Strictly Lobar Cerebral Microbleeds Are Associated With Cognitive Impairment

Chih-Ping Chung, MD, PhD; Kun-Hsien Chou, PhD; Wei-Ta Chen, MD, PhD; Li-Kuo Liu, MD; Wei-Ju Lee, MD; Liang-Kung Chen, MD, PhD*; Ching-Po Lin, PhD*; Pei-Ning Wang, MD*

Background and Purpose—Different distributions of cerebral microbleeds (CMBs) are associated with distinct pathological mechanisms. Lobar CMBs are thought to be related to cerebral amyloid angiopathy, whereas deep or infratentorial CMBs are related to hypertensive vasculopathy. The present study aimed to evaluate the effects of CMBs and their locations on a variety of cognitive domains.

Methods—Study subjects were selected from the community-based I-Lan Longitudinal Aging Study. We assessed cognitive domains, including verbal memory, language, visuospatial executive function, and verbal executive function. CMBs were evaluated using 3T susceptibility-weighted magnetic resonance imaging.

Results—We studied 959 subjects (mean±SD, 62.5±8.6 years; 425 [44.3%] men). CMBs were found in 14.2% of the population. We classified subjects with CMBs into 2 different groups based on the locations of their CMBs: (1) deep or infratentorial (85 subjects, 8.8% of population) and (2) strictly lobar (49, 5.1%). Multivariate linear analysis showed that strictly lobar CMBs were significantly associated with deficits in global cognitive function (Mini-Mental State Examination) and visuospatial executive function, as determined by the copy test of the Taylor complex figure test and the clock drawing test. We adjusted our results for age, sex, years of education, cardiovascular risk factors, and other markers of cerebral small vessel disease, lacunes, and white matter hyperintensity. Deep or infratentorial CMBs were not associated with changes in cognitive function in our population.

Conclusions—Strictly lobar, but not deep or infratentorial, CMBs are associated with changes in cognitive function, especially in visuospatial executive functions. Cerebral amyloid angiopathy may be the underlying pathology associated with CMB-related cognitive impairment. (Stroke. 2016;47:2497-2502. DOI: 10.1161/STROKEAHA.116.014166.)

Key Words: aging ■ cerebral microbleeds ■ cognitive function ■ executive function

Cerebral microbleeds (CMBs) are lesions related to small hemorrhages seen as well-demarcated, hypointense, and rounded lesions on magnetic resonance imaging (MRI) sequences sensitive to magnetic susceptibility.1 The presence of these lesions has been regarded as one of the manifestations of age-related cerebral small vessel disease (CSVD), which include lacunes and white matter hyperintensities (WMH).2 In addition to being an age-related cerebrovascular abnormality,3-5 CMBs are associated with dementia. The prevalence of CMBs is reported to be higher in patients with Alzheimer’s disease (AD) and vascular dementia compared with the general population.6 The mechanisms underlying CMBs and their effects on neuropsychological functions are subjects of active research.

CMB in different locations might be related to different clinical manifestations.3,7 The incidence of both CMB types increases with age. However, deep or infratentorial (DI) and strictly lobar (SL) CMBs have different risk factors. DI and SL CMBs are correlated with hypertension and APOE ε4 genotype, respectively. Therefore, DIs are usually attributed to hypertension vasculopathy, and SL CMBs are attributed to cerebral amyloid angiopathy (CAA).3,7,8

The effects of CMBs on cognitive function in the general population have been evaluated in previous studies. However, there are inconsistent results regarding the location of CMBs that are associated with cognitive loss. In addition, only a few Asian CMB studies have evaluated the effects of CMBs on different cognitive domains. Therefore, the present study aimed to study the possible
links between the presence of CMBs and their locations and cognitive function, as evaluated by an extensive neuropsychological battery in a community-based Taiwanese population.

Methods

I-Lan Longitudinal Aging Study and General Assessment

Please see online-only Data Supplement for more information.9–11

Population of the Present Study

Subjects in the ILAS study (I-Lan Longitudinal Aging Study) who had (1) depression revealed by CES-D, (2) evidence of stroke or brain tumor as indicated by a medical history or a brain imaging study, or (3) an implant contraindicated for MRI were excluded. The study was approved by the Institutional Review Board of National Yang Ming University. All participants had provided signed informed consent.

Cognitive Function Assessment

All participants received a face-to-face neuropsychological examination performed by trained interviewers. In addition to global cognitive performance, which was examined using the Mini-Mental State Examination (MMSE), 4 different cognitive domains (verbal memory, language ability, visuospatial executive function, and verbal executive function) were assessed using extensive neuropsychological tests as follows:

2. Language: category (animal) verbal fluency test.13
3. Visuospatial executive function: the copy test of the Taylor complex figure test14 and the clock drawing test.15
4. Verbal executive function: digit backward test.16

We defined global cognitive impairment as an MMSE score <24 in well-educated people (education ≥6 years) or <14 in less-educated people (education <6 years).17,18

Brain MRI Acquisition

Please see online-only Data Supplement information.

CMB and Other CSVDs Assessment

All images were displayed and viewed using MRICro software (version 1.40, Chris Rorden’s MRICro) by the same neurologist (Dr Chung), who was blind to the subjects’ clinical data during CMBs assessment. CMBs were defined as small, rounded, or circular, well-defined hypointense lesions within brain parenchyma with clear margins and a size of ≤10 mm on the susceptibility weighted imaging image.9,19 Microbleed mimics such as vessels, calcification, partial volumes, and hemorrhages within or adjacent to an infarct were carefully excluded. We used the Microbleed Anatomic Rating Scale20 to measure the presence, amount, and topographical distributions of CMBs in each subject. Microbleeds were categorized as deep, lobar, or infratentorial. Lobar topography was determined according to Stark and Brahby20 and included cortical and subcortical regions (including subcortical U fibers). Lobar CMBs were assessed in the frontal, parietal, temporal, and occipital regions. Deep regions included the basal ganglia (BG), the thalamus, the internal capsule, the external capsule, the corpus callosum, and the deep/periventricular white matter. Infratentorial regions included the brain stem and the cerebellum. Deep/periventricular white matter was defined as white matter adjacent to or within ±10 mm of the lateral ventricular margin. CMBs in 20 random-sampled subjects’ images were evaluated again at a separate time, and the inter-rater k was 0.83 (95% confidence interval 0.79–0.88).

Characteristics of the other manifestations of CSVD, including lacune numbers and WMH severity, were also recorded for every subject using FLAIR-T2-weighted MRI. Lacunes are small CSF-containing cavities, which are smaller than 15 mm in diameter and are located in deep gray or white matter with adjacent WMH.9 The severity of WMH was rated using the modified Fazekas scale,21 which scores 0 as no WMH, 1 as mild WMH, 2 as moderate WMH, and 3 as severe WMH.

Statistical Analysis

Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). To compare continuous numeric variables, non-parametric Mann–Whitney tests were performed as appropriate. The χ² test or a Fisher exact test was performed for categorical variables. To adjust for confounding factors (eg, age, sex, years of education, cardiovascular risk factors, lacune numbers, or WMH severity), we used multivariate linear logistic regression analyses to determine whether CMBs were associated with each neuropsychological test.

Results

Population Demographics

Among the 986 recruited subjects, 2 with major depression as revealed by CES-D (Center for Epidemiological Studies Depression), 9 with incidentally found brain tumors observed by MRI, and 16 with problematic images because of head motion were excluded. There were 959 subjects included in the present study with an age (mean±SD [range]) of 62.5±8.6 (50.0–87.7) years old. Four hundred and twenty-five (44.3%) of the subjects were men. The subjects had an average education (mean±SD [range]) of 7.1±5.1 (0–22) years. The prevalence of cardiovascular risk factors in the population was as follows: hypertension, 37.0%; diabetes mellitus, 13.5%; cigarette smoking habit, 26.1%; and hyperlipidemia, 6.0%. The subjects’ average scores for cognitive performance in each neuropsychological test (score, mean±SD [range]) are as follows: MMSE, 26.3±3.5 (8–30); 30-second CVVLT, 7.0±1.6 (0–9); 10-minute CVVLT, 6.5±2.0 (0–9); category verbal fluency, 14.9±4.8 (2–33); Taylor complex figure test, 30.7±6.9 (0–36); clock drawing test, 7.9±2.4 (0–10); and digit backward test, 5.1±3.3 (0–12). There were 36 (3.8%) subjects with global cognitive impairment.

Evaluation of CMBs and Other CSVDs (Lacunes and WMH)

The prevalence, numbers, and topographical distributions of CMBs are listed in Table 1. CMBs were found in 136 (14.2%) of the subjects. Among them, most (83, 8.7%) had only one lesion, 54 (5.6%) subjects had ≥2 CMBs, 16 (1.7%) had ≥5 CMBs, and 5 (0.5%) had ≥10 CMBs. Most CMBs, both in terms of prevalence and number, were found in deep brain regions (75 subjects, 7.8%). Infratentorial and lobar CMBs were found in 26 subjects (2.7%) and 69 subjects (7.2%), respectively. There were 85 subjects (8.8%) with DI CMBs, and 49 subjects (5.1%) with SL CMBs. No CMBs were found in the internal capsule, the external capsule, or the corpus callosum. Assessment of other CSVDs showed that 45 (4.7%) subjects had >1 lacune and 151 (15.7%) subjects had moderate to severe WMH (Fazekas scale score of 2–3).

Comparison of Basic Characteristics of Subjects With and Without CMBs

The results are shown in Table 2. Subjects with CMBs were significantly older and had less years of education.
After adjusting for age and sex, we found no associations between cardiovascular risk factors and the presence of CMBs. There was a strong correlation between the presence of CMBs and the presence of other CSVDs. Subjects with CMBs had significantly higher lacune numbers and more severe WMHs. The results also revealed that global cognitive impairment was twice as common in the CMB-positive group than in the CMB-negative group, although this was statistically not significant.

### Table 2. Clinical and Demographic Characteristics of Patients With and Without Cerebral Microbleeds

<table>
<thead>
<tr>
<th>Presence of Microbleeds, Patient No. (%)</th>
<th>Number of Microbleeds, Sum (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any location</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>55 (5.7)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>25 (2.6)</td>
</tr>
<tr>
<td>DPWM</td>
<td>15 (1.6)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>13 (1.4)</td>
</tr>
<tr>
<td>Lobar</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>28 (2.9)</td>
</tr>
<tr>
<td>Parietal</td>
<td>19 (2.0)</td>
</tr>
<tr>
<td>Temporal</td>
<td>18 (1.9)</td>
</tr>
<tr>
<td>Occipital</td>
<td>24 (2.5)</td>
</tr>
<tr>
<td>Deep or infratentorial</td>
<td>85 (8.8)</td>
</tr>
<tr>
<td>Strictly lobar</td>
<td>49 (5.1)</td>
</tr>
</tbody>
</table>

DPWM indicates deep/periventricular white matter.

### The Presence of CMBs and Cognition

Table 3 shows the comparisons of performance in each neuropsychological test between subjects with and without CMBs. The results indicate that the CMB-positive group had lower scores in all cognitive domains. However, after adjusting for age, sex, years of education, and cardiovascular risk factors in multivariate linear regression analyses, the presence of CMBs was only significantly correlated with poorer global cognitive function (MMSE) and verbal memory (10-minute delayed free recall in CVVLT). Because the presence of CMBs was associated with more severe lacunes and WMHs (Table 2), we further adjusted for the number of lacunes and the severity of WMHs. The results showed that there was only a significant association between the presence of CMBs and MMSE (global cognitive function).

### CMB Locations and Cognition

The relationship between the location of the CMBs and cognition was also validated using multivariate linear regression analyses (Table 3). The results indicate that there is no association between DI CMBs and cognitive function. Because previous studies have shown that BG CMBs are associated with cognitive deficits, we tested the BG region separately. The results indicated that there is no correlation between BG CMBs and performance in any of the cognitive domains after adjusting for age, sex, and years of education (data not shown). On the contrary, subjects with SL CMBs had significant deficits in the MMSE (global cognitive function), the 10-minute delayed free recall in CVVLT (verbal memory), and the copy test of the Taylor complex figure test and the clock drawing test (visual executive function). The results indicated that SL CMBs were significantly associated with global cognitive decline (MMSE) and deficits in visual executive functions after adjusting for age, sex, years of education, cardiovascular risk factors, and other CSVDs. We also observed a trend for an association between a higher prevalence of global cognitive impairment and SL CMBs (8.2% versus 3.5%).

There were only 19 (2%) subjects who had both deep and lobar CMBs in the present study. The results showed that the group of both deep and lobar CMBs had lower scores in all cognitive domains but was not significantly associated with any (data not shown).

### Discussion

The main findings of the present study, which was performed in an Asian community–based population, are that (1) the presence of CMBs was associated with deficient global cognitive functions, and (2) the locations of the CMBs are important in determining their associations with cognitive impairments. SL CMBs, but not DI CMBs, were correlated with deficits in global cognitive and visual executive functions. These associations were independent of age, sex, years of education, cardiovascular risk factors, and other CSVDs (lacunes and WMH).

Consistent with previous studies, our results revealed that executive function is linked with CMBs in the general population. We also show that visuospatial, but not verbal executive functions, are associated with CMBs. Our findings are...
in line with the result of the Epidemiology of Dementia in Singapore Study. They found that CMBs were associated with deficits in executive functions, but that only the deficits in the visuoconstruction domain reached a robust statistical significance. Visuospatial and verbal executive functions involve different neural networks. Compared with the verbal domain, the visuospatial domain is affected by external intellectual training and education, which needs more complex network processing. This may explain the difference of susceptibility to cerebral microvascular lesions between verbal and visual executive domains. Other studies have also shown that age-related cognitive decline occurs earlier and more dramatically in the visuospatial domain compared with the verbal domain and that visuospatial executive deficits usually precede typical memory impairments in the prodromal phases of dementia.

Our results suggest that CMBs should be investigated in the context of early visuospatial ability decline in the elderly to determine whether and how CMBs are involved in the pathophysiology of such deficits.

Notably, our results also showed a significant association between SL CMBs and the 10-minute delayed free recall in CVVLT though the statistical significance was borderline after multiple adjustment, including MRI measures of other CSVDs ($P = 0.056$). Therefore, SL CMBs might be related to neurodegenerative diseases involving recent memory, such as AD. The borderline-significant association between SL CMBs and memory domain is possibly because that our study subjects were at an early or prodromal stage of disease. A future longitudinal follow-up study will be needed to validate this postulation.

Conclusions regarding effects of CMB location on cognition in the general population are controversial. Some studies report that deep CMBs, particularly those in the BG, are associated with cognitive decline, whereas others report that lobar CMBs are associated with deficits in cognitive performance, which is in line with our results. Differences in population-based cohorts may explain why deep or lobar locations of MBs appear more prominently in different studies. Because the locations of the CMBs may reflect different mechanisms of action, distinct underlying pathologies may mediate the relationship between CMBs and cognitive impairment. CAA, a common age–related condition, is characterized by a progressive deposition of amyloid-$\beta$ in the media and adventitia of arterioles, capillaries, and venules in the cerebral cortex and the gray/white matter junction. Several studies have provided evidences showing lobar CMBs as a marker of CAA. The relationship between SL CMBs and cognitive function found in the present study implies that CAA might be the underlying pathology of CMB-related cognitive impairment.

Because CAA pathology is frequently observed in AD, the relationship between CAA, independent of AD pathology, and cognition has been a topic of debate. A recent autopsy study reported that CAA pathology is associated with an increased rate of decline in cognitive functions proximate to death (mean age at death: 88.5 years). These associations were independent of AD pathology, which supports a role for CAA as an important and independent contributor to late-life cognitive impairment. CMBs of certain locations observed by imaging have been suggested as early markers of CAA. The present study, performed in a relatively young and functionally preserved population, may provide clues to the cognitive influence of CAA on domains such as visuospatial executive function at early disease stages. However, further studies on correlations between neuroimaging and pathology are needed to validate the specificity of the relationship between CAA- and CMB-related cognitive impairment.

Several studies have found an association between CSVDs and brain atrophy. Most were investigating the brain volume abnormalities in WMH. Some studies with small population have evaluated the relationship between CMBs and brain volume. One study showed that brain parenchyma fraction was inversely related to the number of CMBs in patients with cerebral autosomal–dominant arteriopathy with subcortical

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### Table 3. Correlation Between Cerebral Microbleeds Locations and Cognitive Functions

<table>
<thead>
<tr>
<th></th>
<th>Whole Brain CMBs</th>
<th>Deep/Infratentorial CMBs</th>
<th>Strictly Lobar CMBs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$+ (n=136)$</td>
<td>$- (n=823)$</td>
<td>$P$ Value*</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.1 (4.5)</td>
<td>26.5 (3.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>Delay free recall (30 s) in CVVLT</td>
<td>6.5 (1.7)</td>
<td>7.1 (1.6)</td>
<td>0.048</td>
</tr>
<tr>
<td>Delay free recall (10 min) in CVVLT</td>
<td>5.8 (2.2)</td>
<td>6.6 (2.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>Category verbal fluency</td>
<td>14.1 (4.9)</td>
<td>15.0 (4.8)</td>
<td>0.264</td>
</tr>
<tr>
<td>Complex figure test</td>
<td>28.7 (8.4)</td>
<td>31.0 (6.6)</td>
<td>0.199</td>
</tr>
<tr>
<td>Clock drawing test</td>
<td>7.3 (2.7)</td>
<td>8.0 (2.3)</td>
<td>0.287</td>
</tr>
<tr>
<td>Digit backward</td>
<td>4.4 (3.4)</td>
<td>5.2 (3.3)</td>
<td>0.750</td>
</tr>
</tbody>
</table>

CMBs indicates cerebral microbleeds; CVVLT, Chinese Version Verbal Learning Test; and MMSE, Mini-Mental State Examination.

*Adjusted for age, sex, and years of education.
†Adjusted for age, sex, years of education, and the presence of cardiovascular risk factors (hypertension, diabetes mellitus, smoking, and hyperlipidemia).
‡Adjusted for age, sex, years of education, the presence of cardiovascular risk factors, the number of lacunes, and the severity of white matter hyperintensity.
infarcts and leukencephalopathy. The other study of AD patients also revealed gray matter atrophy in the temporal lobe and cerebellum in patients with CAA-related CMBs. Therefore, it is possible that brain atrophy plays a role in the mechanisms linking CMBs and cognitive impairment. We did not measure the brain volume in the present study. A future study to evaluate (1) the association between brain atrophy and CMBs and (2) the role of brain volume in the relationship between CMBs and cognitive impairment in the general population should be conducted to validate the postulation.

Nerve tracts, including executive functional tracts, radiate from the cortex in lobar subcortical regions. SL CMBs may influence cognitive functions by strategically damaging and disrupting the functional pathway in white matter. Neural pathway imaging, such as diffusion tensor imaging combined with advanced CMB detection using computer algorithms, will enable us to elucidate this postulated mechanism in the future.

Most Asian community–based studies have only assessed global cognitive function (eg, MMSE) to evaluate the relationship between CMBs and cognition. The present study evaluated whether CMBs and their locations were associated with a variety of cognitive domains. In addition, we used susceptibility weighted imaging on a 3T MRI, which is a tool with better resolution and higher sensitivity, to detect CMBs. We also adjusted for other CSVDs (lacune and WMH) while analyzing the relationship between CMB and cognition. Our results demonstrate the neuropsychological significance of CMBs in an Asian population and provide clues to the underlying mechanisms of CMB-related cognitive impairment. The other strength of our study is that it includes a community-based, functionally preserved study population free of stroke incidence, which enables our results to be applied to the healthy general population. We can, thus, use our results to design strategies for the future early detection of vascular cognitive impairment.

Our study has some limitations. First, the cross-sectional design could not identify causal relationships between CMBs and cognitive impairment. A longitudinal study is needed to accomplish this goal. Second, there may be factors helpful for mechanism evaluation, such as markers for AD and CAA, APOE genotype differences, which we did not evaluate in the present study. In the future, we would also need to obtain other measurements, such as brain volume, amyloid loading, inflammatory and oxidative stress markers, and neural pathway imaging (eg, diffusion tensor imaging), to elucidate the mechanisms involved in the relationship between CMBs and cognitive impairment. Last but not least, because CAA is almost found universally in AD, it is possible that the SL CMBs were a surrogate marker of preclinical or early stage of AD, which could account for the cognitive deficits that were identified in the present study, rather than strictly a result of CAA. The present study is not able to differentiate between the 2.

In summary, the present Asian community–based study reveals an association between CMBs and cognitive function. The locations of CMBs are important in determining the relationship between CMBs and cognition. SL CMBs are associated with deficits in global cognitive and visuospatial executive functions.

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None.

References

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I-Lan Longitudinal Aging Study and General Assessment

All participants were from the I-Lan Longitudinal Aging Study (ILAS), a community-based cohort study conducted in I-Lan County, Taiwan. One aim of ILAS is to explore the complex interrelationships between geriatric syndromes and brain structural abnormalities. The study protocol has been previously described in detail. Inhabitants who met the study inclusion criteria were randomly sampled from the household registration data of the county government. Selected inhabitants were invited to participate by mail or telephone. The inclusion criteria were: (1) having no plans for moving out of I-Lan County in the near future, and (2) having an age of 50 years or older. Subjects who met any one of the following conditions were excluded: (1) unable to adequately communicate with the interviewer, (2) having a disabled status (modified Rankin Scale > 2), (3) limited life expectancy (less than 6 months) due to major illness, and (4) currently institutionalized.

A questionnaire was used to collect data regarding the demographics, years of education, smoking habits, and medical history of the subjects. The heights, weights, and resting blood pressures (BP) of the subjects were measured. All participants received a face-to-face neuropsychological examination administered by trained interviewers. Global cognitive performance and depressive symptoms were assessed by the mini-mental state examination (MMSE) and the Center for Epidemiologic Studies Depression Scale (CES-D), respectively.

Cardiovascular risk factors were either measured or assessed according to self-report. Hypertension was defined as a self-report of current antihypertensive medication prescriptions or a measurement of systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg. Diabetes mellitus (DM) was defined as a self-report of current DM medication use or a measurement of hemoglobin A1c (HgbA1c) ≥ 6.5%. Hyperlipidemia was defined as a self-report of statin use or a measurement of total cholesterol ≥ 240 mg/dL.

Brain MRI Acquisition

All participants underwent a baseline brain MRI at National Yang-Ming University within one month of the neuropsychological assessment. Images were acquired on a 3T MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) with a 12-channel head coil. An axial T2-weighted fluid attenuated inversion recovery (FLAIR) multi-shot turbo spin echo sequence with BLADE technique was acquired with the following parameters: repetition time (TR) = 9000 ms, echo time (TE) = 143 ms, inversion time = 2500 ms, flip angle = 130 degrees, number of excitations = 1, echo train length = 35, matrix size = 320 x 320, field of view (FOV) = 220 x 220 mm², 63 slices, bandwidth = 252 Hz/Px, voxel size = 0.69 x 0.69 x 2.0 mm³ without inter-slice
gap, and acquisition time = 7 minutes and 41 seconds. Three dimensional susceptibility images (SWIs) with the following parameters were used to identify the CMBs: TR = 28 ms, TE = 21 ms, flip angle = 15 degrees, matrix size = 256 x 224, FOV = 256 x 224 mm², 88 slices, bandwidth = 120 Hz/Px, voxel size = 1.0 x 1.0 x 2.0 mm³ without inter-slice gap, and acquisition time = 9 minutes and 13 seconds.