RESEARCH PAPER

Cerebral microbleeds and neuropsychiatric symptoms in an elderly Asian cohort

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ABSTRACT

Objectives Neuropsychiatric symptoms (NPS) are commonly found in patients with cerebral small vessel disease such as white matter hyperintensities and lacunar infarcts. However, the association between cerebral microbleeds (CMBs) and NPS has not been examined. Hence the present study sought to investigate the relation between CMBs and NPS in an elderly population.

Methods This is a cross-sectional study of elderly Asians living in the community, who were assessed on a comprehensive neuropsychological battery and underwent clinical examinations as well as brain MRI scans. The 12-item neuropsychiatric inventory (NPI) was administered to a reliable informant. Total scores for individual symptoms and for NPI global performance were calculated by multiplying frequency and severity. The NPI total score is the sum of individual symptom scores.

Results A total of 802 participants were included in the analysis. Participants with multiple CMBs had higher NPI total score compared to those with no CMB (1.06 vs 2.66, p=0.03). On individual symptom scores, higher score on depression (0.16 vs 0.53, p=0.02) and disinhibition (0.01 vs 0.14, p=0.04) was found in those elderly with multiple CMBs, independent of demographic and vascular risk factors. NPI total score compared to those with no CMB (1.06 vs 2.66, p=0.03). On individual symptom scores, higher score on depression (0.16 vs 0.53, p=0.02) and disinhibition (0.01 vs 0.14, p=0.04) was found in those elderly with multiple CMBs, independent of demographic and vascular risk factors, history of stroke, and other small vessel and large vessel disease markers.

Conclusions The presence of multiple CMBs is associated with high global neuropsychiatric disorder burden, in particular symptoms of depression and disinhibition. Future studies are recommended to investigate the importance of CMBs in the pathogenesis and longitudinal progression of neuropsychiatric disorders in the general elderly population.

INTRODUCTION

Cerebral microbleeds (CMBs) are associated with adverse clinical outcomes such as cognitive impairment and functional decline. CMBs often occur concomitantly with other markers of small vessel disease such as white matter hyperintensities and lacunar infarcts. However, the association between cerebral microbleeds (CMBs) and NPS has not been examined. Furthermore, the clinical importance of CMBs in the development of post-stroke depression has been highlighted in hospital-based samples. However, the association between CMBs and NPS in a population-based sample has not been investigated. In this study, we examine the association between CMBs graded on MRI with NPS in elderly people living in the community in Singapore.

METHODS

Study population

The Epidemiology of Dementia In Singapore (EDIS) study participants were drawn from the Singapore Epidemiology of Eye Disease study, a multiethnic population-based study among persons aged 40–85 years, which included Chinese, Malays and Indians. There are two phases in the EDIS study. In phase 1, participants aged 60 years and above (n=3800) were screened using the Abbreviated Mental Test and a self-report of progressive forgetfulness. Screen-positive participants (n=937) agreed to take part in the second phase of this study, where they underwent the Mini-Mental State Examination, the Montreal Cognitive Assessment, and a locally validated neuropsychological battery (the vascular dementia battery, VDB), uniform clinical examination and MRI scan of the brain. Details of the study methodology have been described elsewhere. Ethical approval was obtained from the National Healthcare Group Domain-Specific Review Board. Written informed consent was obtained in the preferred language of the participants.

Assessment of NPS

To ensure the reliability of the information, suitable informants with frequent interactions with study participants for at least 10 hours a week were administered the 12-item neuropsychiatric inventory (NPI). The NPI is a structured interview investigating the presence, frequency, severity and caregiver distress of 12 symptoms. Details and the administration procedure have been described elsewhere. For each symptom, the total score is calculated by multiplying frequency and severity. The NPI total score is the sum of individual symptom scores.

Vascular risk profile

A vascular risk profile was recorded for all study participants, which included: (1) hypertension: defined as a previous diagnosis of hypertension or the use of antihypertensive medication; (2)
hyperlipidaemia: defined as a previous diagnosis of hyperlipidaemia or the use of lipid-lowering medication; (3) diabetes mellitus: defined as a previous diagnosis of diabetes mellitus, or the use of glucose-lowering medication; (4) cardiovascular disease: defined as a previous diagnosis of the following—myocardial infarction, congestive heart failure, atrial fibrillation, coronary angioplasty or stenting; (5) history of smoking.

**Neuroimaging protocol**

MRI scans were performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil. Several MRI brain sequences were performed to allow morphological and microstructure assessments, including T1-weighted, fluid-attenuated inversion recovery (FLAIR), T2-weighted and susceptibility-weighted imaging (SWI). A number of standardised and advanced MRI brain sequences were performed including SWI to detect CMBs. The SWI sequence parameters were: repetition time, 27 ms; time-to-echo, 20 ms; flip angle, 15°; field of view, 256 mm; image matrix, 192×256 mm; field of view phase, 75%; slice thickness, 1.50 mm.

The presence, location and number of CMBs were graded on SWI according to the Brain Observer Micro Bleed Scale. CMBs were defined as focal, rounded areas of hypointensity (T1 and T2-weighted images), 2–10 mm in diameter with blooming on T2*-weighted scans. CMBs were categorised into lobar (cortical, subcortical or periventricular white matter) and deep (subcortical grey matter, the white matter of the corpus callosum, internal and external capsule). The number of CMBs were counted, and classified into ‘no CMB’, ‘one CMB’ and ‘multiple CMBs (>1 CMBs)’.

All scans were graded by one radiologist and two clinicians who were blinded to all other participant characteristics. Grading of MRI markers of cortical infarcts, intracranial stenosis, WMH and lacunar infarcts was conducted using the following criteria:

1. Cortical infarcts were defined as focal lesions involving cortical grey matter, signal following cerebrospinal fluid intensity, hyperintense rim on fluid attenuated inversion recovery images and tissue loss of variable magnitude, with prominent adjacent sulci and ipsilateral ventricular enlargement.14

2. Intracranial stenosis was defined as narrowing exceeding 50% of the luminal diameter in any of the intracranial vessels assessed on three-dimensional time of flight MR angiography. The images were first visually assessed on the reconstruction images, and the final decision on stenosis (>50%) was made on the source images.

3. Lacunes were defined as lesions 3–15 mm in diameter, with low signal on T1-weighted image and FLAIR, high signal on T2-weighted image and a hyperintense rim with a centre following cerebrospinal fluid intensity on fluid attenuated inversion recovery.14

4. WMHs were graded using the Modified Fazekas scale.15

All scans were graded by 1 radiologist and 2 clinicians who were blinded to all other subject characteristics. Any disagreement was brought to consensus for the final decision.

**Diagnosis of Dementia**

Weekly research consensus meetings were held among clinicians, psychologists and research personnel. Details from the clinical assessment, blood investigations, neuropsychological testing and MRI scans were reviewed. The diagnosis of No cognitive impairment was given to participants who had no objective cognitive impairment on the VDB and no functional loss. The diagnosis of Cognitive impairment–No dementia (CIND) was given to participants who had impairment on at least one cognitive domain on the VDB, without significant loss of independence in daily activities, and hence did not meet the criteria for dementia. The diagnosis of dementia was made according to Diagnostic and Statistical Manual Fourth Edition criteria.16 CIND was further classified into CIND-mild (impairment in 1–2 domains on the VDB) and CIND-moderate (impairment in 3 or more domains on the VDB).

**Statistical analysis**

The association of NPI total score and individual symptom score with CMBs (no CMB, presence of 1 CMB and presence of multiple CMBs) was assessed using analysis of variance analyses in two steps, controlling for confounder: step 1, controlling for demographic factors and vascular risk factors that differed significantly across groups; step 2, further controlling for NPI symptoms.

**Table 1 Characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole group</th>
<th>No CMB</th>
<th>Presence of 1 CMB</th>
<th>Presence of multiple CMBs</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=802</td>
<td>n=522</td>
<td>n=162</td>
<td>n=118</td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>70.3±6.6</td>
<td>69.4±6.4</td>
<td>70.8±6.3</td>
<td>73.5±7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>433 (54.0)</td>
<td>289 (55.4)</td>
<td>95 (58.6)</td>
<td>49 (41.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>520 (64.8)</td>
<td>320 (61.3)</td>
<td>111 (68.5)</td>
<td>89 (75.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>283 (35.3)</td>
<td>192 (36.8)</td>
<td>55 (34.0)</td>
<td>36 (30.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>284 (35.4)</td>
<td>168 (32.2)</td>
<td>60 (37.0)</td>
<td>56 (47.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Chinese</td>
<td>235 (29.3)</td>
<td>162 (31.0)</td>
<td>47 (29.0)</td>
<td>26 (22.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Malay</td>
<td>651 (81.2)</td>
<td>410 (78.5)</td>
<td>136 (84.0)</td>
<td>105 (89.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Indian</td>
<td>595 (74.2)</td>
<td>380 (72.8)</td>
<td>120 (74.1)</td>
<td>95 (80.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>293 (36.5)</td>
<td>194 (37.2)</td>
<td>59 (36.4)</td>
<td>40 (33.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>59 (7.4)</td>
<td>22 (4.2)</td>
<td>14 (8.6)</td>
<td>23 (19.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>215 (26.8)</td>
<td>136 (26.1)</td>
<td>37 (22.8)</td>
<td>42 (35.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of Stroke, n (%)</td>
<td>45 (5.6)</td>
<td>20 (3.8)</td>
<td>10 (6.2)</td>
<td>15 (12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE total score, mean±SD</td>
<td>23.6±4.2</td>
<td>24.0±3.8</td>
<td>23.6±4.0</td>
<td>21.8±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MoCA total score, mean±SD</td>
<td>18.9±5.5</td>
<td>19.5±5.2</td>
<td>18.8±5.5</td>
<td>16.6±5.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CMB, cerebral microbleed; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
for other small and large vessel disease markers. Subsequently, CMBs were stratified according to brain regions (lobar and deep) to correlate with NPS. All analyses were performed using standard statistical software (Statistical Package for Social Science (SPSS) V.23; IBM Corporation, Armonk, NY, USA).

RESULTS
A total of 957 participants were recruited into the study and among them, 94 either did not complete MRI scans or had MRI scans that could not be graded and 61 did not have a reliable informant at the time of NPI assessment. Hence, a total of 802 participants who completed cognitive assessment, MRI scan and NPI investigation, were included in further analysis.

Characteristics of the study population are presented in table 1. Of the 802 participants, 180 (22.4%) had at least 1 NPS. Figure 1 shows percentages of the presence of individual symptoms in no CMB, presence of one CMB and presence of multiple CMBs’ groups. The presence of multiple CMBs was significantly associated with the presence of other small and large vessel disease markers (table 2).

NPI results are presented in table 3. Participants with multiple CMBs had higher NPI total score compared to those with no CMB (1.06 vs 2.66, p=0.03). On individual symptom scores, higher score on depression (0.16 vs 0.53, p=0.02) and disinhibition (0.01 vs 0.14, p=0.04) was found in those elderly with multiple CMBs, independent of all covariates. Significant difference between no CMB and one CMB group was seen on apathy (0.04 vs 0.25, p=0.04) and appetite (0.14 vs 0.42, p=0.01) symptoms but not on NPI total score (1.06 vs1.61, p=0.2).

Subsequent analysis was conducted to associate lobar and deep microbleeds with NPS. Presence of multiple lobar microbleeds was independently associated with total score on depression (F(660)=6.04, p=0.01) and disinhibition (F(660)=11.21, p=0.001) symptoms, while presence of multiple deep microbleeds was associated with depression score (F(718)=5.72, p=0.02) but not disinhibition score. After removing 30 cases with mixed lobar and deep microbleeds, 57 cases with strictly multiple lobar microbleeds were included in the analysis, and the association between presence of strictly multiple lobar microbleeds and NPS was not attenuated. However, no analysis was performed among subjects with strictly multiple deep microbleeds, due to the small sample size of this group (n=12). There was no significant interaction between the presence of multiple lobar and deep microbleeds on depression and disinhibition scores.

DISCUSSION
This is the first study examining the association between CMBs and neuropsychiatric symptoms in an elderly population sample. The main finding of the current study is that the presence of multiple CMBs is independently associated with higher NPI total score and, notably, higher scores on depression and disinhibition symptoms.

CMBs, particularly lobar CMBs, have been reported as being novel indicators for risk and progression of post-stroke depression. Nevertheless, such association has only been explored in patients with well-established cerebrovascular disease in tertiary healthcare facilities. Results from the present study not

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**Table 2** Distribution of small and large vessel disease markers

<table>
<thead>
<tr>
<th></th>
<th>No CMB (n=522)</th>
<th>Presence of 1 CMB (n=162)</th>
<th>Presence of multiple CMBs (n=118)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH (Fazekas score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33 (6.3%)</td>
<td>6 (3.7%)</td>
<td>2 (1.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>295 (56.5%)</td>
<td>85 (52.5%)</td>
<td>33 (28.0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>175 (33.5%)</td>
<td>58 (35.8%)</td>
<td>56 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16 (3.1%)</td>
<td>13 (8.0%)</td>
<td>27 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>Number of lacunes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>506 (96.9%)</td>
<td>151(93.2%)</td>
<td>74 (62.7%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>16 (3.1%)</td>
<td>11 (6.8%)</td>
<td>24 (20.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of cortical infarcts</td>
<td>10 (1.9%)</td>
<td>5 (3.1%)</td>
<td>10 (8.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of intracranial stenosis</td>
<td>57 (10.9%)</td>
<td>30 (18.5%)</td>
<td>23 (19.5%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

WMH, white matter hyperintensities.

---

**Figure 1** Percentages of the presence of individual NPS. CMB, cerebral microbleed; NPS, neuropsychiatric symptoms.
only confirm the relation between the presence of lobar CMBs and depressive symptoms, but also extend this association to an elderly population with lower prevalence of cerebrovascular disease burden and vascular risk factors. Moreover, our results showed an association with NPS only when multiple CMBs were present, suggesting a threshold effect. Previously, a higher number of CMBs was associated with worse cognitive function.\(^\text{17}\) Combined, these findings highlight the importance of taking into consideration both location and quantity when investigating the role of CMBs in the development of worse clinical outcomes, such as cognition and neuropsychiatric disorders. Disinhibition symptom in the present study was also found to be associated with multiple lobar CMBs. Emotional incontinence, such as disinhibition of emotional control, has been found among patients with Alzheimer disease (AD).\(^\text{19}\) and its severity increases along with dementia severity.\(^\text{20}\) It has been proposed that the occurrence of emotional and behavioural disinhibition shares a similar underlying mechanism with abnormalities in brain frontal regions such as anterior cingulate and dorsolateral prefrontal cortices.\(^\text{21}\) While CMBs, especially those occurring in the temporal lobe, are more common in cerebral amyloid angiopathy\(^\text{22}\) that underlies AD pathology, our finding on the association between CMBs and disinhibition may suggest that lobar CMB may predict future development of AD.

Depression and disinhibition could be due to disorders in neural circuitry, involving different neurotransmitter systems and molecular mechanisms.\(^\text{23}\) The various parts of the brain involved in depression include the cortex (dorsal and medial prefrontal cortex, dorsal and ventral anterior cingulate cortex, orbital frontal cortex and the insula), subcortical limbic regions (amygdala, hippocampus, dorsomedial thalamus) and basal ganglia (striatum).\(^\text{24}\) Orbitofrontal circuit lesions lead to personality changes that are characterised by disinhibition.\(^\text{25}\) The occurrence of emotional and behavioural disinhibition shares a similar underlying mechanism with abnormalities in brain frontal regions such as anterior cingulate and dorsolateral prefrontal cortices.\(^\text{21}\) Thus microbleeds in cortical or subcortical regions could disrupt neuronal circuitry and lead to depression. Our study suggests that cortical rather than subcortical lesions result in disinhibition.

Nevertheless, the causal direction of the association between CMBs and NPS in the present study cannot be established due to the cross-sectional study design. An alternative explanation for the association could be through cognitive impairment being related to both NPS and CMBs. Future studies should take cognitive performance into consideration when investigating the causal relationship between CMBs and NPS.

Our finding that the presence of multiple CMBs was associated with demographic and risk factors such as older age, history of hypertension, smoking and stroke, is consistent with previous studies.\(^\text{26} \ 2\text{7}\) In addition, we found that more Malays had multiple CMBs compared with Chinese and Indian ethnic groups (47.5%, 30.5% and 22.0%, respectively). The prevalence of dementia has been reported to be higher in Malays compared with Chinese,\(^\text{28}\) which was attributed to a higher cerebrovascular burden and higher frequency of Apo E\(\epsilon\)4 carriers among Malays. However, further studies are required to investigate the mechanism(s) underlying these ethnic differences, which may include the increased prevalence of multiple CMBs in Malays.

The present study has several limitations. The main limitation of the study is that only participants who were screened positive were included in the present analysis. It has been described previously\(^\text{1}\) that participants who declined participation in phase 2 were older, and had a lower education level and socioeconomic status. This may have led to an underestimate in the prevalence of cerebrovascular disease as well as neuropsychiatric disorders\(^\text{12}\) in the present study. Hence these findings need to be confirmed in other studies. Among the strengths, the inclusion of small and large vessel disease markers promotes the investigation into the independent effect of neuroimaging markers on NPS. Furthermore, the analytical approach with stepwise adjustment confirms the robustness of our findings.

### Table 3 Neuropsychiatric inventory results

<table>
<thead>
<tr>
<th></th>
<th>No CMB (n=522)</th>
<th>Presence of 1 CMB (n=162)</th>
<th>Presence of multiple CMBs (n=118)</th>
<th>p Value (model 1)</th>
<th>p Value (model 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI total score</td>
<td>1.06±3.81*</td>
<td>1.61±5.70†</td>
<td>2.66±7.90*†</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Delusions</td>
<td>0.03±0.53</td>
<td>0.01±0.08</td>
<td>0.00±0.00</td>
<td>0.78</td>
<td>0.81</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.04±0.57</td>
<td>0.11±0.98</td>
<td>0.13±1.14</td>
<td>0.12</td>
<td>0.31</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.09±0.58</td>
<td>0.11±0.70</td>
<td>0.28±1.40</td>
<td>0.047</td>
<td>0.15</td>
</tr>
<tr>
<td>Depression</td>
<td>0.15±0.85*</td>
<td>0.16±0.80†</td>
<td>0.53±1.85†</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.02±0.30</td>
<td>0.04±0.48</td>
<td>0.01±0.09</td>
<td>0.41</td>
<td>0.45</td>
</tr>
<tr>
<td>Elation</td>
<td>0.01±0.27</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.64</td>
<td>0.65</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.04±0.39†</td>
<td>0.25±1.44†</td>
<td>0.31±1.67</td>
<td>0.02</td>
<td>0.047</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.01±0.10*</td>
<td>0.01±0.80†</td>
<td>0.14±0.85†</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.20±0.98</td>
<td>0.20±0.84</td>
<td>0.44±1.88</td>
<td>0.09</td>
<td>0.24</td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>0.04±0.62</td>
<td>0.01±0.11</td>
<td>0.14±1.16</td>
<td>0.34</td>
<td>0.36</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.29±1.18</td>
<td>0.37±1.47</td>
<td>0.40±1.80</td>
<td>0.41</td>
<td>0.50</td>
</tr>
<tr>
<td>Appetite</td>
<td>0.14±1.08†</td>
<td>0.42±1.97†</td>
<td>0.27±1.26</td>
<td>0.45</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Significant difference between no CMB and presence of multiple CMB groups.
†Significant difference between presence of one CMB and presence of multiple CMB groups.
‡Significant difference between no CMB and presence of one CMB groups based on the most stringent model.
CONCLUSIONS
We found that the presence of multiple cerebral microbleeds, particularly multiple lobar CMBs, is associated with higher global neuropsychiatric burden, particularly with depression and disinhibition. The importance of CMBs in the pathogenesis and longitudinal progression of neuropsychiatric disorders in the general elderly population warrants further investigation.

Contributors XX designed the study, analysed the data and drafted the manuscript. QLC, SH and WKG participated in the data acquisition and revised the paper. MKI, TYV and C-YC revised the paper. CL-HC and NV designed the study, provided supervision and were involved in critical revision of the manuscript.


Competing interests None declared.

Patient consent Obtained.

Ethics approval National Healthcare Group Domain-Specific Review Board and Singapore Eye Research Institute.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
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