Cerebral Microbleeds and Depression in Lacunar Stroke

W.K. Tang, MD; Y.K. Chen, PhD; J.Y. Lu, MPhil; Winnie C.W. Chu, MD; V.C.T. Mok, MD; Gabor S. Ungvari, MD, PhD; K.S. Wong, MD

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

Methods—A cohort of 235 patients with acute lacunar stroke admitted to the stroke unit of a university-affiliated regional hospital in Hong Kong was recruited. Three 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 Genetic Depression Scale score of ≥7. The presence and location of CMB were evaluated with MRI.

Results—In comparison with the non-PSD group, PSD patients were more likely to have lobar CMB (33.3% versus 19.9%; \( P=0.022 \)). Lobar CMB remained an independent predictor of PSD in the multivariate analysis, with an odds ratio of 2.08 (\( P=0.032 \)).

Conclusions—The results suggest that lobar CMB may play a role in the development of PSD. The importance of CMB in the pathogenesis of depression in stroke survivors and the general elderly population warrants further investigation. (Stroke. 2011;42:2443-2446.)

Key Words: depression ▪ microbleeds ▪ stroke

Cerebral microbleeds (CMB) are focal deposits of hemosiderin that indicate previous microhemorrhages. They are related to cerebral amyloid angiopathy, hypertension, and atherosclerosis.1

CMB are common in ischemic stroke2 and associated with advanced small artery disease of the brain.3 Recent evidence suggests that they may be one of the important factors causing emotional liability in stroke.4 The significance of CMB in the development of depression after a stroke remains unknown.

Depression is the most common and serious affective disorder after stroke. The neuroanatomical model of poststroke depression (PSD) remains unclear. There is no compelling evidence for the hypothesis of a close relationship between lesion location and PSD.5 It was recently suggested that chronic vascular burden may be an important factor in the pathogenesis of PSD.6

White matter hyperintensities have been shown to be associated with late life depression,7 possibly affecting its symptom severity.8 White matter hyperintensities are conceptualized as a sign of vascular damage to brain structures and they contribute to the development of vascular depression.9 CMB are also indicators of underlying vascular damage; hence, it is surprising that no previous study has examined the relationship between CMB and depression in stroke or other patient populations.

Cerebral small vessel disease causes lacunar strokes,10 which account for 25% of all ischemic strokes.11 Most lacunar strokes are thought to arise secondary to an abnormality in the walls of the small deep perforating (lenticulostriate) arteries.12 A recent autopsy study suggested that lacunar infarcts may predict PSD.13 There is a lack of large-scale studies on PSD in lacunar stroke. The aim of this study was to determine the relationship between CMB and PSD in lacunar stroke survivors.

Subjects and Methods

Subjects
A total of 3219 patients with first-ever or recurrent acute ischemic stroke were admitted to the Acute Stroke Unit of the Prince of Wales Hospital between June 2004 and July 2008. Prince of Wales Hospital is a university-affiliated general hospital serving a population of 800 000 in Hong Kong. Of the 3219 patients, 1353 received an MRI examination. All patients who underwent MRI were screened for the inclusion and exclusion criteria. The inclusion criteria for the study were: (1) Chinese ethnicity; (2) Cantonese as the primary language; (3) age 18 years or older; (4) well-documented (clinical presentation and CT scan of the brain) first or recurrent acute lacunar stroke occurring within 7 days before admission (a lacunar stroke was defined as at least 1 symptomatic infarction [diameter 2–15 mm] in

Received January 19, 2011; accepted March 15, 2011.
Patricia D. Hurn, MD, was the Consulting Editor for this paper.
From the Department of Psychiatry (W.K.T., J.Y.L.), Chinese University of Hong Kong, Hong Kong SAR, China; Department of Neurology (Y.K.C.), Dongguan People’s Hospital, Dongguan, Guangdong, P.R. China; Department of Imaging & Interventional Radiology (W.C.W.C.), Chinese University of Hong Kong, Hong Kong SAR, China; Department of Medicine and Therapeutics (V.C.T.M., K.S.W.), Chinese University of Hong Kong, Hong Kong SAR, China; The University of Notre Dame Australia/Marian Centre (G.S.U.), Perth, Australia. Correspondence to W.K. Tang, MD, Department of Psychiatry, Shatin Hospital, Shatin, NT, Hong Kong SAR, China. E-mail tangwk@cuhk.edu.hk
© 2011 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.614586

2443
the internal capsule, thalamus, basal ganglia, coronal radiate, centrum ovale, or the infratentorial region confirmed by brain MRI, and patients with any cortical and subcortical nonlacunar infarct [diameter >15 mm] were excluded); and (5) ability and willingness to give consent. The exclusion criteria included: (1) transient ischemic attack, cerebral hemorrhage, subdural hematoma, or subarachnoid hemorrhage; (2) history of a central nervous system disease such as tumor, Parkinson disease, and others; (3) history of depression or substance abuse/dependence before the index stroke; and (4) moderate or severe dementia defined as a Mini-Mental State Examination\textsuperscript{14} score <17.

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

A research nurse who was blind to the Geriatric Depression Scale scores collected the demographic data (age, sex, and years of education), history of previous stroke and intracranial hemorrhage, and assessed the function before the index stroke and the stroke severity using the modified Rankin Scale\textsuperscript{15} and the National Institutes of Health Stroke Scale\textsuperscript{16} within 2 days of admission. A research assistant assessed all subjects with the Mini-Mental State Examination and the Lubben Social Network Scale\textsuperscript{17} scores 3 months after the onset of the index stroke. The Lubben Social Network Scale is a composite social network scale specifically designed for use with the elderly. It measures the level of social support that patients receive and their social interaction with relatives and friends. It contains 10 items and the maximum score is 50; a higher score indicates better social support. The Lubben Social Network Scale has been validated in Chinese and translated for the elderly in Hong Kong.\textsuperscript{18}

Assessment of PSD

Three months after the onset of the index stroke, a research assistant who was blind to the subjects’ radiological data administered the validated 15-item Geriatric Depression Scale.\textsuperscript{19} 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 Geriatric Depression Scale score of ≥7.\textsuperscript{20}

Radiological Examination

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

Diffusion-weighted imaging spin-echo echo planar imaging (repetition time/echo time/excitation=180/122/4; matrix=128×128; field of view=230 mm; slice thickness/gap=5 mm/1 mm; echo planar imaging factor=90; acquisition time=55 seconds) with 3 orthogonally applied gradients was used with b values of 1000 and 500. Axial gradient echo images were acquired as the second sequence with imaging parameters of repetition time/echo time/excitation of 350/30/2; flip angle of 30 degrees; slice thickness/gap of 5 mm/0.5 mm, field of view of 230 mm, matrix 256×256, and acquisition time of 5 minutes and 4 seconds. Axial spin echo T1 (repetition time/echo time/excitation=425/142; field of view=230 mm, slice thickness/gap=5 mm/0.5 mm, matrix 256×256, and acquisition time=4 minutes and 28 seconds) and turbo spin echo T2 (repetition time/echo time/excitation=2500/120/1, turbo factor of 15, field of view=230 mm, slice thickness/gap=5 mm/0.5 mm, matrix of 256×256, and acquisition time=1 minute and 39 seconds) images were also acquired.\textsuperscript{21}

A neurologist (Y.K.C.) who was blind to the psychiatric diagnoses assessed the MRI as follows. CMB were defined as small (2–10 mm) hypointense lesions on a T2-weighted gradient echo sequence, but symmetrical basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded.\textsuperscript{21} CMB were divided into lobar (cortex and subcortical white matter), deep (basal ganglia, internal and external capsules and thalamus), and posterior fossa (brain stem and cerebellum) groups.\textsuperscript{22} Lobar CMB were further divided into frontal, temporal, parietal, and occipital lobe CMB. The number of CMB in each location was recorded.

White matter hyperintensities on MRI were defined as hyperintensities ≥5 mm on T2 images. The severity of white matter hyperintensities was assessed using the age-related white matter changes scale\textsuperscript{23} on both sides of the frontal, parietal-occipital, temporal, basal ganglia, and infratentorial regions. The age-related white matter changes score was the sum of scores in both sides of all regions.

The total area of lacunar 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. The total volume was calculated by multiplying the total area by the sum of the slice thickness and the gap. Intrarater reliability tests were performed on 20 subjects; the k values for the volume and number of infarcts were 0.96 and 0.94, respectively.

Statistical Analysis

All statistical tests were performed by SPSS for Windows (release 14.0; SPSS). The demographic and clinical variables and radiological characteristics of the PSD subjects were compared with those without PSD using the χ\textsuperscript{2} test, Fisher exact test, Student t test, and the Mann-Whitney U test, as appropriate. Risk factors with a value of P<0.10 were then analyzed by multivariate logistic regression analysis using a forward stepwise selection strategy. Based on the results of the univariate and the initial regression analyses, further regression models were constructed to examine the locations of CMB. In the analysis, the odds ratio of any independent risk factor was interpreted as the risk of subsequent PSD when all other risk factors were held constant. The level of significance was set at 0.05.

Results

Altogether, 235 patients met the entry criteria and formed the study sample. Patients who were excluded from the study had a higher National Institutes of Health Stroke Scale score (5.8±5.1 versus 4.2±3.0; P<0.001). The age (67.8±12.3 versus 66.5±11.3; P<0.091) and sex (55.7% versus 60.9%; P=0.241) distribution of the excluded and included groups were similar.

Of the 235 patients screened, 84 (35.7%) had PSD. The demographic and MRI characteristics and stroke-related data are shown in Tables 1 and 2. The PSD and control groups did not differ in terms of age and history of hypertension, previous stroke or intracranial hemorrhage, and prestroke functioning. PSD patients were more likely to be female and have a history of diabetes mellitus, a lower level of education, social support, and cognitive function, and more severe stroke (Table 1). The proportion of patients with lobar CMB was significantly higher in the PSD group (33.3% versus 19.9%; P=0.022; Table 1).

The following variables were entered into the regression model: sex and history of diabetes mellitus; lobar CMB and severe white matter hyperintensities; the Lubben Social Network Scale, Mini-Mental State Examination; education (years); and interaction between education and Mini-Mental State Examination and National Institutes of Health Stroke Scale scores. Lobar CMB was a significant independent imaging predictor of PSD with an odds ratio of 2.09 (Table 2). The regression model was repeated after excluding patients with recurrent stroke; lobar CMB was still a significant predictor (odds ratio, 2.5; P=0.015; data not shown). Finally, 3 additional regression models were constructed by entering frontal, temporal, and occipital CMB instead of lobar CMB,
Table 1. Demographic Characteristics, Psychosocial Risk Factors, Stroke Severity, and Radiological Characteristics by Poststroke Depression Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>PSD</th>
<th>No PSD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>67.1±12.1</td>
<td>65.9±10.7</td>
<td>0.438</td>
</tr>
<tr>
<td>Female</td>
<td>42 (50.0%)</td>
<td>50 (33.1%)</td>
<td>0.011†</td>
</tr>
<tr>
<td>Education (y)</td>
<td>4.3±4.3</td>
<td>6.0±4.9</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>20 (23.8%)</td>
<td>29 (19.2%)</td>
<td>0.405†</td>
</tr>
<tr>
<td>Previous intracranial hemorrhage</td>
<td>4 (20%)</td>
<td>4 (13.8%)</td>
<td>0.700†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (70.2%)</td>
<td>117 (77.5%)</td>
<td>0.220†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (47.6%)</td>
<td>50 (33.1%)</td>
<td>0.028†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.845 (1.006–3.386)</td>
<td>2.192 (1.212–3.965)</td>
<td>0.009</td>
</tr>
<tr>
<td>NIHSS total score</td>
<td>1.126 (1.019–1.244)</td>
<td>1.074 (0.962–1.199)</td>
<td>0.203</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.4±7.4</td>
<td>32.5±8.0</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Presence of lobar CMB</td>
<td>3.5±9.7</td>
<td>1.9±5.6</td>
<td>0.570†</td>
</tr>
</tbody>
</table>

Presence of CMB in any region:
- Any region: 27 (32.1%) vs 45 (29.8%) (0.709†)
- Lobar: 28 (33.3%) vs 30 (19.9%) (0.022†)
- Frontal: 11 (13.1%) vs 9 (6.0%) (0.060†)
- Temporal: 12 (14.3%) vs 11 (7.3%) (0.083†)
- Parietal: 14 (16.7%) vs 18 (11.9%) (0.309†)
- Occipital: 12 (14.3%) vs 9 (6.0%) (0.032†)
- Deep: 18 (21.4%) vs 31 (20.5%) (0.871†)
- Infratentorial: 16 (19.0%) vs 24 (15.9%) (0.538§)

Fazekas PVH score:
- 0: 10 (11.9%) vs 13 (8.6%) (0.724†)
- 1: 39 (46.4%) vs 85 (56.3%) (0.022†)
- 2: 25 (29.8%) vs 36 (23.8%) (0.226†)
- 3: 10 (11.9%) vs 17 (11.3%) (0.659§)

Fazekas DWMH score:
- 0: 17 (20.2%) vs 32 (21.2%) (0.226†)
- 1: 41 (48.8%) vs 78 (51.7%) (0.226†)
- 2: 13 (15.5%) vs 32 (21.2%) (0.889§)
- 3: 13 (15.5%) vs 9 (6.0%) (0.889§)

Presence of symptomatic or silent lacunar infarcts:
- Subcortical white matter: 45 (53.6%) vs 68 (45.0%) (0.209†)
- Basal ganglia: 35 (41.7%) vs 60 (39.7%) (0.772†)
- Thalamus: 18 (21.4%) vs 24 (15.9%) (0.289†)
- Infratentorial: 25 (29.8%) vs 46 (30.5%) (0.911†)

CMB indicates cerebral microbleeds; DWMH, deep white matter hyperintensities; LSNS, Lubben Social Network Scale; MMSE, Mini-Mental State Examination; NIHSS, National Institute of Health Stroke Scale; PVH, periventricular hyperintensities; SD, standard deviation.

*† t test.
††t2 test.
‡ Mann-Whitney U test.
§ Fisher exact test.

Table 2. Multivariate Logistic Model of the Clinical Determinants of Poststroke Depression

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar CMB</td>
<td>2.094 (1.066–4.115)</td>
<td>0.032</td>
</tr>
<tr>
<td>LSNS score</td>
<td>0.940 (0.905–0.976)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.845 (1.006–3.386)</td>
<td>0.048</td>
</tr>
<tr>
<td>Female</td>
<td>2.192 (1.212–3.965)</td>
<td>0.009</td>
</tr>
<tr>
<td>NIHSS total score</td>
<td>1.126 (1.019–1.244)</td>
<td>0.020</td>
</tr>
<tr>
<td>MMSE</td>
<td>1.074 (0.962–1.199)</td>
<td>0.203</td>
</tr>
<tr>
<td>Education</td>
<td>0.962 (0.900–1.028)</td>
<td>0.248</td>
</tr>
<tr>
<td>Education and MMSE</td>
<td>0.994 (0.972–1.018)</td>
<td>0.218</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CMB, cerebral microbleeds; DWMH, deep white matter hyperintensities, LSNS, Lubben Social Network Scale; MMSE, Mini-Mental State Examination; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

*Logistic regression.

and none of these CMB variables was significant (data not shown).

Discussion

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

The finding that only lobar CMB are associated with PSD suggests that CMB, besides being a marker of underlying vascular pathology, also may directly affect the risk of depression. The importance of the location of CMB has been reported in other poststroke pathologies, namely thalamic CMB in emotional liability and frontal and basal ganglia CMB in executive dysfunction.

The main limitation of this study is that the severity of stroke was mild and the assessment of PSD was performed only once at the 3-month follow-up. Patients who could not give consent because of dementia or aphasia-associated left-side infarcts were also excluded. This selection bias may limit the generalizability of the findings. In addition, the measurement of CMB should have been performed using a 3.0-T MRI machine, which would have improved the detection rate and visibility of CMB.

In conclusion, the results indicate that lobar CMB are associated with a higher risk of PSD and may contribute to its pathogenesis. Further investigation is needed to clarify whether CMB have any impact on the clinical presentation, treatment response, and outcome of PSD. Because the prevalence of CMBS is as high as 23.5% in community-dwelling elderly individuals, it would be logical to examine whether CMB also might contribute to the risk of depression in the general elderly population.

Sources of Funding

This work was supported by the Research Grants Council of the Hong Kong Special Administrative Region.

Disclosure

None.
References


Cerebral Microbleeds and Depression in Lacunar Stroke

Stroke. 2011;42:2443-2446; originally published online July 14, 2011;
doi: 10.1161/STROKEAHA.111.614586

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/9/2443

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/