Cerebral Microbleeds as a Predictor of 1-Year Outcome of Poststroke Depression

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Background and Purpose—Cerebral microbleeds (CMBs) are common in stroke survivors and community-dwelling elderly. The clinical significance of CMBs in the outcome of poststroke depression (PSD) is unknown. This study examined the association between the 1-year outcome of PSD and CMBs.

Methods—The study population comprised 774 Chinese patients with acute ischemic stroke who were admitted to the acute stroke unit of a university-affiliated regional hospital in Hong Kong. Three and 15 months after the onset of the index stroke, a research assistant administered the locally validated 15-item Geriatric Depression Scale. PSD was defined as a Geriatric Depression Scale score of ≥7. Of the 213 patients with PSD at the 3-month follow-up, 135 (63.4%) attended the 15-month follow-up, at which time 89 (65.9%) patients remained depressed (nonremitters), and 46 (34.1%) had recovered (remitters). The presence and location of CMBs were evaluated with magnetic resonance imaging.

Results—In comparison with the remitters, nonremitters were more likely to have lobar CMBs (18.4% versus 4.3%; P=0.024). Lobar CMBs remained an independent predictor of PSD in the multivariate analysis, with an odds ratio of 4.96 (P=0.039).

Conclusions—The results suggest that lobar CMBs may influence the outcome of PSD. The importance of CMBs in the clinical course of depression in stroke survivors warrants further investigation. (Stroke. 2014;45:00-00.)

Key Words: depression ■ magnetic resonance imaging ■ outcome measures ■ stroke

Depression is the most common and serious affective disorder after stroke. The rate of remission of poststroke depression (PSD) at 1 year varies from 44% to 60%.1-4 Possible clinical predictors of nonremission are older age, lower level of education, more severe stroke, and depression at baseline.5 No data have been published on brain imaging variables as possible predictors of nonremission in PSD.

White matter hyperintensities have been shown to be associated with late-life depression,6 possibly affecting its severity7 and outcome.7 White matter hyperintensities are conceptualized as a sign of vascular damage to brain structures, and they are known to contribute to the development of vascular depression.8

Cerebral microbleeds (CMBs) are focal deposits of hemosiderin that indicate previous microhemorrhages. They are related to cerebral amyloid angiopathy, hypertension, and atherosclerosis.9 CMBs are common in ischemic stroke10 and are regarded as an indicator of underlying vascular damage. CMBs influence the risk11 and severity12 of PSD, hence it is possible that CMBs also affect the outcome of PSD. No previous study has examined the relationship between CMBs and the outcome of PSD or other patient populations. The aim of this study was thus to determine the relationship between CMBs and PSD in stroke survivors.

Materials and Methods

Patients

Five thousand nine hundred sixty-two patients with first-ever or recurrent acute ischemic stroke were admitted to the Acute Stroke Unit of the Prince of Wales Hospital between June 2006 and January 2012. Prince of Wales Hospital is a university-affiliated general hospital serving a population of 800,000 in Hong Kong. Of the 5962 patients, 2354 received an MRI examination; 966 patients did not attend the 3-month follow-up because they could not be contacted (n=448), refused participation (n=317), physical frailty (n=144), and deceased (n=72). The study sample comprised 774 (32.9%) patients who fulfilled the study entry criteria listed below. Patients who were excluded (n=1580) were older (67.7±12.5 vs 66.3±10.3; P=0.008), more likely to be women (45.4% vs 40.7%; P=0.003), and had higher average National Institutes of Health Stroke Scale (NIHSS)13 score (5.2±5.3 vs 3.9±3.3; P<0.001).

The inclusion criteria for the study were (1) Chinese ethnicity; (2) Cantonese as the primary language; (3) aged ≥18 years; (4) well-documented (clinical presentation and computed tomographic scan of the brain) first or recurrent acute stroke occurring within 7 days before admission; and (5) ability and willingness to give consent. The exclusion criteria were (1) transient ischemic attack, cerebral hemorrhage,
subdural hematoma, or subarachnoid hemorrhage; (2) another stroke before the 3-month follow-up; (3) history of a central nervous system disease, such as tumor, Parkinson disease, etc; (4) history of depression, substance abuse/dependence, or other psychiatric disorders before the index stroke; (5) moderate or severe dementia defined as a Mini-Mental State Examination (MMSE) score of <20; and (6) severe aphasia and hearing or visual impairment.

Of the 774 patients screened, 213 were diagnosed with PSD 3 months after the index stroke. One year after the baseline assessment (ie, 12 months after the index stroke), 135 (63.4%) patients with PSD attended the follow-up. Patients who did not attend the follow-up (n=78) were more likely to be men (62.8% versus 48.9%; P=0.049) and to have a higher NIHSS score (5.5±4.7 versus 4.5±3.0; P=0.051). The age distribution (65.7±11.0 versus 67.2±10.5; P=0.319) and the proportions of patients with lobar (26.9% versus 20.0%; P=0.244) or any (17.9% versus 13.3%; P=0.363) CMBS of the 2 groups were similar.

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants signed a consent form.

Collection of Demographic and Clinical Data
Within 2 days of admission, a research nurse collected the demographic (age, sex, and years of education) and clinical (hypertension, diabetes mellitus, hyperlipidemia, previous stroke, and intracranial hemorrhage) data and assessed the patients’ functional status before the index stroke and the stroke severity using the modified Rankin Scale14 and the NIHSS.13 A research assistant assessed all patients using the MMSE and the Lubben Social Network Scale (LSNS)16 3 months after the index stroke. The LSNS is a composite social network scale specifically designed for use with the elderly. It measures the level of social support patients receive and their social interactions with relatives and friends. It contains 10 items and the maximum score is 50, with higher scores indicating better social support. The LSNS has been translated into Chinese and validated for use with the elderly in Hong Kong.17 At the 15-month follow-up, recurrence of stroke and details of antidepressant treatment and psychotherapy received were also recorded.

Assessment of PSD
Three and fifteen months after the index stroke, a research assistant who was blind to the patients’ radiological data administered the validated 15-item Geriatric Depression Scale (GDS).18 The timing of the assessment was chosen to avoid the period of transient emotional adjustment to the disability caused by the stroke. PSD was defined as a GDS score of ≥7.19 Patients who had PSD at the 3-month follow-up but no PSD at the 15-month follow-up were classified as remitters.

Radiological Examination
MRI with diffusion-weighted imaging and conventional sequences, including a gradient echo (blood product sensitive) sequence, was performed with a 1.5-T system (Sonata, Siemens Medical, Erlangen, Germany) within 7 days of admission.

Diffusion-weighted imaging spin-echo echo-planar imaging (long repetition time [TR]/echo delay times [TE]/excitation=180/122/4; matrix=128×128; field of view [FOV]=230 mm; slice thickness/gap=5 mm/1 mm; echo-planar imaging factors=90; acquisition time=55 s) with 3 orthogonal applied gradients was used with a b value of 1000 and 500. Axial gradient echo images were acquired as the second sequence with imaging parameters of TR/TE/excitation=350/30/2, flip angle of 30°, slice thickness/gap=5 mm/0.5 mm, FOV=230 mm, matrix 256x256, and acquisition time=5 minutes 4 s. Axial SE T1 (TR/TE/excitation=425/14/2; FOV=230 mm; slice thickness/gap=5 mm/0.5 mm; matrix=256x256; and acquisition time=4 minutes 28 s) and turbo spin-echo T2 images were also acquired (TR/TE/excitation=2500/120/1; turbo factor of 15; FOV=230 mm; slice thickness/gap=5 mm/0.5 mm; matrix=256x256; and acquisition time=1 minute 39 s) axial fluid attenuated inversion recovery (TR/TE/inversion-time/excitation=9000/117/2500/2; turbo factor of 31; FOV=230 mm; slice thickness/gap=5 mm/1 mm; matrix=256x256; time of acquisition=3 minutes 20 s) sequences were also acquired.

A neurologist (Y.K.C.) who was blind to the psychiatric diagnosis and clinical data other than age and sex assessed the MRIs as follows.

1. CMBS were defined as multiple ovoid foci with marked loss of signal intensity on T2-weighted, gradient-recalled echo MRI. Symmetrical basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded based on their typical distribution and location.20 CMBS were divided into lobar (corpus and subcortical white matter), deep (basal ganglia, internal and external capsules, and thalamus), and posterior fossa (brain stem and cerebellum) groups.21 Lobar CMBS were further divided into frontal, temporal, parietal and occipital lobe CMBS.

2. White matter hyperintensities on MRI were defined as hyperintensities ≥3 mm on T2 images. The severity of white matter hyperintensities was assessed using the Fazekas scale22 on both sides of the frontal, parietal and occipital, temporal, basal ganglia, and infratentorial regions. The Fazekas Scale score was the sum of scores for both sides of all regions.

3. Infarcts: the total area of acute infarcts on diffusion-weighted imaging was measured with manual outlines. Acute infarcts were defined as areas of restricted water diffusion identified on diffusion-weighted images with b values of 1000 together with hypointensity on the corresponding apparent diffusion coefficient map. Acute infarcts were divided into cortical (frontal, temporal, parietal and occipital), subcortical (subcortical white matter, basal ganglia, and thalamus), and infratentorial (brain stem and cerebellum). The total volume was calculated by multiplying the total area by the sum of the slice thickness and the gap. The number of old infarcts was also recorded. Chronic infarcts were defined as focal hyperintensities on T2-weighted and hypointensities on T1-weighted images with size ≥3 mm. Lesions <3 mm were considered as dilated perivascular space. Intra-rater reliability tests were performed on 20 patients; the κ values for the volume and number of infarcts were 0.96 and 0.94, respectively.

Statistical Analysis
All statistical tests were performed using SPSS for Windows (version 20.0; SPSS Inc, Chicago, IL). The demographic and clinical variables and radiological characteristics of the remitters were compared with those of the nonremitters using Fisher exact test, Student t test, or the Mann–Whitney U test, as appropriate. Risk factors with a value of P<0.10 were then analyzed with multivariate logistic regression analysis using a forward stepwise selection strategy. Only MRI characteristics were entered in the first model and clinical variables were added in the second model. If the correlations between any of these putative risk factors were ≥0.50, then additional models were examined to rule out collinearity. In the analysis, the odds ratio of any independent risk factor was interpreted as the risk of nonremission of PSD when all other risk factors were held constant. The level of significance was set at 0.05.

Results
The final sample (n=135) had the following characteristics: 69 (51.1%) were women; 26 (19.3%), 95 (70.4%), 58 (43.0%), and 67 (49.6%) patients had a previous history of stroke, hypertension, diabetes mellitus, and hyperlipidemia, respectively. The mean age and education (in years) were 65.7±11.0 and 5.9±4.6, respectively. The mean NIHSS score on admission was 4.5±2.9. The Barthel Index, modified Rankin Scale, MMSE, GDS, and LSNS scores at the baseline assessment were 18.8±2.9, 1.5±1.0, 26.6±2.8, 9.8±2.3, and 28.3±8.3, respectively. Seven (5.2%) patients had another stroke before the 1-year follow-up assessment, 8 (5.8%) received antidepressant treatment, and 3 (2.2%) received psychotherapy.
Of the 135 patients who attended the 1-year follow-up, 89 (65.9%) were diagnosed as still having PSD (nonremitters), whereas 46 (34.1%) were no longer depressed (remitters). Compared with the remitters, nonremitters had higher baseline NIHSS ($P=0.013$) and GDS ($P=0.001$) scores. There was a trend that they had lower MMSE ($P=0.077$) and LSNS ($P=0.055$) scores (Table 1). Nonremitters were more likely to have CMBs (25.3% versus 10.9%; $P=0.049$) and specifically lobar CMBs (18.4% versus 4.3%; $P=0.024$). There was no significant association between baseline GDS score and presence of lobar CMBs (Spearman $p=−0.043$; $P=0.620$). The median of the difference between the baseline and follow-up GDS scores in patients with and without lobar CMBs were 1 and −2, respectively (Mann–Whitney $U$ test; $P=0.077$). There was a trend that nonremitters were more likely to have CMBs in the parietal ($P=0.097$), occipital ($P=0.094$), and basal ganglia ($P=0.094$) regions, and occipital lobe infarcts ($P=0.095$; Table 2).

The presence of lobar CMBs was significantly correlated with the presence of CMBs in any region ($r=0.784$; $P<0.001$) and CMBs in the parietal ($r=0.759$; $P<0.001$) and occipital ($r=0.549$; $P<0.001$) regions. To avoid collinearity, only the presence of lobar CMBs was entered into the first regression model (Model A). The presence of lobar CMBs was the only MRI characteristic that predicted nonremission of PSD with an odds ratio of 4.958 ($P=0.039$). In the second model (Model B), the presence of CMBs in any region and in the parietal and occipital lobes were also entered, but the odds ratio of lobar CMBs remained unchanged. In the third model (Model C), lobar CMBs and the baseline NIHSS, GDS, MMSE, and LSNS scores were entered; lobar CMBs remained a significant predictor. Other predictors included baseline NIHSS and GDS scores. The $R^2$ of this model was 0.208 (Table 3).

### Discussion

To the best of our knowledge, this is the first report of an association between CMBs and outcome of PSD. The results suggest that lobar CMBs are associated with nonremission of depression in patients with well-established cerebrovascular disease.

Microbleeds not only have hemosiderin deposits, but also affect the surrounding gliosis and cause frank necrosis or infarction, indicating that they may be of clinical importance. The finding that only lobar CMBs are associated with nonremission of PSD suggests that CMBs, besides being a marker of underlying vascular pathology, may also directly affect the outcome of PSD. The importance of the location of CMBs has

### Table 1. Demographic Characteristics, Psychosocial Risk Factors, and Stroke Severity of Nonremitters and Remitters of Poststroke Depression

<table>
<thead>
<tr>
<th></th>
<th>Nonremitters (n=89)</th>
<th>Remitters (n=46)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.5±11.1</td>
<td>64.0±10.5</td>
<td>0.215*</td>
</tr>
<tr>
<td>Women</td>
<td>47 (52.8%)</td>
<td>22 (47.8%)</td>
<td>0.583†</td>
</tr>
<tr>
<td>Education, y</td>
<td>5.5±4.3</td>
<td>6.9±5.1</td>
<td>0.100*</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>20 (22.7%)</td>
<td>6 (13.0%)</td>
<td>0.178†</td>
</tr>
<tr>
<td>Previous intracranial hemorrhage</td>
<td>2 (2.2%)</td>
<td>3 (6.5%)</td>
<td>0.443*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (70.5%)</td>
<td>33 (71.7%)</td>
<td>0.876†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (47.7%)</td>
<td>16 (34.8%)</td>
<td>0.151†</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>46 (51.7%)</td>
<td>21 (45.7%)</td>
<td>0.467†</td>
</tr>
<tr>
<td>Smoker</td>
<td>51 (57.3%)</td>
<td>33 (71.7%)</td>
<td>0.101†</td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td>0.3±0.6</td>
<td>0.2±0.6</td>
<td>0.313*</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>18.4±3.1</td>
<td>19.1±2.4</td>
<td>0.239*</td>
</tr>
<tr>
<td>MMSE score</td>
<td>26.3±2.8</td>
<td>27.2±2.8</td>
<td>0.077*</td>
</tr>
<tr>
<td>NIHSS total score</td>
<td>4.9±3.2</td>
<td>3.6±2.3</td>
<td>0.013*</td>
</tr>
<tr>
<td>LSNS score</td>
<td>27.2±8.7</td>
<td>30.2±7.2</td>
<td>0.055*</td>
</tr>
<tr>
<td>GDS score</td>
<td>10.3±2.4</td>
<td>8.9±1.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>Repeated stroke</td>
<td>5 (5.6%)</td>
<td>2 (4.3%)</td>
<td>1.000‡</td>
</tr>
<tr>
<td>Received antidepressant treatment</td>
<td>6 (6.7%)</td>
<td>2 (4.3%)</td>
<td>0.716†</td>
</tr>
<tr>
<td>Received psychological treatment</td>
<td>3 (4.4%)</td>
<td>0 (0.0%)</td>
<td>0.550‡</td>
</tr>
</tbody>
</table>

GDS indicates Geriatric Depression Scale; LSNS, Lubben Social Network Scale; MMSE, Mini-Mental State Examination; and NIHSS, National Institutes of Health Stroke Scale.

* Mann–Whitney $U$ test unless otherwise specified.

† Fisher exact test.
been reported in the outcome of other poststroke pathologies; for instance, lobar CMBs have been implicated in the reversion of cognitive impairment.24 No data have been published on brain imaging variables as possible predictors of nonremission in PSD. Lobar regions comprise the cerebral cortex and subcortical white matter. Alterations of the integrity of white matter seem to be related to the outcome of late-life depression.7,25 For instance, frontal microstructural white matter abnormalities may be associated with a low remission rate of late-life depression.26 White matter abnormalities and the resulting dysfunctions of the frontosubcortical circuits at the level of the dorsolateral prefrontal cortex may affect the course of late-life depression.25 It is possible that CMBs in the lobar region adversely affect the outcome of PSD via a similar mechanism.

The remission rate of PSD in this study was somewhat lower than the figures of 44% to 60% reported in the literature.1–4 One possible explanation is the low rate of antidepressant or psychological treatment received by our patients. In line with the literature, the baseline stroke severity and depression severity predicted nonremission of PSD. In a recent study of 138 stroke survivors, nonremission of PSD was associated with more disabling stroke and severe depression.3

The main limitation of this study was the small sample size and the relatively high attrition of patients for follow-up, which reduced its statistical power. Furthermore, the stroke severity of the final study sample was mild. Patients who could not give consent because of dementia or aphasia-associated left-side infarcts were excluded. This selection bias may limit the generalizability of the findings particularly to patients with more severe stroke. In addition, measurement of CMBs using a 3.0-T MRI machine would have improved the detection rate of CMBs.27 Furthermore, only a small proportion of patients received treatment for their depression. Hence, the results show the impact of CMBs on the natural course of PSD. The effect of CMBs on the treatment outcome of PSD, which was not the aim of this study, would be ideally studied in a controlled clinical trial. Finally, there was a lack of relationship between CMBs count and nonremission of PSD.

In conclusion, the results indicate that lobar CMBs are associated with a higher risk of nonremission of PSD. Further investigations are warranted to clarify whether CMBs have any effect on the response of PSD to pharmacological and psychological treatments. As the prevalence of CMBs is as high as 23.5% in community-dwelling elderly,26 it would be logical to examine whether CMBs might also contribute to the outcome of depression in the general elderly population.

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### Disclosures

None.

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