td>
<td>視床</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ICH：脳内出血, DM：糖尿病, MB：微小出, SBI：無症状性脳梗塞, PVH：脳室周囲高信号, SWML：皮質下白質変病。

の被験者は、今回の研究の中核群に比べて MB の頻度がはるかに高く（それぞれ 17％, 4.4％）、それに呼応して脳卒中全発症率も高かった（それぞれ 1,000 人 / 年あたり 34.0 件, 20.9 件）。これはあり得ることである。なぜなら、上記の研究の被験者集団には脳卒中の高リスク者が含まれていたが、我々の研究の被験者は比較的健康的患者であったからである。いずれにしても、以前の研究と今回の研究に共通していることは、脳血管疾患のない人々にみられる MB が、将来の脳梗塞発症の有力な予測因子であるという所見である。ただし、MB の存在は、脳卒中の発症の脳梗塞のメカニズムについてより深く解説するにあたり、MB の発症の関係についてより解説できるが、その解説が示された。

MB の分布は、ICH リスクに影響を及ぼす重要な因子であると考えられる。一般に、大脳基底核または視床の MB は、高血圧性または動脈硬化性微小血管病に関与していると考えられている。Warlraw らは、皮質脳卒中よりもラクノ梗塞の方が MB が観察される頻度が高く、白質病変の発症率が高くなると報告している 18。以上を総合すると、これらの所見は、MB とラクノ梗塞の間で小血管疾患などの共通する病理的作用が存在するという考えを裏づけている 17。同様に、本研究でも、ICH 発症例 10 例のうち、MB を伴う 9 例では被殻、視床、小脳に出血が認められたことより、ICH の主な原因の 1 つである。本研究の被験者には、脳アミロイド血管症に起因する脳卒中はみられなかったが、これはおそらく、本研究では 60 歳以上の高齢被験者がきわめて少なかった（全体の 3.6％）ためであると思われる。さらに、MB はアルツハイマー病 20 や、皮質下梗塞および脳梗塞の伴う常染色体優性遺伝性脳動脈病 21,22 などの、脳梗塞病の多くをなされることが多い。脳梗塞の MB の存在が脳梗塞領域における ICH 発現に関与しているか否かについては、さらに詳しい研究が必要である。

本研究では、被験者の 4.4％に MB が観察され、この割合は、Rotterdam Scan Study で報告された値（23.5％） 23 に比べて低いもののが、Framingham study（4.7％） 24 や Roob の報告（6.4％） 4 で示された値と同様である。MB の頻度は、コホートの特性、特に年齢状態および年齢分布に依存していた。したがって、本研究の統計量と Rotterdam Scan Study の差の値は、後の研究に脳血管疾患の既往のある被験者を含めていくこと、後の評価のためが年齢が高かったこと（平均年齢が 62.1 歳、69.6 歳）に起因していると思われる。さらに MB の検出、欧米諸国より日本における方がより一部を占められると思われる。なぜなら、一般住民を対象とした研究では、ICH は日本国内の脳卒中症例全体の約 20％を占めており 21, 欧米諸国のICH 発症率（10％未満） 25 と異なっていたためである。脳卒中病歴は脳卒中発症よりも、日本国内の ICH 症例全体の 83％を占めていると報告されている 26。
集することはできなかった。第三に、追跡不能例の人口統計学的データは、初期評価時のMRI所見も含め、他の被験者と変わらなかったものの、追跡不能となった136例については、定期的な追跡調査データが得られなかった。最後に、本研究の被験者はいずれも自主的に脳検診を受けた人々であるため、被験者選択に偏りがあった可能性があり、一般住民を対象とした他のコホート研究の被験者とは、人口統計学的特性（医療機関を受診する動機、経済的レベルなど）が異なる可能性がある。

結 論

健常高齢者の場合でも、MBの存在は、その後の虚血性脳卒中およびICHの有力な危険因子となる。MBを有する高齢者の脳卒中予防には、危険因子の注意深い管理が必要である。特に、受診時にMBを有し、後に脳卒中をきたした者にはいずれも高血圧が認められたため、MBを有する患者には集中的な降圧療法を実施し、将来的な虚血性脳卒中や出血性脳卒中の発現を予防すべきである。

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情報開示

なし。

References