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. A recent meta-analysis revealed that MBs were present in 44% of patients with recurrent ischemic stroke and 83% with recurrent ICH. On the other hand, MBs only occur in approximately 5% to 6% of subjects without cerebrovascular disease or neurological symptoms. The occurrence of MBs in healthy elderly subjects is associated with advanced age or chronic hypertension. 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.

Even in healthy elderly individuals, silent brain infarctions and subcortical white matter lesions are generally thought to be strong risk factors for subsequent stroke. These asymptomatic ischemic lesions often coexist with MBs in patients with stroke; 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. 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. 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>
<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>
<tbody>
<tr>
<td>Age per 1 y</td>
<td>1.08 (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>
</tr>
<tr>
<td>Sex, male</td>
<td>1.46 (0.77–2.78)</td>
<td>0.25</td>
<td>1.61 (1.06–2.46)</td>
<td>0.03</td>
<td>0.80 (0.41–1.56)</td>
<td>0.51</td>
<td>0.86 (0.58–1.25)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypertension</td>
<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>
<td>1.54 (0.91–2.61)</td>
<td>0.10</td>
<td>2.03 (1.50–2.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.14 (0.52–2.51)</td>
<td>0.75</td>
<td>1.52 (0.96–2.41)</td>
<td>0.07</td>
<td>1.66 (0.82–3.36)</td>
<td>0.16</td>
<td>0.76 (0.46–1.26)</td>
<td>0.29</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>0.93 (0.55–1.57)</td>
<td>0.79</td>
<td>1.09 (0.79–1.52)</td>
<td>0.59</td>
<td>2.04 (1.17–3.54)</td>
<td>0.01</td>
<td>1.31 (0.97–1.77)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.96 (0.91–4.22)</td>
<td>0.08</td>
<td>1.09 (0.62–1.94)</td>
<td>0.76</td>
<td>1.39 (0.63–3.11)</td>
<td>0.42</td>
<td>1.51 (0.91–2.50)</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking</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>
<td>1.07 (0.55–2.10)</td>
<td>0.84</td>
<td>1.11 (0.75–1.64)</td>
<td>0.61</td>
</tr>
<tr>
<td>Alcohol habit</td>
<td>1.45 (0.68–3.07)</td>
<td>0.34</td>
<td>1.18 (0.75–1.86)</td>
<td>0.47</td>
<td>1.32 (0.63–2.80)</td>
<td>0.47</td>
<td>1.07 (0.69–1.69)</td>
<td>0.76</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 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 had already experienced symptomatic cerebrovascular events in subjects without a history of hemorrhagic or ischemic 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
Microbleeds Are Associated With Subsequent Hemorrhagic and Ischemic Stroke in Healthy Elderly Individuals
Hirokazu Bokura, Reiko Saika, Takuya Yamaguchi, Atsushi Nagai, Hiroaki Oguro, Shotai Kobayashi and Shuhei Yamaguchi

Stroke. 2011;42:1867-1871; originally published online May 19, 2011; doi: 10.1161/STROKEAHA.110.601922

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/7/1867

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/05/19/STROKEAHA.110.601922.DC1
http://stroke.ahajournals.org/content/suppl/2012/08/21/STROKEAHA.110.601922.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at: http://stroke.ahajournals.org/subscriptions/
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 ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, and/or a history of hypertension with anti-hypertension therapy. Diabetes mellitus was defined as a fasting serum glucose level ≥ 126 mg/dl, hemoglobin A1c level ≥ 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°) 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. 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. SWML was graded on a scale of 0 to 3 according to the Fazekas’ grading scheme, where 0 = absent, 1 = punctate, 2 = beginning of confluence, and 3 = confluence. 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
Full Article

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; Reiko Saika, MD, PhD1; Takuya Yamaguchi, MD, PhD1; Atsushi Nagai, MD, PhD1; Hiroaki Oguro, MD, PhD1; Shotai Kobayashi, MD, PhD1; Shuhei Yamaguchi, MD, PhD1

1 Department of Neurology, Faculty of Medicine, Shimane University; and 2 Shimane University Hospital, Izumo, Japan

背骨および目的：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）が認められることも多い。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：島根県病院で当院にて自己血液検査を受けた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、各被験者に起き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14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、虚血性脳卒中（ハザード比=4.48, 95% CI: 2.20-12.2）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深部脳卒中であった。

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

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（intracerebral hemorrhage: ICH）患者または無症候性脳血管疾患患者の場合、MB の存在によって高い適中率で将来の出血性脳卒中や虚血性脳卒中再発が予測できる 23。最近実施されたメタアナリシスでは、虚血性脳卒中再発患者の44％、ICH再発患者の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 45。健常高齢者におけるMB出現は加齢や慢性高血圧と関連がある 6。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件しかない 7。

一般に、健常高齢者の場合も、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 56。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 57。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および無症候性脳虚血発症と、将来的な脳卒中発症の間に独立した関連があるか否かを検討するため、前向き研究を実施した。さらに、MBの分布はその基盤に、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。脳卒中の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 8。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年に島根県病院研究所で自己血液検査を受けた、連続2238例を対象に前向き研究を実施した。検査には、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聴取、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
<table>
<thead>
<tr>
<th>変数</th>
<th>MB</th>
<th>SBI</th>
<th>PVH</th>
<th>SWML</th>
</tr>
</thead>
<tbody>
<tr>
<td>年齢（1歳あたり）</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 (1.06～1.13)</td>
</tr>
<tr>
<td>男性</td>
<td>1.46 (1.77～2.78)</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>高血压</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>糖尿病</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>脳卒中既往家族歴</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>虚血性心疾患</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>喫煙</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>飲酒</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>

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回の割合で問合票を郵送した。医学的要因が事前に報告された場合は、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、被験者が過血症の神経内科医に脳血管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を収集した。これらの情報源から得られた情報をに基づき、脳卒中の種類（脳梗塞、一過性脳虚血発作、ICH、くも膜下出血）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。

図：MBなし（n=2,009）とMBあり（n=93）のリスク指標に対するKaplan-Meier曲線

表1 無症候性のMRI病変の危険因子

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、ロジスティッ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。

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%)は脳幹領域にMBが存在した。その他の無症候性脳病変も認められ、262例(12.5%)に無症候性脳梗塞が、105例(5.0%)に脳室間隔高信号域(+)が、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、
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含む重症疾患により12例が死亡し、1例がICHにより死亡した。44例(21.4%)が脳卒中発症し、このうち22例は脳梗塞、10例はICH、4例は心臓臓器出血、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[18例 (19.4%)]はMBのない被験者[26例 (13.0%)]に比べて、脳卒中発症頻度が有意に高かった（p < 0.0001)。

Kaplan-Meier法とロジスティック回帰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、脳卒中既往歴、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）はともに虚血性脳卒中の有意な危険因子であつたが、MBの方がはるかに有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）。

他の因子と将来的脳卒中イベントとの間に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が脳葉領域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例はいずれも深部脳領域にMBが存在しており、このうち50%は脳葉領域にもMBが認められた。MBの位置（深部脳領域のみ、深部脳領域と脳葉領域の両方など）は、ICHか虚血性脳卒中かの違いに有意な影響を及ぼしていなかった。深部脳領域

表2 将来・間聴的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>因子</th>
<th>虚血性脳卒中</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>(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、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、その存在は将来的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制式であり、過去の研究では、MBのある者のICH発症リスクはMBのない者の7倍であったが、将来の出血性脳卒中または虚血性脳卒中はどちらもMBに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、被験者はすでに脳卒中或いは脳梗塞をきたした患者であった。さらに、研究結果において、MBを有する者は、脳卒中発症リスクが5倍以上高かった（p < 0.0001）。

MBを有する者は、脳卒中発症リスクが5倍以上高かった（p < 0.0001）。

最近実施された陥断研究において、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。この研究
表3 追跡調査期間中に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：微小出血、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なった。それぞれ17％（4.4％）、それに相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）。これは因を得ることである。なぜなら、上記の研究の被験者群において脳卒中のリスクが高まっていたが、我々の研究の被験者は比較的健康な者があったからである。いずれにしてみ、以前の研究と今回の研究の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、本研究及び以前の研究では、性別、高血圧に基づく補正を行った結果、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ると考えられている。Wardlaw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15。以上を総合すると、これらの所見は、MBとラクナ梗塞の間に小血管疾患との共通する病理学的背景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（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幹領域にMBが認められること、この種のMBの発生頻度が深部脳領域のMBとは明らかに異なることである16。脳幹のMBは脳アミロイド血管症と関係があると言われる19。脳アミロイド血管症は、高齢者にみられる脳幹の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発血はみられなかったが、これはおそらく、本研究では80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、皮質下梗塞および白質脳症を伴う常染色体優性遺伝性脳動脈症21.22などを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、さらに詳しく継続研究が必要である。

本研究では、被験者の4.4％にMBが観察された。この割合は、Rotterdam Scan Studyで報告された値(23.5％)23に比べると低いものの、Framingham study (4.7％)24やRoobの報告(6.4％)1で示された値と同様である。MBの頻度は、コートの特性、特に臨床症状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、後者の被験者が高齢だったこと（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25、欧米諸国のICH発症率（10％未満）25とは異なっているためである。深部脳出血は脳発血よりも多く、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。

本研究で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、抗血栓薬の潜在的重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
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。

研究費の源

本研究の一部は、Mitsubishi Pharma Research Foundationの助成金およびJSPS（日本学術振興会）の科学研究費補助金を受けて实施された。

情報開示
なし。

References