Asymptomatic Cerebral Microbleeds Seen in Healthy Subjects Have a Strong Association With Asymptomatic Lacunar Infarction

Michiya Igase, MD^{*,†}; Yasuharu Tabara, PhD^{*,†}; Keiji Igase, MD^{††}; Tokihisa Nagai, MD^{*}; Namiko Ochi, MD^{*,†}; Tomoko Kido, MD^{*,†}; Jun Nakura, MD^{*}; Kazuhiko Sadamoto, MD^{††}; Katsuhiko Kohara, MD^{*}; Tetsuro Miki, MD^{*,†}

Background: Cerebral microbleed (CMB), which is conspicuous on gradient-echo T2*-weighted magnetic resonance imaging, is a risk factor of intracerebral hemorrhage (ICH). CMBs have been detected even in neurologically healthy persons, who also seem prone to be affected by stroke, not only ICH but also cerebral infarction.

Methods and Results: The presence of CMB was investigated in brain dock participants, making reference to silent lacunar infarction (SLI). Participants comprised 377 neurologically healthy persons and 21 (5.6%) had CMB detected, which was associated with a high incidence of hypertension, other conventional risk factors having no significant correlation with CMB. In a simple correlation analysis, CMB showed a positive association with age and systolic blood pressure (SBP). Logistic regression analysis revealed that SLI was the factor most strongly associated with CMB. Moreover, individuals who had both CMB and SLI had higher SBP than other groups.

Conclusions: The etiology of CMB is similar to that of SLI. (Circ J 2009; 73: 530–533)

Key Words: Aging; Cerebrovascular circulation; Hypertension; Metabolic syndrome

Gradient-echo T2*-weighted magnetic resonance imaging (MRI) is highly sensitive in the detection of old and recent cerebral hemorrhage.¹ Cerebral microbleeds (CMB), which appear as rounded foci <5 mm in size and hypointense on T2*-weighted MRI, are distinguishable from other intracerebral hemorrhages (ICH), and distinct from flow voids, leptomeningeal hemosiderosis or non-hemorrhagic subcortical mineralization. Reduction in the gradient-echo MRI signal is caused by hemosiderin deposits.²

CMB are commonly present on T2*-weighted MRI among patients with symptomatic stroke³ and are considered to be a risk factor for the occurrence of ICH.^{4,5} However, it has been recently reported that even neurologically healthy persons have asymptomatic CMB on MRI⁶ and although the incidence in those who are healthy is lower than that in patients with a hemorrhagic history, the presence of these lesions seems to have a close correlation to risk factors for primary ICH.⁷ Thus, CMB never should be a negligible finding on MRI because their existence may portend lethal stroke.

Silent lacunar infarction (SLI), which is defined as vascular lesions ≥3 mm in diameter on MRI and detected in 20% of healthy elderly people, is also increasingly found in mass screenings using MRI and is considered to be an excellent

predictor of stroke.^{8,9} Moreover, it is well known that the incidence of clinical stroke is significantly higher in subjects with SLI than in those without.

Given the importance of these 2 MRI findings in stroke patients, it would contribute to the prevention of future stroke to confirm both the frequency of CMB and the background of healthy subjects. Therefore we investigated the presence of CMB in relation to the coexistence of SLI in healthy participants who visited for routine medical check-ups.

Methods

Three hundred and seventy seven subjects, who visited the Anti-Aging Center (AAC) at Ehime University Hospital for a medical check-up, including brain dock, between February 2006 and September 2007 were enrolled in this study in which all subjects were confirmed to be neurologically healthy (M/F=149/228; mean age, 67.6±7.8 years (range 38–91)). All participants completed a simple self-administered questionnaire regarding their life-style and underwent a physical and neurological examination by a staff member. Current smoker was defined as someone who smokes every day, and habitual drinking was defined as alcohol consumption on more than 1 day per week. Body mass index (BMI) was calculated as kg/m² and clinical blood pressure (BP) was measured after resting for at least 5 min while seated. Blood samples collected after overnight fasting were used for evaluation of risk factors. Visceral fat area was measured by computed tomography. Cranial MRI was performed with a 3.0-tesla Signa EXITE HD 3.0T (GE Yokogawa Medical, Tokyo, Japan) and T2*-weighted gradient-echo MRI was done in the axial plane. Standard T1- and T2-weighted images were also obtained. CMBs were defined as a small hypointense signal (<5 mm in diameter) with a well-defined

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^{*}Department of Geriatric Medicine, ^{**}Department of Fundamental Medical Science, Ehime University Graduate School of Medicine, [†]Anti-Aging Center, Ehime University Hospital, Toon and ^{††}Department of Neurosurgery, Washokai Sadamoto Hospital, Matsuyama, Japan

Mailing address: Michiya Igase, MD, Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Sitsukawa, Toon 791-0295, Japan. E-mail: migase@m.ehime-u.ac.jp

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Table 1. Patient Characteristics

	CMB(+) (n=21)	CMB(-) (n=356)	P value
Male sex (%)	38.1 (8)	39.6 (141)	0.890
Age (years)	72.1±5.8	67.3±7.8	0.006
Current smoker (%)	4.8 (1)	5.3 (19)	0.692
Habitual drinker (%)	23.8 (5)	30.6 (109)	0.469
Antiplatelet therapy, n (%)	9.6 (2)	4.5 (16)	0.265
BMI (kg/m ²)	22.8±3.7	23.1±3.0	0.984
SBP (mmHg)	146.5±23.0	139.2±20.0	0.091
DBP (mmHg)	81.5±12.3	78.3±11.7	0.225
HR (beats/min)	69.2±11.6	67.0±10.7	0.700
TC (mmol/L)	209.0±37.4	215.3±33.7	0.405
TG (mmol/L)	96.1±45.3	103.8±60.2	0.567
HDL-C (mmol/L)	68.5±23.0	67.5±19.0	0.825
LDL-C (mmol/L)	119.5±27.4	126.8±31.2	0.324
HOMA-IR	1.5±0.8	1.7±2.2	0.827
VFAT (cm ²)	114.9±73.0	104.1±65.0	0.248
U-Alb/Cr (mg/g Cr)	21.4±35.0	27.5±67.0	0.680

CMB, cerebral microbleed; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment index for insulin resistance = $\text{IRI}(\mu\text{U/ml}) \times \text{FBS}(\text{mg/dl}) / 405$; VFAT, visceral fat areas; U-Alb/Cr, urinary albumin/Cr.

margin on the T2*-weighted images and these were allocated and quantified independently by 2 experienced neurologists on a consensus basis without knowledge of the clinical information. Inter-observer agreement was found to be very good. Lesions were categorized as cerebral cortex, thalamus, basal ganglia, cerebellum, cerebral white matter or brainstem. Symmetrical signal loss in the basal ganglia was ignored because of physical calcification and iron deposition. SLI⁸ was defined as small lesions of hyperintensity on T2-weighted MRI corresponding to distinctive low-intensity areas on the T1-weighted MR image. For the assessment of white matter lesions, we determined the grade of paraventricular hyperintensity (PVH) in all MRI sections according to the Japan Brain Dock Guideline:¹⁰ 0, absent or only “rim”; 1, limited lesion-like “caps”; 2, irregular “halo”; 3, irregular margins and extension into the deep white matter; 4, extension into the deep white matter and subcortical portion. An MRI study that yielded borderline results was automatically assigned to the lower grade.

In order to scrutinize the association between CMBs and SLI, participants were divided into 4 groups according to their presence or absence: group A, absence of both CMB and SLI; group B, SLI but without CMB; group C, CMB but without SLI; group D, coexistence of CMB and SLI.

Statistical Analysis

All values are expressed as mean±standard deviations or number of participants (%). A 2-sided unpaired t-test was used to estimate differences between 2 groups in mean

Table 2. Logistic Regression Analysis for CMB

	OR (95%CI)	P value
Age	1.083 (1.01–1.162)	0.026
BMI	0.945 (0.726–1.229)	0.672
SBP	1.012 (0.987–1.037)	0.343
HR	1.002 (0.956–1.051)	0.923
TC	0.997 (0.981–1.014)	0.728
TG	0.999 (0.988–1.011)	0.916
HDL-C	1.015 (0.984–1.047)	0.343
HOMA-IR	0.835 (0.511–1.366)	0.473
VFAT	1.000 (1.000–1.000)	0.281
SLI	5.813 (2.037–16.59)	0.001

OR, odds ratio; CI, confidence interval; SLI, silent lacunar infarction. Other abbreviations see in Table 1.

Figure 1. Comparison of systolic blood pressure among the 4 groups. *P<0.05 vs Group A.

values of continuous measures and prevalence rates, respectively. Statistical analyses for differences among 4 groups were performed by one-way ANOVA with significances evaluated with the Bonferroni post hoc analysis. The χ^2 test for independence was used for comparison of CMB with SLI. The odds ratio (OR) with a 95% confidence interval for the presence of CMBs was calculated using multiple logistic analysis, even after adjustment for significant covariates. Statistical significance was defined as P<0.05, 2-tailed. All statistical analyses were performed using the SPSS program, version 10.0 (SPSS, Chicago, IL, USA) for Windows XP.

Results

The overall incidence of CMBs was 5.6% (21/377) and they were present in 5.4% (8/149) of men and 5.7% (13/228) of women (**Table 1**). CMB occurred in the cere-

Table 3. Correlation Between the Severity of PVH and the Presence of CMB

	PVH grade					P value
	0	1	2	3	Total	
CMB(-)	226 (63%)	106 (30%)	21 (6%)	3 (1%)	356 (100%)	0.001
CMB(+)	9 (43%)	6 (29%)	4 (19%)	2 (9%)	21 (100%)	
Total	235 (62%)	112 (30%)	25 (7%)	5 (1%)	377 (100%)	

PVH, paraventricular hyperintensity. Other abbreviation see in Table 1.

bral cortex (n=6), thalamus (n=6), basal ganglia (n=5), cerebellum (n=4), cerebral white matter (n=2), and brain stem (n=1). In all cases, there was a solitary CMB lesion, except for 1 case of 3 CMB lesions. CMB was profoundly associated with an incidence of hypertension (ie, 17 (81%) patients had a history of hypertension; other factors such as gender, antiplatelet therapy, BMI, total cholesterol level, triglyceride level, high-density lipoprotein-cholesterol level, low-density lipoprotein-cholesterol level, insulin resistance, visceral fat area, and micro-albuminuria did not influence the presence of CMBs, albeit in 1 case of smoking habit). Simple correlation analysis explicitly showed that CMB had a positive correlation with age ($P=0.006$) and systolic BP (SBP) ($P=0.091$), which had no clinical significance (Table 1).

Of the 377 patients, 38 (10.1%) had SLI and 8 of those (21.1%) had CMBs, whereas only 13 of 339 without SLI (3.8%) had CMBs ($P<0.001$, Fisher's exact test). Furthermore, logistic regression analysis revealed that SLI might be the factor most strongly associated with the occurrence of CMBs (OR 5.813, $P=0.001$) (Table 2).

In the 4-group analysis, individuals with both CMB and SLI (group D) had higher SBP compared with the other groups ($P=0.007$) (Figure 1); however, there was no significant difference among the 4 groups for the other conventional risk factors (data not shown). Fascinatingly, the CMB group had more severe grades of PVH than the control group and there was a significant correlation between the severity of PVH and the presence of CMB ($P<0.0001$) (Table 3).

Discussion

This study demonstrated that the overall incidence of CMB in the AAC participants was 5.6%, which would reflect the incidence of CMB in healthy Japanese populations. So far, the prevalence of CMB has been investigated in various healthy populations; for instance, in elderly subjects without cerebrovascular diseases it was between 5% and 6%,¹¹ and Tsushima et al⁶ reported that CMB incidence was 3.1% in 450 neurologically healthy Japanese adults. In addition, it was closely related to the presence of hypertension ($P<0.0001$) and heavily cigarette smoking ($P=0.003$). The prevalence of CMB obtained from our study seems to be higher, which may be attributable to the older age of our subjects and/or higher accuracy in detecting CMB by using a high field system (3 tesla MRI).

Tsushima et al⁷ showed that CMB occurs more frequently in deep structures as compared with lobar hemispheres, and our study revealed that CMB was preferentially seen in deep structures compared to few CMB seen in the lobar hemispheres, which are a common site for hypertensive cerebral hemorrhages. Accordingly, these results suggest associated modifiable risk factors such as high BP.

In this study, 21.1% of all subjects with SLI had CMB compared with 3.8% subjects without SLI ($P<0.001$, Fisher's exact test), which may be accounted for by the similar etiology of SLI and CMB. Why does CMB coexist with SLI? Wardlaw et al³ demonstrated that their coexistence on MRI suggest that they share common pathophysiological mechanisms involving increased permeability of cerebral micro-vessels. Lee et al¹² investigated whether CMB might be a risk factor for ICH in hypertensive patients with leukoaraiosis, concluding that CMBs may be applicable for predicting the risk of ICH in such patients. Naka et al¹³ have

also shown that a combination of CMB and advanced white matter hemorrhage is a major risk factor for subsequent recurrent stroke. In our data, the CMB group seemed to show more severe grades of PVH than the control group, and there was a significant correlation between the severity of PVH and presence of CMB ($P<0.001$). According to these results, both CMB and SLI have a close correlation with small-artery disease. On the other hand, exclusive risk factors for CMB have been recently proven; that is, a high level of blood homocysteine, known as a strong risk factor for cardiovascular disease, appears to be associated with ischemic small artery disease, such as leukoaraiosis, rather than with bleeding-prone small-artery diseases such as CMB.¹⁴

Earlier studies have highlighted the relationship between CMB and some conventional factors (eg, age, BP, smoking, white matter lesion and lacunar infarction seen on MRI, and gender);^{15,16} however, they only evaluated factors for ischemic diseases. To address this issue, we divided our participants into 4 groups, leading to a conclusion that individuals who have CMB, but not SLI, did not have any significant correlation with conventional risk factors including smoking, lipid profile and sugar metabolism, whereas age and SBP, which are known risk factors for hypertensive ICH, had a significant correlation with CMB. Taken together, it suggests that the mechanisms of CMB are similar to those for hypertensive ICH.

Moreover, Kato et al¹⁷ have shown that the number of CMB in atherothrombotic infarction patients is not statistically different from the number in controls; on the contrary, the number of CMB in patients with ICH or SLI was significantly greater than that in controls, so the risk factors for CMB might be completely different from the so-called conventional risk factors^{18–20} for atherothrombotic infarction. More recently, Vernooij et al²¹ showed that strictly lobar CMB are related to cerebral amyloid angiopathy, whereas CMB in a deep or infratentorial location result from hypertensive or atherosclerotic microangiopathy. However, further evaluation are essential to elucidate these issues.

Perspectives

CMB may be a target for damage by high BP and the meaning of CMB in physically healthy persons should be ascertained by future examinations.

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