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Does microbleed predict haemorrhagic transformation after acute atherothrombotic or cardioembolic stroke?

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ABSTRACT

Objectives: Cerebral microbleeds (MBs) are known to be indicative of bleeding-prone microangiopathy and may predict incident intracerebral haemorrhage. However, there is controversy concerning the causal relationship between the presence of MBs and haemorrhagic transformation (HTf) after ischaemic stroke.

Methods: Of the 1034 patients with acute ischaemic stroke who were consecutively admitted to our hospital, 377 patients with stroke due to large-artery atherothrombosis or cardioembolism were selected for participation in this study. We examined the MBs using T2*-weighted gradient-echo MRI performed within 24 hours after admission, and the incidence of HTf was assessed using follow-up brain MRI during the hospitalisation period.

Results: Of the 377 patients with stroke, 234 were male (62.1%) and the mean age was 66.2 $\pm$11.7 years. MBs were initially found in 109 patients (28.9%), and newly incident HTf was noted during the hospitalisation period in 74 patients (19.6%). The presence of MBs was not increased in the patients with HTf (24.3% vs. 30.0% in the patients without HTf; $p = 0.331$). In addition, the number of MBs was not higher in the patients with HTf (0.7 ± 1.5 vs. 1.8 ± 8.1; $p = 0.234$). This lack of significance between MBs and HTf persisted after stratification by stroke mechanism.

Conclusions: This study suggests that underlying MBs do not predict incident HTf after acute ischaemic stroke. The clinical significance of MBs should be differentially evaluated according to the type of disease (intracerebral haemorrhage vs. HTf).

Microbleeds (MBs) visualised on brain T2*-weighted gradient-echo (GRE) MRI are indicative of chronic cerebral microangiopathy caused by various conditions, including hypertension and ageing.[1–3] It has been suggested that the lesions may predict subsequent haemorrhagic events such as intracerebral haemorrhage[4–6] and haemorrhagic transformation (HTf) of ischaemic stroke.[7 8] HTf was determined to be one of the most important risk factors leading to poor outcome in patients with acute ischaemic stroke. However, the MBs do not appear to predict an incident HTf after thrombolysis in acute ischaemic stroke.[9 10] Irrespective of thrombolysis, a prior study showed that the presence of MBs may be associated with HTf after acute ischaemic stroke,[8] but the results have not yet been confirmed. In this study, we sought to investigate whether MBs that are present at baseline are associated with subsequent HTf in patients with acute ischaemic stroke by analysing data on a larger, consecutive series of patients with specific types of ischaemic stroke associated with haemorrhagic transformation—large-artery atherothombosis and cardioembolism.

METHODS

A total of 1034 acute ischaemic stroke patients who had been admitted to Seoul National University Hospital within 7 days after ictus were consecutively enrolled in this study between October 2002 and March 2006. Among the patients, subjects with the following conditions were excluded from this study according to the classification of Trial of Org 10172 in Acute Stroke Treatment (TOAST):[11] patients with only transient ischaemic attack (n = 110), stroke due to small-vessel disease (n = 289), stroke of undetermined aetiology (n = 184), or stroke of other determined aetiology (n = 15). Patients whose work-ups were not complete due to various reasons were further excluded. Therefore, our study population consisted of a total of 377 patients with stroke due to large-artery atherothombosis (n = 217) and cardioembolism (n = 160).

Baseline demographic and clinical characteristics were collected at admission and included age at onset, gender, hypertension (previous use of antihypertensive medication, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at discharge), diabetes (previous use of antidiabetic medication, fasting blood glucose >7.0 mmol/L or postprandial blood glucose after 2 hours >11.1 mmol/L at discharge), hyperlipidaemia (previous use of lipid-lowering agents, total cholesterol >6.0 mmol/L or low-density lipoprotein [LDL] cholesterol >4.14 mmol/L at admission), history of transient ischaemic attack or stroke, previous use of antiplatelet or anticoagulant medications, systolic and diastolic blood pressure level at admission, glucose level, total cholesterol level, prolonged prothrombin time or activated partial thromboplastin time, initial National Institutes of Health Stroke Scale (NIHSS) score, and type of treatment during the acute stage (thrombolysis, anticoagulant or antiplatelet medications).

All participants underwent brain MRI before the initiation of thrombolytic or anti-thrombotic therapy (within 24 hours after admission) and follow-up brain GRE MRI. The MRI studies were performed using a 1.5-Tesla superconducting magnet (GE Medical System, Milwaukee, WI, USA). The standardised MRI protocol consisted of axial T2-weighted spin echo (repetition time (TR)/echo

time (TE), 2500–4500/80–112 ms; flip angle, 20°; slice thickness, 5 mm; gap width, 2 mm), axial GRE sequences (TR/TE, 200–500/15 ms; flip angle, 20°; slice thickness, 5 mm; gap width, 2 mm) and diffusion-weighted imaging (repetition time (TR)/echo time (TE), 4000/73 ms; flip angle, 90°; slice thickness, 5 mm; gap width, 2 mm). We examined the MBs present at baseline by analysing the GRE image obtained at admission. MBs were defined as focal homogeneous hypointense areas with a diameter of 2–5 mm. Signal loss lesions secondary to globus pallidus calcification or thrombus in the cerebral artery were excluded. We determined the number and location of MBs in each patient. The cerebral lesions (MBs and ischaemic stroke lesions) were located in the cortical areas, deep grey matter, brain stem and cerebellum. Old ischaemic or haemorrhagic stroke lesions were also evaluated. Leukoaraiosis was classified as being absent, or present as a punctate, early confluent or confluent abnormality (as seen on T2-weighted MR images) according to the method proposed by Fazekas *et al.*,[12] and early confluent or confluent lesions were compared in this study. HTf was identified by follow-up brain GRE MRI and, according to the prespecified criteria,[13] the severity of HTf was graded into four categories: haemorrhagic infarction (HI)-1 (small petechiae along the margins of the infarct); HI-2 (more confluent petechiae within the infarct but without space-occupying effect); parenchymal hematoma (PH)-1 (blood clots not exceeding 30% of the infarct area); and PH-2 (blood clots exceeding 30% of the infarct area with significant space-occupying effect).

Spearman's rank correlation analysis was used to test inter-observer reliabilities of MB numbers. Associations between variables and incident HTf were examined by Pearson's χ^2 test, Fisher's exact test and Student's t test. The numbers of MBs were compared according to the presence or the severity of HTf using a nonparametric analysis (Mann–Whitney U test), because the numbers of MBs were not normally distributed (Kolmogorov–Smirnov test; $p<0.05$). All analyses were performed using SPSS statistical software (Version 12.0.1). In all tests, $p<0.05$ was noted as significant.

RESULTS

The inter-observer reliability of MB numbers between the reading of observer 1 (S-HL) and observer 2 (B-SK) was high ($r = 0.87$, $p<0.001$). Of the 377 patients included in this study, 234 patients were male (62.1%) and the mean age of the subjects was 66.2 ± 11.7 years. There were 232 patients with hypertension (61.5%), 118 with diabetes (31.3%) and 64 with hyperlipidaemia (17.0%). Prior to admission, 100 patients (26.5%) had a history of transient ischaemic attack or stroke, 40 patients (10.6%) had been prescribed antiplatelet agents and 27 patients (7.2%) had been prescribed anticoagulants. Incident HTf was found in 74 patients (19.6%), and symptomatic HTf was found in 13 patients (3.4%). Patients with incident HTf were likely to receive thrombolytic treatment ($p<0.001$) and to have a higher NIHSS score ($p<0.001$) (table 1). The interval between the first imaging and the follow-up imaging ranged from 1 to 17 days (mean, 6.0 ± 7.3 days; median, 8 days).

Baseline MBs revealed by GRE MRI were present in 109 patients (28.9%) and were most frequently located in the cortical area (70 patients, 18.6%). The number of lesions ranged from 0 to 122. As illustrated in table 2, among the patients with incident HTf during the hospitalisation period, baseline MBs were found in 18 patients (24.3%) and the association between MBs and HTf was not significant ($p = 0.331$). Reclassification of the subjects according to the location of the MBs (cortical, deep grey matter, brain stem and cerebellum) did not affect the results. When we limited the outcome to symptomatic HTf, an association between the presence of MBs and symptomatic HTf was not found ($p = 0.637$ by Pearson's χ^2 test).

We also found that there was no association between the number of MBs and the incident HTf ($p = 0.234$ by Mann–Whitney U test) (table 2). According to the severity of HTf, no significant differences were found (No HTf, 1.8 ± 8.1; HI-1, 1.1 ± 2.2; HI-2, 0.4 ± 1.0; PH-1, 0.4 ± 1.0; PH-2, 0.6 ± 1.2; $p>0.05$ in all comparisons using Mann–Whitney U test). Among the radiological variables, patients with stroke lesions located in the grey matter were more likely to have incident HTf during hospitalisation ($p = 0.001$).

We performed two subgroup analyses based on stroke mechanism and stroke location in order to identify any significant relationships among the subgroups. In the initial analysis based on stroke mechanism (large-artery atherothrombosis and cardioembolism), neither subgroup showed significant association between MBs and incident HTf (data not shown).There were also no significant results in the subgroup analysis based on stroke location (cortical and deep grey matter) (data not shown).

DISCUSSION

In this study, underlying MBs observed on the initial GRE MR images were not associated with incident HTf occurring during hospitalisation after acute ischaemic stroke. The presence, number and location of MBs were not related to the incidence of HTf, and there were no significant differences among the groups classified according to HTf severity. In addition, no significant relationships were found between HTf and any of the subgroups. Stroke location (cortical-subcortical or deep grey matter), use of thrombolytic agents and high initial NIHSS score were associated with the subsequent haemorrhagic transformations.

MBs indicate previous extravasation of blood, signifying bleeding-prone cerebral microangiopathy.[5–7 14] It has been suggested that MBs may predict the incidence of intracerebral haemorrhage.[4 15 16] A previous study of 41 patients who underwent intra-arterial thrombolysis demonstrated that the presence of baseline MBs could be a risk factor for symptomatic HTf.[7] On the other hand, a subsequent retrospective study of 44 patients who had received intravenous thrombolysis did not replicate the positive association between MBs and HTf reported in the previous study.[10] Furthermore, a recent prospective study, which was a part of the DEFUSE trial, showed that MBs were detected in 11 out of 70 patients with intravenous thrombolysis, and none of the 11 patients with MBs at baseline had symptomatic HTf compared with 7 of the 59 patients who did not have baseline MBs (11.9%).[9] Considering these results, MBs are not likely to be associated with risk of HTf after thrombolysis. In this context, the predictive value of MBs for subsequent HTf should be re-evaluated in all types of HTf. A study on the effects of MBs on early cerebral bleeding after acute ischaemic stroke reported that MBs were found in 20 of 100 patients with acute ischaemic stroke and in 10 of 26 patients with HTf ($p<0.001$).[8] However, the study had an important limitation: in 11 of the 20 patients with MBs, GRE MRI was performed after the initiation of either systemic thrombolysis or anti-thrombotic treatment (mainly high-dose heparin), both of which may contribute to MBs or HTf formation.[8 17] In this study, all of the GRE MRIs were performed before the initiation of thrombolytic or anti-thrombotic therapy, and they did not confirm the positive

Table 1 Demographic, clinical and laboratory findings in patients with stroke due to large-artery atherothombosis or cardioembolism

	HTf		
	Absent (n = 303)	Present (n = 74)	p Value
Demographic			
Gender (male)	188 (62.0%)	46 (62.2%)	0.985
Age at admission (years)	66.1 ± 12.2	66.8 ± 9.8	0.643*
Clinical			
Hypertension	186 (61.4%)	46 (62.2%)	0.902
Diabetes	92 (30.4%)	26 (35.1%)	0.427
Hyperlipidaemia	54 (17.8%)	10 (13.5%)	0.376
Smoking	100 (33.0%)	25 (33.8%)	0.898
History of transient ischaemic attack	21 (6.9%)	1 (1.4%)	0.093†
History of stroke	62 (20.5%)	16 (21.6%)	0.897
Previous use of antiplatelet agents	32 (10.6%)	8 (10.8%)	0.950
Previous use of anticoagulation	19 (6.3%)	8 (10.8%)	0.174
Initial NIHSS score	5.5 ± 5.9	10.3 ± 7.1	<0.001*
Acute treatment			
Thrombolysis	19(6.3%)	20(27.0%)	<0.001
Antiplatelet agents	115(38.0%)	31(41.9%)	0.533
Anticoagulation	179(59.1%)	29(39.2%)	0.002
Laboratory			
Glucose (mmol/L)	6.44 ± 2.19	6.75 ± 2.10	0.294*
Total cholesterol (mmol/L)	4.72 ± 1.05	4.55 ± 0.99	0.208*
Systolic blood pressure (mmHg)	151.0 ± 25.5	149.9 ± 25.0	0.745*
Diastolic blood pressure (mmHg)	86.7 ± 15.1	85.8 ± 13.2	0.636*
Mean blood pressure (mmHg)	108.1 ± 17.1	107.2 ± 15.1	0.657*
Prolonged PT/aPTT (%)	63 (20.8%)	16 (21.6%)	0.875

Pearson's χ^2 test, *Student t tests and †Fisher's exact test were used.
aPTT, activated partial thromboplastin time; HTf, haemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time.

association between the presence of baseline MBs and subsequent incidence of HTf.

The underlying histopathologies of intracerebral haemorrhage include rupture of penetrating arterioles damaged by hyaline degeneration and microaneurysm formation caused by long-standing hypertension or ageing.[18–20] However, the pathophysiological mechanism of HTf formation after acute ischaemic stroke is different from that of intracerebral haemorrhage.

Table 2 Analysis of radiological variables

	HTf		
	Absent (n = 303)	Present (n = 74)	p Value
Presence of MBs			
Whole brain	91 (30.0%)	18 (24.3%)	0.331
Cortical	59 (19.5%)	11 (14.9%)	0.361
Deep grey matter	55 (18.2%)	10 (13.5%)	0.344
Brain stem	35 (11.6%)	6 (8.1%)	0.394
Cerebellum	24 (7.9%)	3 (4.1%)	0.247
Number of MBs	1.8 ± 8.1	0.7 ± 1.5	0.234*
Location of stroke			
Cortical	208 (68.6%)	59 (79.7%)	0.060
Deep grey matter	71 (23.4%)	32 (43.2%)	0.001
Brain stem	45 (14.9%)	6 (8.1%)	0.128
Cerebellum	52 (17.2%)	17 (23.0%)	0.246
Leukoaraiosis (early confluent or confluent)	79 (26.1%)	19 (25.7%)	0.944
Absent	115 (38.0%)	38 (51.4%)	
Punctate	109 (36.0%)	17 (23.0%)	
Early confluent	48 (15.8%)	15 (20.3%)	
Confluent	31 (10.2%)	4 (5.4%)	
Old stroke lesion			
All stroke	96 (31.7%)	21 (28.4%)	0.582
Ischaemic stroke	90 (29.7%)	19 (25.7%)	0.493
Haemorrhagic stroke	10 (3.3%)	2 (2.7%)	0.793

Pearson's χ^2 test and *Mann–Whitney U test were used.
HTf, haemorrhagic transformation; MBs, microbleeds.

Ischaemic injury to the microvasculature in extensive brain infarction is central to the risk of parenchymal haemorrhage following thrombolytic treatment in stroke.[21] An experimental study demonstrated a correlation between the development of HTf and the loss of basal lamina architecture.[22] Because the histopathological findings of MBs are similar to those of symptomatic intracerebral haemorrhage, MBs may not be associated with development of HTf in acute ischaemic stroke, as found in this study.

There were some caveats of this study. First, our study was conducted in a retrospective manner, and brain imaging was not performed using a predetermined protocol. Despite this limitation, we were able to determine the presence of incident HTf because follow-up brain imaging was performed in most of the patients (1001 out of 1034; 97%). Second, this study did not evaluate the long-term effects of HTf, which is a major poor prognostic factor in acute stroke. Third, this study did not include patients with stroke due to small-vessel occlusion because a rarity of incident HTf in this subtype of stroke might have influenced the study results. Fourth, to focus on the association between the MBs and HTf, we did not conduct a multivariate analysis for identification of independent factors. Finally, the development of HTf was more frequent in cardioembolic stroke than in strokes due to other mechanisms.[23 24] Our result showed a similar tendency (cardioembolism, 33%, 53/161; large-artery atherothombosis, 10%, 22/219); however, there was no association between the presence of MBs and incident HTf after stratification by stroke mechanism.

This study suggests that underlying MBs may not predict incident HTf in acute ischaemic stroke. MBs reflect bleeding-prone microangiopathy in the brain, but do not predict all forms of subsequent bleeding. The predictive values of CMBs should be differentially evaluated according to the type of disease (intracerebral haemorrhage vs. HTf).

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