Relations of Blood Inflammatory Marker Levels With Cerebral Microbleeds

Kaori Miwa, MD; Makiko Tanaka, MD; Shuhei Okazaki, MD; Shigetaka Furukado, MD; Manabu Sakaguchi, MD; Kazuo Kitagawa, MD

Background and Purpose—Cerebral microbleeds (CMB) are observed in the elderly and have been regarded as one of the manifestations of small vessel disease. Although inflammatory processes have attracted much attention not only in large-artery disease, but also in small vessel disease, their involvement in CMB remains to be determined. The purpose of this study is to clarify relations between inflammatory marker levels and CMB.

Methods—Four hundred thirty-one patients without histories of cerebrovascular diseases were prospectively enrolled. The presence and number of CMB were assessed on gradient-echo magnetic resonance imaging. As common inflammatory markers, serum levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and interleukin-18 (IL-18) were evaluated.

Results—CMB were found in 65 patients (15%). In 35 patients, at least one CMB was found in deep locations, but 30 patients had strictly lobar CMB. Levels of hsCRP, IL-6, and IL-18 were higher in patients with CMB than in those without. Logistic regression analyses showed that each 1SD increase in each inflammatory marker level was significantly associated with the presence of CMB after adjustment for age and sex, and after additional adjustment for cardiovascular risk factors, silent lacunar infarction, and white matter hyperintensity. The OR (95% CI) of hsCRP, IL-6, and IL-18 was 1.81 (1.35–2.46), 1.73 (1.18–2.61), and 2.41 (1.44–4.52), respectively. Furthermore, the inflammatory marker levels were associated with both deep and lobar CMB.

Conclusions—Higher levels of hsCRP, IL-6, and IL-18 are associated with CMB, in both deep and lobar locations, suggesting the involvement of inflammation in CMB. (Stroke. 2011;42:3202-3206.)

Key Words: cerebral microbleeds ■ inflammation ■ high-sensitivity C-reactive protein ■ small vessel disease
of patients had been referred from another hospital or department for risk assessment and primary or secondary prevention of stroke. At the time of referral, comprehensive neurological evaluations were performed by stroke neurologists, including measurement of the carotid intima-media thickness (IMT), which reflects the severity of atherosclerosis; patients also underwent MRI, which indicates imaging evidence of stroke. When neither neurological symptoms nor a history of stroke or transient ischemic attack were identified, the patient was considered to be eligible for this study. Most MRIs were performed to evaluate suspicious neurological symptoms (e.g., headache, vertigo, dizziness, numbness, syncope, or subjective memory impairment). During the study period, 804 patients were identified as candidates (Figure 1). We then excluded 49 patients in whom MRI examinations were not completed. Patients with a history of stroke or transient ischemic attack (n=275), or brain surgery (n=8), were excluded to eliminate any effects of clinical evident disease on CMB and the inflammatory markers. In addition, patients with collagen disease (n=11), subclavian artery stenosis (n=7), retinal artery occlusion (n=6), Bell’s palsy (n=3), or migraine (n=2), while the remaining individuals (n=235) were diagnosed as normal despite transient nonspecific symptoms. Baseline characteristics are summarized in Table 1, which demonstrates a higher prevalence of vascular risk factors. The study was approved by the local ethical review board, and all patients gave written informed consent.

MRI Protocol
MRI was performed with a 1.5T Signa Horizon (GE Medical System). The image protocol included: T1-weighted, fluid-attenuated inversion

Table 1. Baseline Characteristics According to CMB Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>No CMB</th>
<th>CMB</th>
<th>Deep CMB</th>
<th>Lobar CMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>431</td>
<td>366</td>
<td>65</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Age, y</td>
<td>69.3 (8.6)</td>
<td>68.9 (8.6)</td>
<td>71.7 (8.6)*</td>
<td>71.7 (8.1)</td>
<td>71.8 (8.2)</td>
</tr>
<tr>
<td>Male, %</td>
<td>52</td>
<td>51</td>
<td>60</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.0 (3.0)</td>
<td>23.0 (2.9)</td>
<td>23.4 (3.3)</td>
<td>24.4 (3.2)*</td>
<td>22.4 (3.1)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15</td>
<td>15</td>
<td>19</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>19</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>71</td>
<td>68</td>
<td>76</td>
<td>85</td>
<td>67</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134 (14)</td>
<td>134 (14)</td>
<td>134 (14)</td>
<td>136 (14)</td>
<td>131 (17)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76 (11)</td>
<td>77 (11)</td>
<td>75 (12)</td>
<td>76 (14)</td>
<td>73 (10)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19</td>
<td>19</td>
<td>16</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>107 (25)</td>
<td>106 (23)</td>
<td>114 (31)*</td>
<td>120 (33)†</td>
<td>109 (29)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.5 (0.7)</td>
<td>5.5 (0.7)</td>
<td>5.6 (0.7)</td>
<td>5.8 (0.7)</td>
<td>5.4 (0.6)</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>37</td>
<td>37</td>
<td>33</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>58 (16)</td>
<td>59 (16)</td>
<td>55 (16)</td>
<td>54 (15)</td>
<td>56 (18)</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>122 (31)</td>
<td>122 (31)</td>
<td>122 (31)</td>
<td>119 (33)</td>
<td>128 (33)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>125 (65)</td>
<td>122 (64)</td>
<td>143 (72)*</td>
<td>158 (82)†</td>
<td>126 (56)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>67.8 (18.5)</td>
<td>69.6 (17.6)</td>
<td>62.6 (13.8)†</td>
<td>59.7 (15.3)†</td>
<td>66.1 (11.1)</td>
</tr>
<tr>
<td>Antiplatelet/Warfarin use, %</td>
<td>35/3</td>
<td>33/2</td>
<td>41/6</td>
<td>42/8</td>
<td>40/4</td>
</tr>
<tr>
<td>IHD/PAD, %</td>
<td>8/4</td>
<td>8/3</td>
<td>9/8</td>
<td>9/11*</td>
<td>10/4</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>1.01 (0.5)</td>
<td>0.99 (0.5)</td>
<td>1.14 (0.5)*</td>
<td>1.23 (0.5)*</td>
<td>1.06 (0.5)</td>
</tr>
<tr>
<td>SRI, %</td>
<td>36</td>
<td>30</td>
<td>67†</td>
<td>82†</td>
<td>50†</td>
</tr>
<tr>
<td>PVH, median (IQR)</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
<td>3 (2–6)†</td>
<td>5 (2–6)†</td>
<td>3 (1.75–6)†</td>
</tr>
<tr>
<td>DWMH, median (IQR)</td>
<td>4 (2–9)</td>
<td>4 (1–6)</td>
<td>8 (3–12)†</td>
<td>8 (3–12)†</td>
<td>8 (2.75–11)†</td>
</tr>
<tr>
<td>hsCRP, mg/dl, median (IQR)</td>
<td>0.05 (0.02–0.11)</td>
<td>0.04 (0.02–0.09)</td>
<td>0.08 (0.05–0.18)†</td>
<td>0.11 (0.06–0.22)†</td>
<td>0.07 (0.03–0.16)*</td>
</tr>
<tr>
<td>IL-6, pg/dl, median (IQR)</td>
<td>1.40 (0.83–2.38)</td>
<td>1.34 (0.81–2.13)</td>
<td>2.02 (0.99–3.73)*</td>
<td>2.35 (0.91–3.83)*</td>
<td>1.78 (1.11–3.13)†</td>
</tr>
<tr>
<td>IL-18, pg/dl, median (IQR)</td>
<td>188.7 (143.3–269.4)</td>
<td>188.7 (135.8–257.6)</td>
<td>224.7 (171.8–296.7)†</td>
<td>249.0 (192.3–304.4)†</td>
<td>212.4 (165.2–292.1)†</td>
</tr>
</tbody>
</table>

CMB indicates cerebral microbleeds; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; PAD, peripheral artery disease; SRI, silent lacunar infarction; IMT, intima-media thickness; PVH, periventricular hyperintensities; IQR, interquartile range; DWMH, deep white matter hyperintensities; hsCRP, high-sensitivity C-reactive protein; IL, interleukin.

*P<0.05.
†P<0.01 compared with the CMB-negative group.
recovery sequence (FLAIR), T2-weighted, and GRE. GRE parameters were as follows: 22 axial images; field of view, 220 mm; slice thickness, 5 mm; interslice gap, 1.5 mm; 256×256 matrix; echo time, 20 ms; repetition time, 640 ms; and flip angle, 20°.

MRI Assessment
MRI assessment was performed by 2 trained observers who were blinded to clinical information. CMB were defined as punctate hypointense lesions <10 mm on GRE. Location and number of CMB were assessed. The locations of CMB were classified as: lobar (cortex, subcortex, and white matter), or deep or infratentorial (basal ganglia, thalamus, brain stem, and cerebellum). Microbleed mimics (eg, vessels, mineralization, air-bone interfaces, partial volume artifact at the edges of the cerebellum) were excluded. SLI were defined as focal lesions >3 mm and <15 mm with the hypointense lesion with a hyperintense rim on FLAIR images (when located supratentorially), with corresponding hypointensity on T2-weighted images and corresponding hypointensity on T1-weighted images. The degree of WMH was visually rated on FLAIR images using the Scheltens scale with slight modifications; ie, scores of 0 to 6 were given for deep WMH of the frontal, temporal, parietal, and occipital lobe (DWMH; range, 0–24) and scores of 0 to 2 were given for 3 periventricular hypointensities (PVH; range, 0–6). In a random sample of 10%, interrater reliability for the presence of CMB was k=0.86 and for the number of CMB was intraclass correlation coefficient=0.84.

Risk Factors
Hypertension was defined as blood pressure ≥140/90 mm Hg on measurements taken on at least 2 occasions, or use of antihypertensive medications. Diabetes was defined as fasting plasma glucose level ≥126 mg/dL, HbA1c level ≥6.1%, or use of antidiabetic therapy. Hyperlipidemia was defined as low-density lipoprotein cholesterol level ≥140 mg/dL, total cholesterol level ≥220 mg/dL, or triglycerides level ≥150 mg/dL; or use of cholesterol-lowering therapy. Estimated glomerular filtration rate (eGFR) was used as the Modification of Diet in Renal Disease method modified by the Japanese coefficient. Body mass index was calculated as weight [kg]/height [m]². Smoking was classified as current. Habitual alcohol intake was defined as alcohol drinking of >20 g/d.

Measurement of Inflammatory Markers
After MRI examination, blood was drawn with minimally traumatic venipuncture for measurement of serum inflammatory markers. Blood was centrifuged at 3000 rpm at 4°C for 15 minutes, and aliquots were stored at −80°C. Circulating hsCRP was measured by the latex turbidimetric immunosay with a sensitivity of 0.01 mg/dL (Shionogi Biomedical Laboratory Inc). Serum IL-6 and IL-18 were measured by enzyme-linked immunosorbent assay (High-sensitivity Quantikine Kit, R&D System; and Human IL-18 enzyme-linked immunosorbent assay Kit, MBL Co., Ltd., respectively). The detection limit was 0.10 mg/mL for IL-6, and 12.5 pg/mL for IL-18. The intraassay variation was 7.8% for IL-6 and 5.6% for IL-18; corresponding interassay coefficients were 7.2 and 7.6%, respectively.

Evaluation of Carotid Atherosclerosis
The carotid intima-media thickness was measured as previously described. Briefly, we calculated IMT by averaging the thickness at 12 sites: the near and far walls of both right and left distal common carotid artery, carotid bifurcation, and internal carotid artery.

Statistical Analysis
Baseline characteristics were compared using Student t test or χ² test as appropriate. Multivariate logistic regression analysis was performed with the presence of CMB as the dependent variable, with inclusion of independent clinical variables associated at the P<0.20 on univariate analysis in addition to age, sex, and traditional cardiovascular risk factors. CMB were categorized into dichotomous and trichotomous (CMB [−], single, multiple [≥2]) variables. We also examined CMB by location (deep, strictly lobar).

Results
Patient Characteristics
CMB were observed in 65 of 431 patients (15%); 32 patients had single CMB, and 33 patients had multiple CMB (Table 1, Figure 2). The presence of CMB were most commonly found in deep location (35/65 [54%]), followed by lobar location (30/65 [46%]; Table 1). All CMB (n=339) of 65 patients were equally distributed in lobar (55%) and deep areas (45%; Figure 2).

Relations Between CMB and Inflammatory Marker Levels
By univariate analysis, age, fasting glucose and triglyceride levels, IMT, prevalence of SLI, and degrees of PVH and DWMH were higher in patients with CMB than in those without, and eGFR was lower in patients with CMB than in those without. Similar associations were observed between traditional risk factors and deep CMB, but no association was observed between these parameters, except for MRI findings, and lobar CMB (Table 1). All inflammatory markers showed higher levels in patients with CMB (median, 0.08 for hsCRP, 2.02 for IL-6, and 224.7 for IL-18) than in those without (median, 0.04, 1.34, 188.7 respectively; Table 1, Figure 3). All inflammatory marker levels were also higher in patients with deep CMB (median, 0.11, 2.35, 249.0, respectively), lobar CMB (median, 0.07, 1.78, 212.4, respectively) or with single CMB (median, 0.08, 1.78, 219.0, respectively) or multiple CMB (median, 0.08, 2.31, 227.6, respectively) than in those without. However, no significant difference was seen between deep and lobar CMB, or between single and multiple CMB (Figure 3). The associations between inflammatory marker levels and CMB were summarized in Table 2. Logistic regression analyses showed that each 1SD-increase in each inflammatory marker level was significantly associ-
ated with the presence of CMB after adjustment for age and sex (Model 1), and after additional adjustment for hypertension, diabetes, hyperlipidemia, eGFR, PVH, DWMH, SLI, and IMT (Model 2). The OR (per 1SD increase; 95% CI) of each inflammatory marker (hsCRP, IL-6, IL-18) for the presence of CMB was 1.81 (1.35–2.46), 1.73 (1.18–2.61), and 2.41 (1.44–4.52), respectively (Model 2).

Furthermore, the associations between each inflammatory marker level and deep CMB or lobar CMB remained significant after adjustment for age and sex (Model 1) and after additional adjustment for traditional risk factors, IMT, eGFR, and other MRI findings (Model 2; Table 2).

### Discussion

We found that the levels of hsCRP, IL-6, and IL-18 were higher in patients with CMB than in those without. All these associations were independent of cardiovascular factors, IMT, WMH, and SLI, which have been partly shown to be associated with inflammatory markers as well.

In our study, there was no location-specific association of CMB with inflammation. This indicates that CMB is a marker for the general severity of SVD and also can be seen as the common downstream product of 2 separate pathways: hypertensive vasculopathy and cerebral amyloid angiopathy. Our data raise the possibility that inflammation may be important to pathogenesis of any CMB.

Numerous studies have shown associations of inflammation markers with myocardial infarction and stroke. However, a few studies examined stroke subtype, even less hemorrhagic stroke. The predictive value of hsCRP for hemorrhagic stroke has not been confirmed. Moreover, in the prospective study, CMB were shown to be indicative of a higher recurrent ischemic stroke risk. Therefore, CMB could be considered better as part of spectrum of SVD rather than as only hemorrhagic representation.

Endothelial dysfunction and disruption of blood–brain barrier (BBB) has been suggested as a main initial pathogenic feature in SVD. In severe WMH, inflammatory cells accumulated around vessels, in which the presence of hypoxia inducing factor-1α, macrophages, and matrix metalloproteinases support an inflammatory etiology. In the elderly, hemosiderin deposits occurred around capillaries, which might represent age-related vulnerability in BBB. Furthermore, CMB of severe cerebral amyloid angiopathy could be confirmed as the presence of β-amyloid in the vessel wall, where activated microglia and T lymphocytes expressing heme oxygenase-1 activity and late complement activation were prominent. They also reported that extravasated hemosiderin migrates through enlarged Virchow-Robin spaces, propagates an inflammatory reaction, and contributes to the formation of lacunar infarcts. These findings support our speculation that inflammation reflects vascular dysfunction leading to SVD, including CMB.

In this study, both IL-6 and IL-18 levels are associated with CMB. Although both cytokines are expressed in carotid atheromatous plaque, IL-6, but not IL-18, was associated with risk of recurrent ischemic stroke. IL-6 is a multifunctional cytokine that plays important roles in the regulation of the immune responses and inflammation, and is a main inducer of hepatic production of CRP. In contrast, IL-18 was originally

<table>
<thead>
<tr>
<th>CMB, Dichotomous</th>
<th>CMB, Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td>CMB Positive</td>
<td>CMB, Location</td>
</tr>
<tr>
<td>hsCRP 1.85 (1.41–2.45)§</td>
<td>1.81 (1.35–2.46)§</td>
</tr>
<tr>
<td>IL-6 1.97 (1.36–2.90)§</td>
<td>1.73 (1.18–2.61)‡</td>
</tr>
<tr>
<td>IL-18 2.48 (1.40–4.49)§</td>
<td>2.41 (1.44–4.52)‡</td>
</tr>
</tbody>
</table>

Values were log transformed for analysis.

CMB indicates cerebral microbleeds; SD, standard deviation; CI, confidence interval.

*Model 1: Adjusted for age and sex.
†Model 2: Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, eGFR, IMT, the presence of SLI, and the WMH (PVH, DWMH) grade.
§P<0.05.
‡P<0.01 compared with the CMB-negative group.
identified as an interferon-γ-inducing factor, and can enhance the production of other inflammatory molecules such as IL-1β, tumor necrosis factor-α, and the inducible form of nitric oxide synthase. The precise pathway between inflammation process and SVD is largely unknown and needs additional investigation.

Our results have some limitations. First, the cross-sectional design limits causal inferences. Second, our results are limited to the cohort of elderly individuals with highly prevalent vascular risk factors, and therefore they are not generalized to the general population. Although the prevalence of CMB (15%) in this study is higher than that in the general population, it is in line with other estimates of elderly and hypertensive subjects. The significance of CMB and inflammation in patients with a history of stroke remains unclear and needs additional investigation. Third, hsCRP levels were low because of ethnic differences and of reflecting the prevalence of relatively controlling vascular risk factors. The differences in hsCRP levels probably indicate the difficulty of determining thresholds and replication. Fourth, the sample size was relatively small, and most patients with CMB had only 1.

In conclusion, our study demonstrated that higher inflammatory marker levels were evident in subjects with CMB, regardless of location. If inflammation can be proven to be a component of CMB in the prospective study, patients with inflammatory pattern may be more prone to bleeding complications in addition to hypertension treatment; a selective screening of this process may warrant and specific treatment reducing the level of inflammation might be tested.

Acknowledgments
We thank Ms C. Kurano and K. Nishiyyama for their secretarial assistance.

Sources of Funding
The present study was supported in part by the Smoking Research Foundation of Japan.

Disclosures
None.

References
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Stroke. 2011;42:3202-3206; originally published online August 25, 2011;
doi: 10.1161/STROKEAHA.111.621193

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血中炎症マーカー値と脳内微小出血の関連

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Department of Neurology, Osaka University Graduate School of Medicine.

背景および目的：脳内微小出血（CMB）は高齢者にみられ、小血管病変の微候の1つと考えられている。炎症過程は、大血管病変のみならず小血管病変においても非常に注目されているが、CMBへの関与は明らかにされていない。本研究の目的は、炎症性マーカー値とCMBとの関連を明らかにすることである。

方法：脳血管疾患の既往のない患者431例を対象に、CMBの有無および深度を、グラディエントエコーMRにより評価した。一般的な炎症マーカーとして、感度を再現性蛋白（hsCRP）、インターロイキン6（IL-6）、インターロイキン18（IL-18）の血清中濃度を評価した。

結果：CMBは65例（15%）で認められた。35例では1箇所以上のCMBを深度に認めたが、30例では脳葉に限局したCMBであった。CMBを有する患者のhsCRP、IL-6、およびIL-8濃度は、CMBのない患者と比較して高かった。年齢および性別について補正した後、さらに心血管系危険因子、無症候性ラクナ梗塞、および白質高信号域について補正したロジスティック回帰分析では、各炎症マーカー値の1SDの上昇はCMBの存在と有意に関連していることが示された。hsCRP、IL-6、およびIL-8のOR（95% CI）は、それぞれ1.81（1.35～2.46）、1.73（1.18～2.61）、および2.41（1.44～4.52）であった。さらに炎症マーカー値は、深部および脳葉の両方のCMBと関連していた。

結論：高濃度のhsCRP、IL-6、およびIL-8は、深部および脳葉の両方のCMBと関連しており、CMBへの炎症の関与が示唆される。

Stroke 2011; 42: 3202-3206

表2 炎症マーカー値の1SD上昇あたりのCMB状態のオッズ比（95% CI）

<table>
<thead>
<tr>
<th>炎症マーカー</th>
<th>CMB、部位</th>
<th>CMB、有無</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>深部</td>
<td>脳葉</td>
</tr>
<tr>
<td>1.81（1.41～2.45）</td>
<td>1.81（1.35～2.46）</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>深部</td>
<td>脳葉</td>
</tr>
<tr>
<td>1.97（1.36～2.90）</td>
<td>1.99（1.24～3.31）</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td>深部</td>
<td>脳葉</td>
</tr>
<tr>
<td>2.48（1.40～4.49）</td>
<td>2.80（1.30～6.26）</td>
<td></td>
</tr>
</tbody>
</table>

数値は解析対象変数の値を示す。

CMB：脳内微小出血、SD：標準偏差、CI：信頼区間。

*モデル1：年齢および性別について補正。

**モデル2：年齢、性別、髄液圧、糖尿病、高脂血症、推定系球体通過率、内中脳葉複合体厚、無症候性ラクナ梗塞、および白質高信号域（脳葉周囲、深部）グレードについて補正。

$p < 0.05$。

CMB（+）群に対して$p < 0.01$。