Cerebral Microbleeds and Cognition in Patients With Symptomatic Small Vessel Disease

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Background and Purpose—Cerebral microbleeds (CMBs) are common in cerebral small vessel disease. They may cause cognitive impairment, possibly via white matter tract disruption but previous studies have produced inconsistent results. We determined whether CMB number and location are associated with impaired cognition in symptomatic small vessel disease and whether any association was independent of other magnetic resonance imaging markers of small vessel disease.

Methods—One hundred sixteen patients with lacunar stroke and radiological leukoaraiosis were studied. Neuropsychological assessment was performed. CMBs on gradient echo images were assessed using the Brain Observer Microbleed Rating Scale criteria. Magnetic resonance imaging measures, including diffusion tensor imaging, were also analyzed. Associations between cognitive function and the presence, number, and location of CMBs were determined.

Results—CMBs were present in 46 (39.7%) patients. CMB number correlated weakly with executive function ($r = 0.22; P = 0.022$) but not with other cognitive indices. CMBs count in the top decile ($\geq 29$ CMB, $N=12$) was more strongly associated with poor executive function; this association remained significant after controlling for T2-lesion load, brain volume, lacune count, and mean diffusivity ($b=-0.51; P=0.043$).

Conclusions—In symptomatic small vessel disease, CMB number was weakly associated with executive dysfunction. There seemed to be a threshold effect with the association being largely accounted for by an association of impaired executive function with high CMB count. No association of CMBs with other cognitive domains, including processing speed, was found. (Stroke. 2013;44:00-00.)

Key Words: cerebral ischemic small vessel disease ■ cerebral microbleeds ■ magnetic resonance imaging

Cerebral ischemic small vessel disease (SVD) is associated with stroke and cognitive impairment. Magnetic resonance imaging (MRI) characteristics of SVD include lacunar infarcts, T2 hyperintensities (leukoaraiosis), and cerebral microbleeds (CMBs). CMBs are signal voids on T2*-weighted gradient echo MRI, resulting from paramagnetic properties of focal deposits of hemosiderin-containing macrophages, ranging in diameter between 0.82 and 1.5 mm. CMB incidence is up to 80% in patients with subcortical vascular dementia. They are also common in the monogenic form of SVD, cerebral autosomal-dominant angiopathy with subcortical infarcts and leukoencephalopathy.

SVD is associated with a characteristic cognitive impairment, with prominent impaired executive function and information processing speed, but relatively preserved episodic memory. The correlation of cognition with T2-lesion load is weak, but stronger correlations have been detected with diffusion tensor imaging (DTI). The association between DTI and cognition has been regarded as support for SVD causing cognitive impairment via white matter tract disruption causing a disconnection syndrome. Associations have also been reported between cognition and both brain atrophy and lacunar infarct count.

Recent studies suggest CMBs play a role in cognitive impairment, although results have been inconsistent. CMB frequency increases with age, reported in 17.8% of those aged 60 to 69 years and 38.3% of those aged 80 to 99 years. Healthy adults with CMBs showed a reduction in the attention and calculation section of the Mini-Mental State Examination (MMSE) and information processing and motor speed. In elderly normal subjects, CMBs were associated with cognitive impairment and dementia. This relationship was weakened, but still significant,
after controlling for cerebral infarcts and T2-lesion load. Two large community-based studies\textsuperscript{12,13} reported associations between CMBs with cognition, although in one this was primarily with subcortical CMBs,\textsuperscript{13} whereas in the other it was primarily with lobar CMBs, and the correlation with subcortical CMBs was attenuated after controlling for other markers of SVD.\textsuperscript{12}

Studies in patient groups have produced less consistent results. In stroke or transient ischemic attack, those with CMBs had impaired executive function\textsuperscript{14} and this was particularly associated with CMBs in the frontal region and basal ganglia. In cerebral autosomal-dominant angiopathy with subcortical infarcts and leukoencephalopathy, executive function decline was associated with CMBs.\textsuperscript{15} However in another study in cerebral autosomal-dominant angiopathy with subcortical infarcts and leukoencephalopathy, CMBs were not associated with cognitive function after controlling for other MRI markers.\textsuperscript{16} In Alzheimer disease there was no association between CMBs and cognition.\textsuperscript{17}

Any association with cognition could be causal, perhaps via CMBs resulting in white matter tract disruption. Alternatively, CMBs may merely represent a marker for disease severity, being related to other parameters, which themselves cause cognitive impairment. High CMB counts may reflect worse disease state leading to poor cognitive function. Furthermore, the effect of CMBs on cognition may also depend on CMB location.

We determined whether CMBs correlate with cognition in patients with symptomatic SVD, and if so, whether this association remained after controlling for other MRI markers of SVD. We determined CMB presence and number related to cognition and determined whether there were specific relationships between high CMB count and in particular, CMB location with cognition.

**Methods**

**Patients**

Patients with SVD were recruited as part of the St George’s Cognition and Neuroimaging in Stroke study. One hundred eighty patients were screened, of whom 137 consented. Patients were recruited from stroke services at 3 South London hospitals (St George’s, King’s College, and St Thomas’ Hospitals). The inclusion criteria were a clinical diagnosis of stroke or transient ischemic attack, cause of white matter disease. All patients were fluent in English. The study was approved by local ethics committee. All patients gave written informed consent and were studied at least 3 months after their last transient ischemic stroke/stroke.

**Magnetic Resonance Image Acquisition Protocol**

Imaging was performed on a 1.5-T General Electric Signa HDxt MRI system (General Electric, Milwaukee, WI), with a maximum gradient amplitude of 33 mT·m\textsuperscript{−1} and a proprietary head coil. The imaging protocol included (1) fluid attenuated inversion recovery (FLAIR) sequence: repetition time (TR)/Echo time (TE)/Inversion time (TI)\(=\)9000/130/2200 ms, matrix=256×192, 28 slices of 5 mm thickness; (2) T1-weighted spoiled gradient recalled sequence: TR/TE=11.5/5 ms, flip angle=18°, matrix=256×192, and 176 slices of 1.1 mm thickness; (3) gradient echo sequence: TR/TE=300/30 ms, matrix=256×256, flip angle=15°, and 28 slices of 5 mm thickness; (4) diffusion-weighted sequence-single shot spin echo planar imaging: TR/TE=15 600/93.4 ms, matrix=96×96, 55 slices, and isotropic voxels of 2.5 mm\textsuperscript{3}. Eight b=0 s·mm\textsuperscript{−2} volumes were acquired, followed by diffusion sensitized images with gradients applied (b=1000 s·mm\textsuperscript{−2}) in 25 noncollinear directions and the negative of these.

All sequences were acquired across the whole brain using a field-of-view of 240×240 mm\textsuperscript{2} without slice gaps. Total imaging time was \(\approx\)45 minutes. Patients were placed in the head coil in a neutral position, with an alignment marker at the nasal bridge to standardize head position. Minimal movement was ensured by using foam pads and a Velcro strap across the forehead.

**Cognitive Function Assessment**

Cognitive assessment was administered within 2 weeks of MRI by neuropsychologists.

Well-established, standardized tests were chosen to include measures sensitive to cognitive impairment associated with SVD. Tasks were grouped into broad cognitive functions, and these were used to construct cognitive indices. Analyses between CMBs and cognition were performed with 4 cognitive indices: executive function, working memory, processing speed, and long-term memory (for full details of tests see online-only Data Supplement).

**MRI Analysis**

All image analyses were performed blind to subject identity.

**Identification of CMBs**

CMBs were analyzed by a consultant neuroradiologist, and the Brain Observer Microbleed Rating Scale was used to guide identification and describe location.\textsuperscript{20} CMBs were identified as well-defined focal areas of low signal on gradient echo, \(<10\) mm in diameter. Symmetrical areas of basal ganglia calcification, flow voids from blood vessels, and low signals averaging from adjacent bone were discounted. Only CMBs meeting the Brain Observer Microbleed Rating Scale certain criteria were analyzed. Brain Observer Microbleed Rating Scale does not classify frontal lobe CMBs that were counted with reference to the Montreal Neurological Institute structural atlas,\textsuperscript{21} provided by Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL version 4.1: http://www.fmrib.ox.ac.uk/fsl). An affine transformation of voxel coordinates representing CMB locations in gradient echo images to the T1-weighted atlas was computed using FSL Functional Magnetic Resonance Imaging of the Brain’s Linear Image Registration Tool (FLIRT).\textsuperscript{22} CMBs within the frontal region defined by the atlas were counted as frontal CMBs.

**Identification of Lacunes**

Presence and location of lacunes were recorded by a consultant neuroradiologist, based on T1-weighted and FLAIR images. A lacune was defined as a cerebrospinal fluid–filled cavity, \(\approx\)15 mm in diameter, with a surrounding rim of high signal intensity following a vascular distribution.

**Brain Volume**

Normalized and non-normalized brain volume was calculated on T1-weighted images, using SIENAX (Structural Image Evaluation, using Normalisation, of Atrophy)\textsuperscript{23} to obtain estimates of brain size with respect to head size corresponding to a measure of brain atrophy.

**T2-Lesion Load**

T2-lesions on FLAIR were delineated by a single rater using DISPLUNC program (David Plummer, University College, London, UK). Lesions \(\geq\)2 mm in diameter were included. Whole brain lesion maps were generated and lesion load calculated as a percentage of non-normalized brain volume.

**DTI Histogram Analysis**

The 8 b=0 volumes were averaged to provide a T2-weighted echo planar imaging, referred to as \(b\). Diffusion-weighted images were processed to remove eddy current distortions using FSL FLIRT.\textsuperscript{24} The geometric average of positive and negative gradient direction images was computed to eliminate gradient cross terms.\textsuperscript{25} Diffusion tensor
elements were calculated followed by fractional anisotropy (FA) and mean diffusivity (MD) maps.

Multimodal registration of the T1-weighted and FLAIR images to the b0 was performed using FLIRT. Resultant affine transformations were applied to FLAIR lesion maps, and 3-class tissue segmentations computed from T1-weighted images using SPM8 (http://www.fil.ion.ac.uk/spm). Normal appearing white matter masks were computed to contain voxels where white matter probability was greater than that of gray matter and cerebrospinal fluid with the additional constraint that voxels were not present in the transformed lesion map.

Normalized histograms of FA and MD values were produced for the white matter masks (100 bins; bin width FA=0.01, MD=4×10−5 mm2/s; range 0≤FA≤1, 0≤MD≤4×10−5 mm2/s). Three histogram parameters were analyzed for FA and MD: normalized peak height, peak value, and median value as they have previously shown strong associations with cognition.9

Statistical Analysis
Statistical analysis was performed using Statistical Package for Social Sciences version 18.0 (SPSS, Chicago, IL). P<0.05 was regarded as significant. Demographic variables between patients with and without CMBs were compared using t tests or χ2 test as appropriate. For all analyses involving cognitive indices, age, sex, and National Adult Reading Test premorbid IQ were used as covariates. For positively skewed continuous variables (eg, CMBs/lacune count; T2-lesion load), logarithm transforms (base=10; start=1) were used to reduce skew.

The following analyses were performed.

1. Relationship between CMBs and other MRI parameters: Pearson correlations were used.
2. Relationship between CMBs and cognition: Relationships between cognition and the absence/presence of CMB were investigated using ANCOVA. Linear relationships between CMB count and cognition were investigated using Pearson partial correlations.
3. Relationship between CMB location and cognition: Two approaches were taken. First, ANCOVA models compared individuals with one or more CMBs in a given location against those without CMBs in that location. Second, relationships with CMBs in the thalamus, basal ganglia, and frontal lobe were investigated using Pearson partial correlations.

Results
Clinical Data
One hundred twenty-one of 137 patients completed the assessment protocol (6 found neuropsychology lengthy, 2 could not complete MRI, 6 withdrew before testing, and 2 had exclusion criteria on further examination of medical records [1 narcolepsy, 1 schizophrenia]). These patients were older (mean age, 77.0 years), predominantly women (68.8%) and predominantly whites (73.3%). They did not differ significantly in other demographics. Five patients were excluded from the analysis owing to motion artifact/warped DTI data. In total, 116 patients were analyzed. The average time from last stroke to testing was 152.1 (range, 9–1924) weeks.

Presence and Location of CMBs
CMBs were detected in 46 (39.7%) patients. Of these, 16 had 1 CMBs, 8 had 2 to 4, 10 had 5 to 9, 6 had 10 to 19, and 6 had ≥20. Characteristics of subjects with and without CMBs are shown in Table 1, and CMB locations are shown in Table 2.

Relationship Between CMBs and Other MRI parameters
CMB count correlated with lesion load, lacune count, and white matter DTI histogram parameters (Table 3). There was no relationship with normalized brain volume.

Relationship Between CMBs and Cognition
There were no significant differences across the 4 spheres of cognition between subjects with and without CMBs (Table 4). The number of CMBs correlated weakly with executive function, after controlling for age, sex, and National Adult Reading Test (r=−0.22; P=0.022) (Table 5). There was no correlation between total CMB count and working memory, processing

Table 1. Clinical and Demographic Characteristics of Patients With and Without Cerebral Microbleeds

<table>
<thead>
<tr>
<th></th>
<th>CMB Positive (n=46)</th>
<th>CMB Negative (n=70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.08 (12.09)</td>
<td>70.92 (7.89)</td>
<td>0.32</td>
</tr>
<tr>
<td>Men</td>
<td>30 (62.5%)</td>
<td>47 (67.1%)</td>
<td>0.49</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>30 (65.2%)</td>
<td>51 (71.9%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>40 (87.0%)</td>
<td>64 (91.4%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143.20 (20.86)</td>
<td>149.94 (21.97)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.61 (10.82)</td>
<td>81.14 (10.98)</td>
<td>0.80</td>
</tr>
<tr>
<td>On statin therapy</td>
<td>42 (91.3%)</td>
<td>56 (80.0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (10.9%)</td>
<td>15 (21.4%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>21 (45.7%)</td>
<td>41 (58.6%)</td>
<td>0.90</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>1.20 (0.45)</td>
<td>1.33 (0.74)</td>
<td>0.28</td>
</tr>
<tr>
<td>Body mass index, kg·m−2</td>
<td>27.15 (4.65)</td>
<td>26.81 (4.84)</td>
<td>0.60</td>
</tr>
<tr>
<td>MRI parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter lesion volume mm3</td>
<td>43.01 (32.78)</td>
<td>23.88 (19.43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lesion load, %</td>
<td>4.33 (3.19)</td>
<td>2.43 (1.80)</td>
<td>0.001</td>
</tr>
<tr>
<td>Normalized brain volume, mm3</td>
<td>1283.89 (95.34)</td>
<td>1302.18 (90.48)</td>
<td>0.291</td>
</tr>
<tr>
<td>Normalized gray matter volume, mm3</td>
<td>715.48 (77.10)</td>
<td>751.51 (68.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>Normalized white matter volume, mm3</td>
<td>568.40 (73.82)</td>
<td>550.98 (67.00)</td>
<td>0.191</td>
</tr>
<tr>
<td>Lacune count</td>
<td>6.41 (6.78)</td>
<td>2.61 (3.60)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values reported are mean (SD) or count (%). Student t test or χ2 statistics reported. CMB indicates cerebral microbleed; and MRI, magnetic resonance imaging.
speed, or long-term memory. The linear association between CMB count and executive function was no longer significant if other MRI parameters (lesion load, lacune count, and normalized brain volume) were included ($r=-0.06; P=0.56$).

Further investigation of the relationship between CMBs and executive function revealed a threshold effect whereby cognition was worst in the top decile for CMB count ($n=12; 10.3%; \geq 9$ CMBs). Excluding the top decile showed no relationship between CMB and executive function ($r=0.03; P=0.77$). Comparing the demographics between the high CMBs and low CMBs showed a difference in ethnicity ($P=0.01$), lacune count ($P<0.001$), and percentage lesion volume ($P<0.001$) and gray matter volume ($P=0.006$).

Table 6 shows multiple regression models used to investigate the effect of CMBs count in the top decile on cognitive function. There was a significant effect for executive function ($b=-0.74; P=0.003$), but not with other cognitive domains. Controlling for ethnicity did not alter this relationship ($b=-0.624; P=0.015$). Controlling for other MRI measures reduced the strength of the association but it remained significant ($b=-0.51; P=0.043$).

The time from the last stroke to testing ranged from 9 weeks to 37 years. We analyzed the effect of this on our results. Time was not related to the number of CMB ($r=0.039; P=0.675$). Adding time as a covariate did not alter the relationship between the cognitive indices and CMBs (eg, executive function, $r=-0.204; P=0.032$).

### Location of CMBs and Cognition

Basal ganglia and frontal CMB counts were associated with executive function, and frontal CMBs were also associated with working memory ($r=-0.22; P=0.02$) (Table 5). These relationships became nonsignificant when (1) controlling for other MRI parameters (Table 5) and (2) exclusion of the top decile subgroup (basal ganglia CMB versus executive function: $r=0.02, P=0.84$; frontal CMB versus executive function: $r=-0.08, P=0.43$; frontal CMB versus working memory: $r=0.13, P=0.20$). No correlations were found between thalamic CMBs and any cognitive index.

### Discussion

In this cohort of patients with symptomatic SVD, CMB number correlated with executive function. The relationship was driven by subjects with high CMBs count, and exclusion of this group made the relationship nonsignificant. In the high CMB group, the relationship between CMBs and executive function remained significant after controlling for other MRI parameters, including DTI measures of white matter ultrastructure. Our analyses suggested there may be a threshold effect with cognitive impairment primarily occurring in individuals with high CMBs count. In contrast to association with executive function, we found no association of CMBs with other cognitive domains.

Previous studies relating CMBs to cognition in normal aging and stroke populations have yielded conflicting results. Most studies in normal populations have suggested an association between CMBs and cognition, whereas those in patients with symptomatic cerebrovascular disease have produced less consistent results.

Many reasons may underlie these differences. First, any association with CMBs could be causal with CMBs themselves resulting in cognitive impairment; alternatively, CMBs might represent markers of other features of SVD, which themselves cause cognitive impairment. As found in our study, and previous studies, CMBs correlated strongly with other markers of SVD, including white matter lesion load, normalized brain volume, lacune count, and white matter ultrastructural damage on DTI. Previous studies have not
controlled for DTI parameters, which are better makers of white matter damage.

Another reason for differences between studies examining the relationship between cognition and CMBs may be differences in the populations studied. To determine the effect of CMBs in SVD, we studied a homogenous group of patients with symptomatic SVD who had presented with lacunar infarcts. Despite confining our study to this group, there was a wide range of CMB count. Our findings may not necessarily apply to other patient groups and normal populations, and these results may not be generalizable to the normal aging population. For example, our population had a significant number of lacunar infarcts and more severe leukoaraiosis. Any effect of CMBs could be small, and other processes damaging white matter connectivity create a ceiling effect.

It is also possible that lobar CMBs, which have been associated with cerebral amyloid angiopathy, relate to a greater extent with cognition. By selecting patients presenting with lacunar infarcts, we chose a group who have frequent subcortical CMBs. The ability to detect associations will depend on both the prevalence of CMBs in the group being studied and the sample size. With a sample size of 116 we have the sensitivity to detect a Pearson correlation of 0.325 with 95% power at $\alpha=0.05$, this corresponds to linear associations such as those between the number of CMB and the cognitive indices. For an analysis comparing executive function in those with CMB count in the top decile against the other subjects, we have the sensitivity to detect a large group difference (Cohen $d=1.01$) with 95% power at $\alpha=0.05$.

CMB location could be more important than number in determining cognitive consequences. Stroke patients with executive dysfunction had more CMBs in the basal ganglia, whereas in a normal aging cohort thalamic CMBs were associated with worse orientation on Mini-Mental State Examination. In a larger nondemented cohort, frontal and temporal CMBs were associated with various cognitive deficits. We found the number of basal ganglia CMBs and frontal CMBs was associated with executive function, and frontal CMBs were associated with working memory. However, these associations were no longer significant after controlling for other MRI parameters. We found no association between thalamic CMBs and cognitive function. Recent evidence with DTI suggests that the disruption of distributed networks, involving the frontal lobe, is important in the executive dysfunction seen in SVD and this may also be the case for CMBs.

Longitudinal studies may provide more robust information about disease progression, and whether CMBs are indeed markers of cognitive decline or markers of severe SVD. In addition, we had relatively few patients with high CMB count. Studying a larger number with many CMBs will allow the relationship between CMBs and cognition to be further elucidated.

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Disclosures
None.
References


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SUPPLEMENTAL MATERIAL

Supplemental Methods:

Performance for each task was transformed into a z-score using psychometric standardisation with age-scaled normative data. An exception was the modified the Wisconsin Card Sort Test, where age and gender-matched published sample data was used. To produce index scores the component task z-scores were combined as mean average for each participant.

Supplemental Table:

S1. Cognitive Indices and Task Measures

<table>
<thead>
<tr>
<th>Cognitive index</th>
<th>Task and normative data reference</th>
<th>Task measure(s) used and additional details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal IQ</td>
<td>WASI Vocabulary(^1)</td>
<td>Total Score</td>
</tr>
<tr>
<td></td>
<td>WASI Similarities(^1)</td>
<td>Total Score</td>
</tr>
<tr>
<td>Performance Intelligence</td>
<td>WASI Block Design(^1)</td>
<td>Total Score</td>
</tr>
<tr>
<td></td>
<td>WASI Matrix Reasoning(^1)</td>
<td>Total Score</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Digit Span Task(^2)</td>
<td>Total Score</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Trail Making Test(^3)</td>
<td>Time to complete Part B (number-letter switching)</td>
</tr>
<tr>
<td></td>
<td>Verbal Fluency (Delis-Kaplan Executive function system)(^4)</td>
<td>Total number of Correct Words generated</td>
</tr>
<tr>
<td></td>
<td>Modified Wisconsin Card Sort Test(^5)</td>
<td>Categories Achieved &amp; Perseverative Errors(^a)</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>Digit Symbol Substitution(^6)</td>
<td>Total Correct</td>
</tr>
<tr>
<td></td>
<td>BMIPB Speed of Information Processing(^7)</td>
<td>Total correct adjusted for motor score &amp; errors (%)(^a)</td>
</tr>
<tr>
<td></td>
<td>Grooved Pegboard Task(^8,9)</td>
<td>Time to complete (average of 2 hands)</td>
</tr>
<tr>
<td>Long Term Memory</td>
<td>WMS-III Logical Memory(^10)</td>
<td>Total Score: Immediate Recall &amp; Delayed Recall(^a)</td>
</tr>
<tr>
<td></td>
<td>WMS-III Visual Reproduction(^10)</td>
<td>Total Score: Immediate Recall &amp; Delayed Recall(^a)</td>
</tr>
</tbody>
</table>

Abbreviations: BMIPB=Birt Memory & Information Processing Battery; WMS-III =Wechsler Memory Scale - Third Edition (UK); WASI=Wechsler Abbreviated Scale of Intelligence.

\(^a\) Composite score used for multiple task measures.
Supplemental References:


7. Coughlan AKOM&CJR. The BIRT Memory and Information Processing Battery (B-MIPB). Wakefield, UK: The Brain Injury Rehabilitation Trust (BIRT); 2007.

