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;42:00-00.)

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.\textsuperscript{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 $\chi^2$ 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.

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

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

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.
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 (5.0%); and subcortical white matter lesion (+) 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, large-vessel occlusion; 6, small-vessel occlusion; and 2, stroke of incomplete ictus. Other 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 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 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 hyperintensity lesion larger than 3 mm in diameter in the T2WI, corresponding to a hypointensity 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\textsuperscript{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\textsuperscript{2}. SWML was graded on a scale of 0 to 3 according to the Fazekas’ grading scheme\textsuperscript{3}, where 0 = absent, 1 = punctate, 2 = beginning of confluence\textsuperscript{t}, and 3 = confluence\textsuperscript{t}. 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

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

Hirokazu Bokura, MD, PhD1; Shotai Kobayashi, MD, PhD2; Shuhei Yamaguchi, MD, PhD1; Hiroaki Oguro, MD, PhD1; Reiko Saika, MD1; Takuya Yamaguchi, MD, PhD3; Atsushi Nagai, MD, PhD1; 1Department of Neurology, Faculty of Medicine, Shimane University; and 2Shimane University Hospital, Izumo, Japan

背中および目的：脳卒中患者、特に脳内出血をきたした患者には、脳内微小出血（MB）が認められることが多い。しかし、脳血管疾患のない人々にみられるMBの臨床的意義は不明である。我々は前向き研究を実施し、MBの存在が健常高齢者における有用な予後情報となるか否かを検討した。

方法：鳥取大学病院で自発的に頚血管を受診した2102例（平均年齢：62.1歳）を対象に、平均36年間の追跡調査を実施した。初期評価によりMBおよび無症候性の脳虚血病変の存在を確認し、MBの位置をマッピングした。追跡調査期間中に、各被験者に生じた脳卒中イベントに関する情報を収集した。

結果：2102例中93例（4.4％）にMBが認められた。追跡調査期間中に44例（21％）が脳卒中を発症した。MBを有する被験者群は脳卒中発症率が有意に高かった。MBの独立した危険因子は年齢および高血圧であった。MBの存在は、脳虚血脳卒中（ハザード比=4.48、95％CI：2.20～122）よりも深部脳出血と一層強く関連していた（ハザード比=50.2、95％CI：16.7～150.9）。出血性脳卒中はいずれも脳深部で生じており、脳深部に位置するMBと関連していた。

結論：健常高齢者であっても、MBの存在は出血性・虚血性脳卒中の予後因子となることが、本研究で証された。

Stroke 2011; 42: 1867-1871

KEYWORDS 高血圧、脳内出血、磁気共鳴画像法、微小出血、予防、危険因子

T2*強調MRIスキャンでは、脳内微小出血（microbleed：MB）は斑点状の低信号病変として示され、脳卒中患者に観察されることが多い。脳内出血（intraependural hemorrhage：ICH）患者または虚血性脳管損疾患患者の場合、MBの存在によって高い適中率で将来性的出血性脳卒中や虚血性脳卒中再発が予測できる1-2。最近実施されたメタアナリシスでは、虚血性脳卒中再発者の44％、ICH再発者の83％にMBが認められることが示されている3。一方、脳血管疾患や神経症状のない人々では、MB出現率は5～6％程度にすぎず4,5。健常高齢者におけるMB出現は肥満や慢性高血圧と関連がある4。脳卒中患者におけるMBの臨床的意義については、さまざまな研究が実施されているが、MBを有する健常者の長期予後を検討した研究はこれまでに1件しかできない7。

一般に、健常高齢者の場合においても、無症候性脳梗塞や皮質下白質変性は、将来的な脳卒中発症の有力な危険因子であると考えられている8,9。脳卒中患者では、こうした無症候性の虚血性病変とMBが併存することが多く10。したがって、これらの病変がそれぞれ脳卒中発症にどのように寄与しているかを理解することは重要である。我々は、健常高齢者にみられるMBおよび無症候性脳血管病変と、将来的な脳卒中発症の間に独立した関連があるかどうかを検討するため、前向き研究を実施した。さらにMBの分布はその基準に、それぞれ別個の血管病理が存在することを示していると考えられ、近年注目を集めている。脳梗塞のMBは脳アミロイド血管病と、脳深部のMBは高血圧性血管病とそれぞれ関連がある11。そこで同じコホートを用いて、MBの分布と将来的な脳卒中イベントの関係を詳しく検討した。

材料および方法

被験者

2001～2007年に鳥取大学病院で自発的に頚血管を受診した、連続2238例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確の神経学的検査、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</th>
<th>SBI</th>
<th>PVH</th>
<th>SWML</th>
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<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>
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<td>男性</td>
<td>1.46 (1.77～2.78)</td>
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<td>1.61 (1.06～2.46)</td>
<td>0.03</td>
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<td>4.21 (2.20～8.08)</td>
<td>&lt; 0.0001</td>
<td>2.27 (1.62～3.19)</td>
<td>&lt; 0.0001</td>
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<td>糖尿病</td>
<td>1.14 (0.52～2.51)</td>
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<td>1.52 (0.96～2.41)</td>
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</tr>
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<td>0.76</td>
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<td>0.55 (0.28～1.06)</td>
<td>0.07</td>
<td>1.03 (0.69～1.54)</td>
<td>0.87</td>
</tr>
<tr>
<td>飲酒</td>
<td>1.45 (1.68～3.07)</td>
<td>0.34</td>
<td>1.18 (0.75～1.86)</td>
<td>0.47</td>
</tr>
</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：無症候性脳硬変、PVH：脳室周囲高信号域、SWML：皮質下白質病変。

神経症の既往がないこと、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（脳不全、肝機能障害、心不全）がないこと、本研究対象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、本研究データ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1年1回の面接において健康状態を確認した。医学的要因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報告することを含める対象者の詳細を収集することによって、すべての情報源の情報の収集を試みた。これらの情報源から得られた情報に基づき、脳卒中や脳腫瘍、脳性疾患、胃癌、真性血友病を併用した。脳梗塞については、Trial of ORG 10172 in Acute Stroke Treatment（TOAST）基準[2]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選択した。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χ²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解析により、無症候性脳硬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法により日積算脳卒中率を推定し、ログランク検定を用いて各群の生存率を比較した。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。

結果

2,102例中93例（4.4%）にMBが認められ、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%）は脳葉領域にMBが存在した。その他の無症候性脳硬変も各部位にみられ、262例（12.5%）に無症候性脳梗塞を、105例（5.0%）に脳室周囲高信号域（+）と、358例（17.5%）に皮質下白質病変（+）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、
表2 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

<table>
<thead>
<tr>
<th></th>
<th>虚血性脳卒中</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>变数</td>
<td>HR (95% CI)</td>
<td>p 値</td>
</tr>
<tr>
<td>MB あり</td>
<td>4.48 (2.20 ～ 12.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SBI あり</td>
<td>2.94 (1.26 ～ 6.82)</td>
<td>0.012</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。

あらゆる無症候性脳病変の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合併症リスク係数を12例死亡し、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、8例は一過性脳虚血発作であった。TOAST基準に従って脳梗塞症例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卒中であった。MBのある被験者（21%）はICHのない被験者（16%）に比べて、脳卒中発症頻度が有意に高かった（p < 0.0001）。Kaplan-Meier法とロジット法を用いて無脳卒中率曲線を作成した（図）。臨床的脳卒中の頻度は、MBのない被験者よりもICH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、皮質下白質病変、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：1.20 ～ 15.6、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）はともに虚血性脳卒中の有意な危険因子であったが、MBの方はさらに有意に強力な予測因子であった。ただし、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）。

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。このような、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誠実であり、過去の研究では、MBのある患者のICH発症リスクはMBのない患者の7倍であった。このうち、MBの存在はICHのさらに強力な危険因子であることが示された。さらに、MBの存在はICHのさらに強力な危険因子であることが示された。さらに、MBの存在はICHのさらに強力な危険因子であることが示された。
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の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）。これは有意である。なぜなら、

上記の研究の被験者群には脳卒中のリスクが含まれていたが、我々の研究の被験者は比較的健康な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、脳血管病のない人々にみられる MB が、将来の脳梗塞発症の有効な予防因子であるという結果である。ただし、今回の研究では、年齢、

性別、高血圧以外の補正を行った結果、両者の間に関

係は認められなかった。本研究は以前の研究よりも被

験者数が多く、したがって、統計学的検出力も高かった

ため、臨床的変数の補正を行った後も、MB の存在と将来

の ICH 発症との関連についてより説得力のある証拠が示

された。

MB の分布は、ICH リスクに影響を及ぼす重要な因子

であると思われる。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症に関連して

あると考えられている。Warldaw らは、皮質脳卒中よりも

ラクナ梗塞の方が MB が観察される頻度が高く、白質病

変の発現率が高くなると報告している10。以上を繰ば

ると、これらの所見は、MB とラクナ梗塞の間に小血管疾

患などの共通する病理的背景が存在するという考えを

裏づける11。同様に本研究でも、ICH 発症例 10 例の

うち、MB を伴う 9 例では被験、視床、小脳に出血が認め

られた（表 3）。

注意しなければならないのは、一部の被験者において

脳葉領域に MB が認められたこと、この種の MB の発生

病理が深部脳領域の MB とは明確に異なることである11。

脳葉の MB は脳アミロイド血管症と関係があると思われ

る11。脳アミロイド血管症は、年齢にみられる脳葉の

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葉出血はみられなかった

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21 や、皮質下梗塞

および白質脳症を伴う常染色体優性遺伝性脳動脈症22,23

などの認知症患者にもみられることが多い。脳葉の MB の

存在が脳葉領域における ICH 発現と関係しているか否

かについては、さらに詳しく繋続研究が必要である。

本研究では、被験者の 44% が MB が観察された。この

割合は、Rotterdam Scan Study で報告された値（23.5%）21

に比べると低いものの、Framingham study (4.7%)2 と

Roob の報告 (6.4%)4 で示された値と同様である。MB の

頻度は、コートの特性、特に臨床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 の値の差は、後の研究に脳血管疾患の既往

のある被験者が含まれていたこと、後者の被験者の方が年

齢が高かったこと（平均年齢はそれぞれ 62.1 歳、69.6 歳）

に起因していると思われる。さらに MB の検出は、欧米

諸国よりも日本における方がより一層重要であると思われる。

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24、欧米

諸国の ICH 発症率（10%未満）25 とは異なるためであ

る。深部脳出血は脳葉出血よりも、日本国内の ICH

症例全体の 83% を占めていることが報告されている26。

本研究にはいくつかの限界がある。第一に、本研究で

は追跡調査期間中の内科的治療に関する情報は得られな

かった。特に、MB を有する患者の出血性イベントリス

クを増大させる可能性のある、抗血栓薬の潜在的必要性

を検討することはできなかった27,28。第二に、主要な追跡

調査の方法が郵送による質問紙調査に依存していたため、

血圧や血糖値のコントロール状況についてもデータを収
結論

疾患高齢者の場合でも、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場合には、良質の高血圧が認められるため、MBを有する患者には集中的な降圧薬治療を実施し、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


