Correlation Between Cerebral Microbleeds and Vulnerable Plaque in Patients with Severe Carotid Artery Stenosis; Comparative Magnetic Resonance Imaging Study

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Goal: There are an increasing idea that the inflammation contributes to vascular diseases in various organs. The pathogenesis of both cerebral small vessel disease such as cerebral microbleeds and carotid plaque may be associated with chronic inflammation. This study was aimed to evaluate the correlation between microbleeds and carotid plaque characteristics. *Materials and Methods:* This study enrolled 85 patients who underwent surgical/endovascular treatments for carotid artery stenosis between January 2009 and July 2016. Their clinical data were precisely analyzed. T2*-weighted magnetic resonance (MR) imaging was performed to detect the cerebral microbleeds. The carotid plaque with high signal intensity on T1-weighted MR imaging was categorized into vulnerable plaque. *Findings:* The microbleeds was detected in 17 of 85 (20%). The prevalence of vulnerable carotid plaque and previous symptomatic lacunar infarction was significantly greater in the patients with microbleeds than in those without ($P = .001$ and $P = .03$, respectively). Multiple logistic regression analysis showed that the vulnerable plaque was significantly associated with the presence of microbleeds when adjusted for age, alcohol intake, antiplatelet drug use, the presence of previous symptomatic lacunar infarction, and coronary artery disease ($P = .009$, OR = 5.38, 95% CI = 1.51-21.0). *Conclusions:* These findings suggest the correlation between microbleeds and vulnerable plaque in patients with severe (>70%) carotid artery stenosis. Systemic, chronic inflammation may play a key role in both small and large arteries' disease of the brain. The knowledge may be valuable to fully understand the entity of cerebrovascular diseases as one of systemic, chronic inflammation.

Key Words: Cerebral microbleeds—carotid artery stenosis—vulnerable plaque—inflammation—magnetic resonance imaging

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Introduction

Nowadays, the fact that the inflammatory response contributes to vascular diseases such as atherosclerosis and small vessel disease has been considered to increased interest.[1,2] Previous reports have demonstrated the association between the coronary artery atherosclerosis and renal dysfunction.[3] A close relationship between the cerebral small vessel disease and chronic kidney disease may be based on systemic, chronic inflammation.[4,5] Thus, systemic inflammation may play an important role in the development of not only large vessel disease but also small vessel disease in the various organs.

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Cerebral microbleeds (CMBs) are small and dot-like low intensity areas that can be visualized on gradient-echo T2*-weighted magnetic resonance (MR) imaging, and are often observed in patients with both ischemic and hemorrhagic stroke especially in Asian populations. In addition, CMBs may be a strong predictor for future risk of stroke.[6-9] Recent studies point out that the inflammatory marker levels are higher in patients with CMBs than those without.[10,11]

On the other hands, carotid artery atherosclerosis is one of the important cause of ischemic stroke. Morphological characteristics of carotid plaque such as the degree of stenosis is widely known to affect the risk of ischemic events.[12] However, recent studies have shown that the components of carotid plaque may be an alternative determinant of subsequent stroke occurrence.[13,14] Indeed, vulnerable plaque are closely associated with systemic inflammation and early stroke recurrence in patients with symptomatic carotid artery stenosis.[15,16] Recently, MR imaging is known to provide the useful information on carotid plaque components.[17-20]

On the basis of these findings, this study was aimed to test the hypothesis that plaque vulnerability is closely related to the existence of CMBs in patients with severe (>70%) carotid artery stenosis.

Materials and Methods

Patients

This study enrolled 85 patients who underwent carotid artery endarterectomy (CEA) or carotid artery stenting (CAS) for carotid artery stenosis at our hospital between January 2009 and July 2016. CEA or CAS was performed in asymptomatic patients with severe (>70%) carotid artery stenosis and in symptomatic patients with moderate to severe (>50%) carotid stenosis. Symptomatic patients were defined as those who experienced amaurosis fugax, transient ischemic attack (TIA), or ischemic stroke in the territory of the ipsilateral internal carotid artery within 6 months. The degree of carotid artery stenosis was evaluated on digital subtraction angiography according to the criteria in North American Symptomatic Carotid Endarterectomy Trial.[21] Following patients were excluded in this study: those without MR imaging of carotid plaque, those with poor imaging quality, those with nearly occlusion, and those who previously underwent carotid revascularization on the ipsilateral side.

Patient's characteristics were investigated retrospectively by reviewing their medical records. Their clinical data were collected, including gender, age, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, alcohol intake, use of antithrombotic drugs, the presence of ischemic symptoms, and past history of symptomatic lacunar infarction, symptomatic nonlober intracerebral hemorrhage (ICH), and coronary artery diseases. Hypertension was defined as blood pressure higher than 140/90 mmHg or current use of antihypertensive drugs. Diabetes mellitus was defined as a hemoglobin A1C value higher than 6.5% or current use of antiglycemic medications. Hypercholesterolemia was defined as serum low-density lipoprotein cholesterol levels higher than 140 mg/dL or current use of lipid-lowering agent. Current smoking was defined as any tobacco smoking on daily basis within 3 months before admission. Current alcohol intake was defined as alcohol consumption of more than 150 g/week within 3 months before admission. Current antiplatelet and anticoagulant drug use was defined as taking medicine within 3 months before admission. Nonlobar ICH was defined as bleeding of putamen, thalamus, brain stem, and cerebellum. Coronary artery disease was defined as having the past history of angina or myocardial infarction.

Radiological Examinations

Imaging examinations were performed with a 1.5-T, whole-body MRI machine (Magnetom Vision; Siemens, Erlangen, Germany) with a standard head coil. For characterization of the carotid plaque, the axial images of the carotid artery were obtained from 3-D gradient-echo sequence. The sequence of T1-weighted imaging was as followed: field of view, 180 mm/100%; repetition time, 500 millisecond; and time to echo, 10 millisecond. Slice thickness was 3 mm. Mean signal intensity of whole carotid plaque and sternocleidomastoid muscle were measured at the narrowest portion of internal carotid artery on T1-weighted MR imaging.[19] Our previous studies have shown that the carotid plaque with high signal intensity on T1-weighted image can be classified into 2 histological categories: intraplaque hemorrhage is expressed as high signal intensity on both T1-weighted image and source image of time-of-flight (TOF), while large lipid-rich necrosis is expressed as high signal intensity on T1-weighted image and iso-signal intensity on source image of TOF.[22-26] The fact has also been proved by other investigators. Thus, Narumi et al reported that T1-weighted image can highly identify the histologically confirmed component of carotid plaque, including fibrous tissue, lipid/necrosis, and hemorrhage. The sensitivity and specificity for discriminating lipid/necrosis/hemorrhage from fibrous tissue were 96% and 100%, respectively.[27] In this study, therefore, we defined the "vulnerable" plaque as that with high signal intensity on T1-weighted images, which included both intraplaque hemorrhage type and large lipid-rich necrotic type. The carotid plaque was categorized with having high signal intensity, when the signal intensity for plaque was greater than 200% of that for sternocleidomastoid muscle on T1-weighted MR imaging (Fig. 1).

T2*-weighted MR imaging was employed to identify the CMBs that were defined as dot-like low intensity areas with a diameter of up to 10 mm.[10] Their number was also

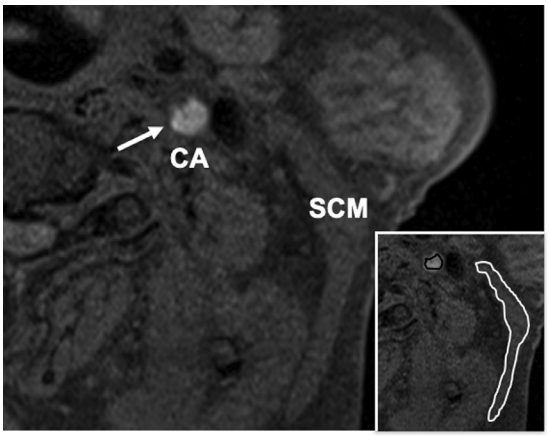

Figure 1. *Measurement of signal intensities of carotid artery (CA) plaque (*white arrow*) and sternocleidomastoid muscle* ***(SCM)*** *on T1-weighted axial MR imaging. Mean signal intensities are measured with the region of interest drawn over the whole plaque (*black distorted circle*) with reference to the whole SCM (*white distorted circle*) at the narrowest portion of internal carotid artery.*

quantified in all patients (Fig. 2). The low intensity lesions with a diameter of more than 10 mm and irregularly shape were excluded, because these lesions were considered as the old scars of ICH. Furthermore, the symmetric hypo-intensity areas in the globus pallidus and the flow voids in cortical sulci were also excluded.[10,28] The numbers of lacunar infarction and nonlobar ICH lesion were also counted on T2-weighted MR imaging.

Statistical Analysis

Continuous data in each group were expressed as means ± standard deviation. A student's *t* test and Mann-Whitney *U* test were used to compare them between 2 groups as appropriate. Categorical data were analyzed by using chi-square test.

Multivariate analyses were performed by using logistic regression models, including variables that yielded a *P* value < .3 in the univariate analyses, which were thought to be associated with the presence of CMBs. The difference was considered statistically significant when a *P* value was < .05.

Results

Clinical Characteristics

Clinical characteristics of the patients are shown in Table 1. T2*-weighted MR imaging demonstrated that 17 of 85 (20%) patients had CMBs, while the other 68 (80%) did not. Clinical features were compared between the patients with CMBs and those without (Table 1). As the results, there were no significant differences in gender, age, and the number of hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol intake, antiplatelet drug use, anticoagulant drug use, the presence of ischemic symptoms, symptomatic nonlobar ICH, and coronary artery disease between them. However, the patients with CMBs had significantly more symptomatic lacunar infarction than those without (*P* = .03).

CMBs and Vulnerable Plaque, Degree of Carotid Artery Stenosis

The mean degree of carotid artery stenosis was 77.1 ± 11.1% in the patients with CMBs and 78.8 ± 9.6% in those without. There was no significant difference between them. T1-weighted MR imaging revealed that carotid artery plaque had high signal intensity and was judged as

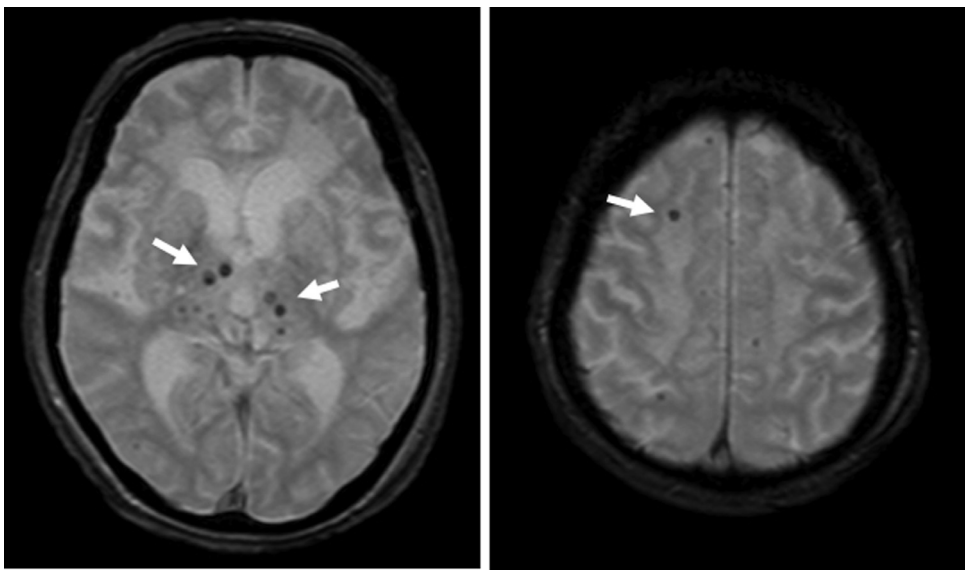

Figure 2. *CMBs is defined as dot-like low intensity areas on T2*-weighted MR imaging with a diameter of up to 10 mm (*white arrow*). Their number was also quantified in all patients.*

Table 1. *Independent predictors of the presence of CMBs among 85 patients with carotid artery stenosis*

	CMBs				
	Positive (n = 17)	Negative (n = 68)	Univariate analysis	Multivariate analysis	OR (95% CI)
Patient's characteristics					
Male	15 (88.2)	59 (86.8)	$P = .83$		
Age (y)	74.4 ± 4.58	72.1 ± 7.64	$P = .26$	$P = .75$	
Medical history					
Hypertension	14 (82.4)	53 (77.9)	$P = .69$		
Diabetes mellitus	9 (52.9)	30 (44.1)	$P = .51$		
Hypercholesterolemia	8 (47.1)	28 (41.2)	$P = .66$		
Smoking	5 (29.4)	21 (30.9)	$P = .91$		
Alcohol intake	4 (23.5)	26 (38.2)	$P = .26$	$P = .49$	
Antiplatelet drug use	9 (52.9)	25 (36.8)	$P = .22$	$P = .52$	
Anticoagulant drug use	2 (11.8)	4 (5.9)	$P = .40$		
Ischemic symptoms	12 (70.6)	41 (60.3)	$P = .43$		
Symptomatic lacunar infarction	6 (35.3)	9 (13.2)	$P = .03$	$P = .34$	
Symptomatic nonlober ICH	0	0	not applicable		
Coronary artery disease	7 (41.2)	18 (26.5)	$P = .23$	$P = .42$	
Radiological findings					
Degree of carotid artery stenosis	77.1 ± 11.1	78.8 ± 9.6	$P = .54$		
Vulnerable plaque	10 (58.8)	13 (19.1)	$P = .001$	$P = .009$	5.38 (1.51-21.0)

Abbreviations: CMBs, cerebral microbleeds; ICH, intracerebral hemorrhage; OR, odds ratio; 95% CI, 95% confidence interval.

vulnerable plaque in 23 of 85 (27.1%) patients. Vulnerable plaque was identified in 10 of 17 (58.8%) patients with CMBs and in 13 of 68 (19.1%) patients without. Therefore, the incidence of vulnerable plaque was significantly higher in patients with CMBs than in those without ($P = .001$; Table 1).

Multiple logistic regression analysis showed that vulnerable plaque was significantly associated with the presence of CMBs in patients with carotid artery stenosis when adjusted for age, alcohol intake, antiplatelet drug use, the presence of symptomatic lacunar infarction, and that of coronary artery disease ($P = .009$, OR = 5.38, 95% CI = 1.51-21.0; Table 1).

Multiplicity of CMBs and Severity of Carotid Artery Stenosis

Of 17 patients with CMBs, the mean number of CMBs was 2.20 ± .98 in 10 patients with vulnerable plaque on T2*-weighted MR imaging, but was 1.43 ± .49 in 7 patients without ($P = .08$). Therefore, the patients with vulnerable plaque had the tendency to have more CMBs in the brain. In addition, the mean number of CMBs was 2.08 ± .95 and 1.25 ± .43 in the symptomatic (n = 12) and asymptomatic patients (n = 5), respectively ($P = .17$). There was no significant difference in the number of CMBs between symptomatic and asymptomatic patients.

Discussion

Previous studies have shown that the CMBs can more frequently be identified in the patients with lacunar infarction.[29] It is quite natural because both lesions are based on the similar atherosclerotic change in the perforating arteries in the brain. This study further demonstrates a close correlation between the CMBs and symptomatic lacunar infarction in patients with carotid artery stenosis, suggesting that atherosclerotic processes may progress in the major cephalic arteries in parallel to the perforating arteries. More importantly, vulnerable plaque at higher risk for TIA/ischemic stroke was more frequently observed in patients with CMBs than in those without. Only 1 report has previously found a similar result that the CMBs may be associated with carotid artery fatty plaque on multidetector row CT angiography.[30] Very recently, however, MR imaging, especially T1-weighted image and 3D-TOF angiography are known more valuable to evaluate the plaque instability in the carotid artery with higher sensitivity and specificity.[17-20, 22-26,31] To our best knowledge, therefore, this study is the first report that prove a correlation between the CMBs and vulnerable carotid plaque on T1-weighted MR imaging. However, the patients with severe (>70%) carotid artery stenosis accounted for about 90% of whole subjects, therefore, we consider that this correlation may be observed under the specific condition in progressed carotid artery stenosis. In this study, the prevalence of vulnerable carotid plaque may be lower when compared with previous reports.[19,23] It is most likely because this study determined the plaque vulnerability with more strict criteria than previous studies.[19]

Endothelial inflammatory response is considered as the principal process of atherosclerosis, which is characterized by recruitment of circulating immune cells.[32] The subjects with CMBs are known to have the higher serum

levels of various inflammatory markers such as TNF-α, myeloperoxidase, IL-6, and IL-18 than those without.[10,11] Previous positron emission tomography studies demonstrated that inflammation-related 18-fluorodeoxyglucose uptake correlated with markers of carotid plaque instability.[15,16,33] Based on these observations, we may hypothesize that inflammatory response is the common underlying pathophysiologic mechanism of atherosclerosis and its development in both perforating artery and major cephalic artery.

Furthermore, the spleen has been considered to have the function as a reservoir of inflammatory cells and to mobilize them in acute phase of stroke and cardiovascular event.[34] The reservoir function may be associated with an increase in proinflammatory mediators, which play an important role in advancing chronic and systemic inflammation. There is the possibility that such chronic and systemic inflammatory response may activate the production of inflammatory agents in atherosclerotic diseases at several vessels simultaneously. Lombardo et al suggested the possible link between carotid artery and coronary artery plaque instability due to inflammation.[35] Another previous report showed that the frequency of CMBs was much higher in the patients with carotid atherosclerosis than those without.[36] Likewise, the correlation between CMBs and vulnerable carotid plaque in this study is considered to show a glance into phenomenon which chronic and systemic inflammation is closely coupled with plural atherosclerotic lesions based on local inflammatory response.

In this study, both ischemic symptoms and coronary artery disease were not associated with the presence of CMBs. The mechanism through which TIA and/or ischemic stroke develop in patients with carotid artery stenosis can be categorized into 2 groups: one is an artery-to-artery embolism due to the rupture of plaque or thrombus formation at the surface of plaque, and another is an impaired cerebral hemodynamics due to severe carotid artery stenosis and poorly developed collaterals. We believe that chronic inflammation may be involved in the occurrence of artery-to-artery embolism, but not to hemodynamically impaired attacks. Therefore, we speculate that there was no statistically significant relationship between plaque vulnerability and other clinical factors, including ischemic symptoms. On the other hands, previous reports showed the robust association between CMBs and carotid artery calcification which can predict coronary heart disease in healthy individuals.[37] In this study, therefore, we investigated the prevalence of patients who developed coronary artery disease, such as angina and myocardial infarction, but we did not perform 3D-CT angiography to examine coronary artery diseases. Therefore, the patients with subclinical coronary artery disease may be missed.

The present study has limitations including its small sample size and retrospective design. Some selection bias may be introduced by investigating the patients who were scheduled to undergo CEA or CAS. The patients who did not undergo the surgical or endovascular interventions were excluded in this analysis. Therefore, prospective studies with a larger number of subjects will be required in the future. Another limitation is that we enrolled only Japanese subjects, therefore, our result should be tested in all ethnic groups, because it is well known that the Asians have the higher prevalence of small vessel diseases, such as lacunar infarction, nonlober ICH, and CMBs than the other racial groups.[38] Furthermore, we did not have investigated the existence of inflammatory response, such as inflammatory markers and histopathologic findings. Therefore, our consideration which the chronic and systemic inflammation may play a key role in the correlation between CMBs and vulnerable carotid plaque might be just inference. Further investigations about the proof of the presence of inflammation should be needed in the future.

Conclusions

This study identifies the correlation between CMBs and vulnerable carotid plaque in Japanese patients who underwent CEA or CAS for carotid artery stenosis. Systemic, chronic inflammation may play a key role in developing both small and large arteries' diseases of the brain. The knowledge may be valuable to fully understand the entity of cerebrovascular diseases as one of chronic, systemic inflammatory responses.

Conflicts of Interest

The authors have no personal, financial interest in any of the drugs, materials, or devices described in this article.

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