

Original Paper

Rapid Formation of Cerebral Microbleeds after Carotid Artery Stenting

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Key Words

Cerebral microbleeds · Carotid artery stenting · MRI

Abstract

Background: Recent studies reported that cerebral microbleeds (CMBs), i.e. small areas of signal loss on T₂*-weighted gradient-echo (GE) imaging, could develop rapidly after acute ischemic stroke. We hypothesized that CMBs rapidly emerge after carotid artery stenting (CAS). **Objective:** We investigated the frequency of and predisposing factors for CMBs after CAS. **Methods:** We retrospectively examined MRI before and after CAS in 88 consecutive patients (average age: 71.7 ± 7.2 years, average rates of carotid stenosis: 72.6 ± 12.8%) who underwent CAS for carotid artery stenosis between March 1, 2009, and September 30, 2010. We defined new CMBs as signal losses that newly appeared on the follow-up GE. We examined the association of new CMBs with demographics, risk factors, and baseline MBs. **Results:** Among 88 patients, 18 (20.5%) had CMBs initially, and 7 (8.0%) developed new CMBs right after CAS. New CMBs appeared on the same side of CAS in all of the 7 patients. New CMBs appeared significantly more frequently

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in the CMB-positive group than in the CMB-negative one (22% vs. 4%, $p = 0.03$) on the pre-CAS MRI. Multivariate analysis also revealed that the presence of CMBs before CAS was an independent predictor of new development of CMBs after CAS (odds ratio: 8.09, 95% confidence interval: 1.39–47.1). **Conclusion:** CMBs can develop rapidly after CAS, especially in patients with pre-existing CMBs. Since the existence of CMBs prior to CAS suggests a latent vascular damage which is vulnerable to hemodynamic stress following CAS, particular attention should be paid to the prevention of intracerebral hemorrhage due to hyperperfusion after CAS.

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Introduction

Cerebral microbleeds (CMBs) are focal hemosiderin deposits adjacent to small vessels resulting from minimal blood leakage from small vessels that appear as signal loss lesions on T_2^* -weighted gradient-echo (GE) magnetic resonance imaging (MRI). CMBs can be regarded as a marker of microangiopathy [1, 2]. A recent review of the literature suggests that there is a strong association between CMBs identified on MRI and histopathological evidence of previous hemorrhage, most commonly in the form of hemosiderin-laden macrophages [3]. Many studies suggested that CMBs could be associated with an increased risk of intracerebral hemorrhage (ICH) and cerebral amyloid angiopathy [4–7] and can develop rapidly after acute ischemic stroke [8].

Cerebral hyperperfusion after carotid artery stenting (CAS) and carotid endarterectomy (CEA) is well known, and is defined as a marked increase in ipsilateral cerebral blood flow following surgical repair of carotid stenosis that results in a risk of ICH [9–17]. We hypothesized that CMBs may develop rapidly after CAS. This study investigated the frequency and predisposing factors of new CMB formation after CAS.

Methods

Patients

We retrospectively examined 88 consecutive patients who underwent CAS for carotid stenosis and MRI before and after CAS between March 1, 2009, and September 30, 2010, in Kokura Memorial Hospital. The preoperative degree of carotid stenosis was evaluated based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [18]. Clinical presentation was classified as symptomatic or asymptomatic. Symptomatic carotid stenosis was defined as either a transient ischemic attack or a nondisabling stroke on the side ipsilateral to CAS within 6 months before CAS. This study was approved by our Institutional Review Board. We have obtained informed consent from the patients.

Magnetic Resonance Imaging

MRI examinations were performed before and one day after CAS with a 1.5-T magnetic resonance system using a standard head coil. The gradient recalled echo (GRE) parameters were as follows: repetition time = 700 ms, echo time = 20 ms, flip angle = 25, matrix = 288×256 , field of view = 220×220 , slice thickness = 5 mm, and interslice gap = 2 mm. Patients with probable cerebral amyloid angiopathy according to the Boston criteria were excluded. The presence of CMBs on GRE MRI was independently evaluated by 2 neurologists (S.M, K.K) blind to the clinical details. CMBs were defined as focal areas of very low signal intensity, with a diameter smaller than 10 mm. The number and location of CMBs were assessed. The location of CMBs were classified as (1) lobar: in the cortex, subcortex, and white matter

of frontal, temporal, parietal, and occipital lobes; or (2) deep or infratentorial: in the caudate, putamen, globus pallidus, internal capsule, thalamus, brainstem, and cerebellum. Hypointense lesions within the subarachnoid space were regarded as pial blood vessels. Symmetric hypointense lesions in the area of the globus pallidus were regarded as calcification. We aligned the GRE slices of the pre- and post-CAS MRI to guarantee a precise comparison. When CMBs were identified on the post-CAS GRE, their prior absence was confirmed by re-examining the corresponding pre-CAS GRE.

Technetium-99m Hexamethylpropyleneamine Oxime SPECT

Technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc -HMPAO) SPECT was performed the next day after CAS. Patients received 15 mCi (555 MBq) ^{99m}Tc -HMPAO, and the first scan for cerebral blood flow imaging was started 5 min later (acquisition time: 20 min). The images were reconstructed in a 128 × 128 matrix with a section thickness of 5 mm on the transverse, sagittal, and coronal planes. An irregular, mirror-shaped region of interest was placed manually and bilaterally over the whole middle cerebral artery territory at the level of the parietal lobe, excluding the infarct, and the corresponding contralateral region. The asymmetry index (AI; affected side counts per pixel/contralateral side counts per pixel × 100%) was calculated. In the present study, hyperperfusion after CAS was defined as an AI increase of >6.1% as described previously [19].

Clinical Assessments

The diagnosis of hypertension was based on either the use of antihypertensives or a systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg during two separate measurements after the acute stroke period. The diagnosis of diabetes mellitus was based on the use of antidiabetic treatment or HbA1c >6.1%. Current smoking was assigned to persons who smoked during the 3 months preceding the last stroke event. Hyperlipidemia was determined when total cholesterol was >210 mg/dl or low-density lipoprotein cholesterol was >130 mg/dl. Demographics including age, sex, and stroke risk factors were obtained.

Cerebral hyperperfusion syndrome (CHS) after CAS was diagnosed according to the following criteria: (1) severe headache, seizure, deterioration of consciousness level or the development of focal neurological signs such as motor weakness; (2) absence of any additional ischemic lesion on CT or MRI; (3) an increase in AI by >6.1%.

Procedural Techniques

All patients were pretreated with aspirin (100 mg/day) and clopidogrel (75 mg/day), or cilostazol (200 mg/day) for at least 3 days before the procedure. Eight patients also took warfarin for complicating atrial fibrillation in addition to antiplatelet drugs. Carotid angioplasty and stent placement were performed by transfemoral catheterization under local anesthesia. The distal protection of a Percusurge Guard Wire System (Medtronic AVE, Santa Rosa, Calif., USA) or EZ filter System (Boston Scientific, Natick, Mass., USA) was used to cross and pre-dilate the stenosis. Pre-dilatation was performed with a controlled-compliant balloon dilation catheter to achieve a minimal lumen for passage of the stent-mounted catheter. The balloon was inflated with 6–10 atm for 30 s. Next, a self-expanding stent was deployed. The stent system used in this series consisted of a Precise (Johnson and Johnson, Miami Lakes, Fla., USA) in 55 cases, a Wallstent RP (Boston Scientific) in 29 cases, and a Driver (Medtronic Inc., Santa Rosa, Calif., USA) in 4 cases. Post-stenting dilatation was performed with a controlled compliant balloon dilation catheter. The balloon size was selected according to the normal luminal diameter of each internal carotid artery just distal to the stenotic segment (diameter at full dilation was usually 4.0–5.0 mm). The balloon was in-

flated with 6–10 atm for 10–30 s. Intravenous heparin was administered during the procedure, which was controlled to an activated clotting time (ACT) of around 300 s and not reversed at completion. A systolic blood pressure of <140 mm Hg was maintained for two days after the procedure. For patients at high risk of CHS, we strictly controlled blood pressure to <120 mm Hg for two days after CAS. Because the carotid sinus reflex usually lowered blood pressure after CAS, intravenous catecholamine was occasionally administered to maintain blood pressure.

Statistical Analysis

Student's t test was used to analyze continuous data, and the χ^2 test was used for categorical data. Multiple logistic regression analysis was performed to estimate the independent predicting factors for the development of new CMBs after CAS. Variables with a p value <0.1 by univariate analysis, age, and risk factors were selected for entry into multiple regression analysis. A 2-tailed p value <0.05 was considered a significant difference. SPSS for Windows (version 13.0, SPSS Inc., Chicago, Ill., USA) was used for all statistical analyses.

Results

A total of 100 patients underwent CAS for intracranial artery stenosis in our hospital during the study period, 12 patients did not undergo GRE MRI. Therefore, we analyzed 88 patients (average age: 71.7 ± 7.2 years, male: 86%, 40 symptomatic and 48 asymptomatic cases, average rates of carotid stenosis: $72.6 \pm 12.8\%$). Carotid stenosis was successfully treated in all patients. No patients had CHS. Demographics of the enrolled patients are shown in table 1. Eighteen patients (20.5%) had CMBs at baseline. The median number of baseline CMBs was 2 (range: 1–5). On the follow-up MRI, we observed 8 new CMBs ipsilateral to CAS in 7 patients (8.0%). The median number of new CMBs among these patients was 1 (range: 1–2). There were no baseline CMBs in 3 patients who developed new CMBs. A representative case with new CMBs after CAS is shown in figure 1.

By univariate analysis, the frequency of new CMB appearance was significantly higher in the initially CMB-positive group than the CMB-negative group (22% vs. 4%, $p = 0.03$). There was no significant association between the appearance of new CMBs and anti-thrombotic therapy or the highest ACT values during CAS procedure. No patients developed CHS after CAS (table 2).

Multivariate analysis adjusted for age and vascular risk factors revealed that the presence of CMBs before CAS was an independent predictor of the appearance of new CMBs after CAS (odds ratio: 8.50, 95% confidence interval: 1.34–53.88; table 3).

Discussion

This study showed that (1) CMBs can develop rapidly after CAS, and (2) the presence of CMBs before CAS was an independent predictor of the appearance of new CMBs after CAS. A recent study suggested that the presence of CMBs and severe small vessel diseases are predictors of the rapid development of CMBs after acute ischemic stroke [8]. Hypertension is associated with CMBs in patients with stroke [20]. In our study, risk factors for stroke, including hypertension, were not associated with the formation of new CMBs after CAS. Such risk factors may be important promoters of CMBs over a longer period but may not contribute to CMBs in the short term. The mechanism underlying the rapid formation of CMBs after CAS remains unknown. We speculate that hemodynamic changes caused by the CAS

Table 1. Univariate factors for the development of new CMBs

	New CMBs		p value
	present (n = 7)	absent (n = 81)	
<i>Demographics</i>			
Age	74.0 ± 7.9	71.5 ± 7.1	0.37
Male sex	7 (100%)	69 (85%)	0.59
Symptomatic clinical presentation	4 (57%)	36 (44%)	0.70
<i>Angiographic findings</i>			
Carotid stenosis (NASCET criteria), %	73.9 ± 15.0	72.5 ± 12.7	0.79
<i>MRI findings</i>			
Presence of CMBs before CAS on GRE	4 (57%)	14 (17%)	0.03
<i>Risk factors</i>			
Hypertension	4 (57%)	60 (74%)	0.38
Diabetes	3 (43%)	26 (32%)	0.68
Hyperlipidemia	3 (43%)	33 (41%)	1.00
Ischemic heart disease	4 (57%)	23 (28%)	0.19
<i>Laboratory findings</i>			
Platelet count, × 10,000 /ml	21.6 ± 12.7	20.4 ± 5.9	0.81
<i>Antithrombotic therapy</i>			
Antiplatelet drug			
Dual therapy (aspirin + clopidogrel)	4 (57%)	53 (65%)	
Triple therapy (aspirin + clopidogrel + cilostazol)	2 (27%)	20 (25%)	
Antiplatelet drug + anticoagulation drug			
Dual antiplatelet drug + warfarin	0	5 (6%)	
Triple antiplatelet drug + warfarin	1 (14%)	3 (4%)	0.55
The highest ACT values during CAS procedure, s	338.9 ± 55.0	340.8 ± 57.3	0.93

Values are number (%), or mean ± SD. p values are calculated using Student's t test and the χ^2 test.

Table 2. Demographics of patients with newly developed CMBs

Case No.	Age years	Stenosis (NASCET criteria), %	CHS after CAS	CMBs before CAS, n	CMBs after CAS, n	New CMB hemisphere
1	68	56	no	1	3	ipsilateral
2	84	78	no	1	2	ipsilateral
3	77	80	no	0	1	ipsilateral
4	79	53	no	0	1	ipsilateral
5	73	70	no	0	1	ipsilateral
6	77	90	no	1	2	ipsilateral
7	60	90	no	1	2	ipsilateral

procedure affect damaged small cerebral vessels in patients with CMBs, and may disrupt the tight junction of cerebral blood vessels, resulting in CMBs.

Several studies reported that low platelet counts were associated with symptomatic hemorrhagic transformation in acute ischemic stroke with atrial fibrillation [21] and a high risk of intracranial hemorrhage after intravenous recombinant tissue plasminogen activator

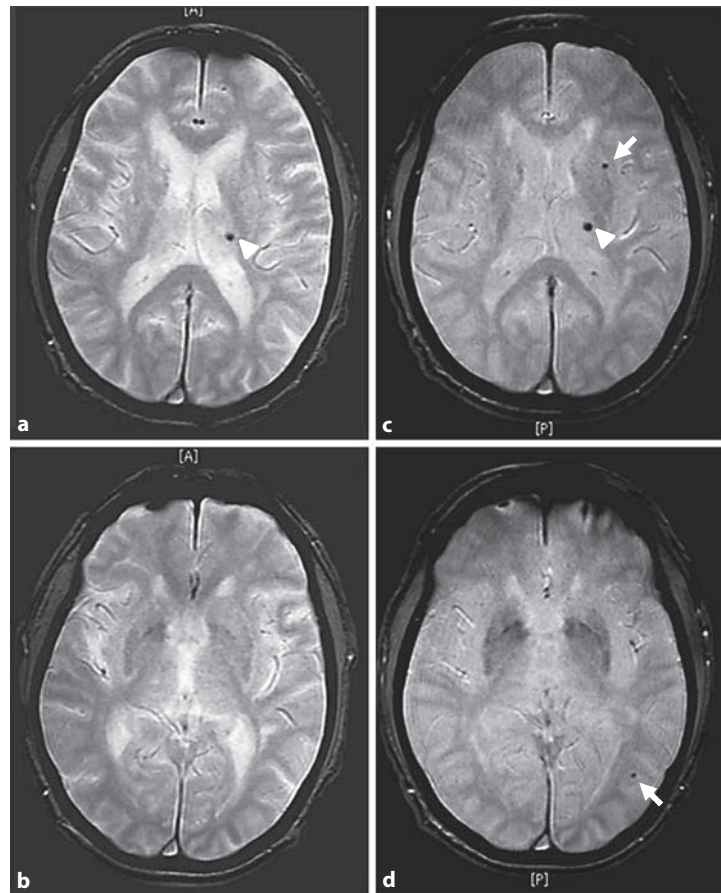


Fig. 1. A representative case developing new CMBs after CAS. T₂*-weighed GE MRI obtained in a 68-year-old man with symptomatic left internal carotid artery stenosis (56%) before CAS (**a, b**) and the next day after CAS (**c, d**). Arrowheads indicate baseline CMBs. Arrows indicate new CMBs.

Table 3. Multiple logistic regression analysis of the development of new CMBs

	OR	95% CI	p value
Presence of CMBs before CAS	8.09	1.39–47.13	0.02
Age	1.08	0.96–1.21	0.20
Hypertension	0.26	0.04–1.80	0.17
Hyperlipidemia	1.31	0.22–7.63	0.77
Diabetes	2.46	0.32–19.10	0.39
Ischemic heart disease	3.10	0.49–19.48	0.23

OR = odds ratio; CI = confidence interval.

therapy for acute ischemic stroke [22]. There was no association between platelet counts and the development of new CMBs after CAS in our study.

Dual antiplatelet therapy with clopidogrel and aspirin has been recommended as a standard therapy for the prevention of thrombotic events in patients undergoing CAS and intracranial artery stenting [23]. All of the patients were treated with at least two antiplatelet drugs, aspirin and clopidogrel, and some patients were also administered cilostazol and/or warfarin. Since we did not find that the development of new CMBs after CAS was associated with antithrombotic therapy, strong antithrombotic therapy during the periprocedural period may not be contraindicated by the presence of CMBs.

CHS is an uncommon but devastating complication following CAS and CEA, and is often fatal once cerebral hemorrhage occurs [9–17]. Before a CAS/CEA procedure, it is very important to evaluate the risks of cerebral hemorrhage in advance. CMBs may be a risk factor for ICH after CAS, and the development of new CMBs may also enhance this risk. Although we had no patients with CHS after CAS in this series, we should pay special attention to the development of CHS in case of preexisting CMBs.

Our study has some limitations. First, although we used defined MRI protocols for all patients before and after CAS, our study has a retrospective design and may have a potential risk for selection bias. It remains unknown whether CMBs are more frequent in patients with severe atherosclerotic changes in the carotid artery who undergo CAS than in those who do not require CAS. Second, this study is limited by its small sample size, and we could not completely evaluate several factors. Third, we used 1.5-T MRI, which is inferior to 3-T MRI for the detection of CMBs. The use of 3-T MRI might have allowed the detection of more CMBs [24].

Our study suggests that new CMBs can occur rapidly after CAS. The presence of baseline CMBs is associated with the development of new CMBs after CAS. A further prospective study with a larger sample size is intended to confirm these results.

Disclosure Statement

The authors report no conflicts of interest.

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