Cerebral Microbleeds Are Frequent in Infective Endocarditis
A Case–Control Study

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Background and Purpose—Cerebral microbleeds (CMBs) have been described using MRI in patients with cardiovascular risk factors or prior stroke and could be an indicator of small vessel disease. CMBs have been reported in isolated cases of infective endocarditis (IE), but their frequency and the association of CMBs with IE have not yet been studied.

Methods—A case–control imaging study in a referral institutional tertiary care center was conducted. Systematic brain MRIs, including T2*-weighted sequences, were performed in 60 patients with IE within 7 days of hospital admission and in 120 age- and gender-matched control subjects without IE. Two neuroradiologists, who were blinded to patient characteristics, independently assessed the presence, location, and size of CMBs using a standardized form.

Results—The interobserver agreement level on the presence of CMBs was high with a κ coefficient range (95% CI) of 0.70 (0.42 to 0.98) for subcortical regions to 0.91 (0.82 to 0.99) for cortical areas. CMBs were more prevalent in patients with IE (57% [n=34]) than in control subjects (15% [n=18]; matched OR, 10.06; 95% CI, 3.88 to 26.07). Moreover, the OR of IE increased gradually with CMBs number with an OR of 6.12 (95% CI, 2.09 to 17.94) for one to 3 CMBs and of 20.12 (95% CI, 5.20 to 77.80) for >3 CMBs.

Conclusion—CMBs are highly frequent in patients with IE. The strong association found between IE and CMBs supports the need for further evaluation of CMBs as additional diagnostic criteria of IE. (Stroke. 2009;40:3461-3465.)

Key Words: cerebral microbleeds • endocarditis • mycotic aneurysm • T2* MRI
Table 1. General Characteristics of IE Cases and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=60)</th>
<th>Control Subjects (n=120)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>62 (24–87)</td>
<td>61 (22–87)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>40 (66.7)</td>
<td>80 (66.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (33.3)</td>
<td>52 (43.3)</td>
<td>0.166</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (16.7)</td>
<td>22 (18.3)</td>
<td>0.793</td>
</tr>
<tr>
<td>Current smoking</td>
<td>23 (38.3)</td>
<td>42 (35.0)</td>
<td>0.655</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (20.0)</td>
<td>53 (44.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>17 (28.3)</td>
<td>60 (50.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic lesion</td>
<td>28 (46.7)</td>
<td>66 (55.0)</td>
<td>0.309</td>
</tr>
<tr>
<td>Hemorrhagic lesion</td>
<td>1 (1.7)</td>
<td>5 (4.2)</td>
<td>0.360</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>27 (45.0)</td>
<td>58 (48.3)</td>
<td>0.617</td>
</tr>
<tr>
<td><strong>IE characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular prosthesis</td>
<td>15 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native valves</td>
<td>45 (75.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>41 (68.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided (exclusive)</td>
<td>4 (6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-organism(s)</td>
<td>47 (78.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococci sp.</td>
<td>18 (30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococci sp.</td>
<td>21 (35.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (13.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite IE†</td>
<td>43 (71.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Values are expressed as no. (percentage) unless otherwise indicated.
*Conditional logistic regression analysis for matched sets.
†Duke modified criteria; other cases were possible according to this classification.

Ethics committee, were analyzed. All patients signed an informed consent. Clinical data included age, gender, presence of a prosthetic heart valve, type of micro-organism, Duke-modified criteria, anticoagulation, and vascular risk factors (Table 1). For all patients, echocardiography and brain MRI were performed within the first week after patient admission.

**Control Subjects**

Subjects were retrospectively selected from the local radiological database between July 2005 and July 2007. Because we wondered whether anticoagulation might influence CMB occurrence, we randomly selected for each case 2 age- (±5 years) and gender-matched control subjects, one under active anticoagulation therapy and the other not. For these subjects, brain MRI was prescribed in the context of clinical treatment. The same clinical data were collected as for cases. The final diagnosis classified in control subjects as vascular, epileptic, infectious, tumoral, or degenerative.

**Brain Imaging Protocol**

For cases and control subjects, the same MRI sequences were performed on a 1.5-T GE system with GRE T2*: (TR/TE 750/17.3, flip angle 20, matrix 416×224, field of view 24×19.5, number of excitations 1), b1000 diffusion-, and T2 fluid-attenuated inversion-recovery-weighted sequences using a 5-mm slice thickness and 0.5-mm slice gap.

**MRI Reading**

Two neuroradiologists (I.K. and A.H.), blinded to patient characteristics independently reviewed and graded MRIs using a standardized form first tested on an independent sample to collect relevant information. Any disagreement was resolved by consensus. After MRI features were collected: (1) as previously described,13,14 CMBs were defined as round T2* hypointensities with diameter ≤5 mm or >5 mm and ≤10 mm. Number and localization were collected. For localization, cortical (ribbon or sulci), subcortical (white matter and basal ganglia), and posterior fossa were distinguished. Cortical ribbon localization comprised CMBs located at the cortical surface or within the cortical ribbon. For cortical sulci localization, we only considered CMBs >3 mm to avoid mistakes with 1.5-mm pial vessels. For basal ganglia, pallidal symmetrical hyposignals were excluded. Global shape and signal content of CMBs (homogeneous or heterogeneous) were noticed; (2) acute and chronic stroke, (3) parenchymal hemorrhage, (4) subarachnoidal hemorrhage with number (unique or multiple) and distribution; and (5) leukoaraiosis was graded with a modified Fazekas score.15

**Statistical Analysis**

Interobserver agreement was evaluated using the simple κ coefficient (for binary variables) and weighted κ coefficient (for ordinal variables). We compared CMB prevalence of between control groups with and without anticoagulant medication using McNemar exact test. Finding no difference between the 2 control groups, we compared CMB prevalence in IE cases with the 2 control groups pooled together using the conditional logistics regression analysis for matched sets. Sensitivity analysis was performed in matched pairs of cases and control subjects without anticoagulant medication. Finally, among the 60 IE cases, we used the χ2 test to compare CMB prevalence according to patient characteristics. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed with the SAS package, release 9.1 (SAS Institute, Cary, NC).

**Results**

**Patients’ Characteristics**

IE case and control characteristics are summarized in Table 1. There was no relevant difference in patient characteristic distribution between cases and control subjects, except for a higher proportion of control subjects with hypercholesterolemia. IE was diagnosed according to the Duke criteria as definite in 43 cases (72%) and as possible in 17 (28%). In control subjects, the final diagnosis was vascular in 70% (n=84), infectious in 15% (n=18), cancer in 6% (n=7), degenerative in 6% (n=7), and epilepsy in 3% (n=4).

**Brain Microbleeds and IE**

Interobserver agreement about CMB presence was high whatever the localization with a κ coefficient (95% CI) ranging from 0.70 (0.42 to 0.98) for subcortical regions to 0.91 (0.82 to 0.99) for cortical areas and a CMB diameter with a κ coefficient (95% CI) of 0.92 (0.84 to 0.99) for CMB ≤5 mm and 0.79 (0.56 to 1.00) for CMB >5 mm. The weighted κ coefficient was 0.94 (95% CI, 0.89 to 0.99) after categorization of the number of CMBs into 3 groups (none, 1 to 3, >3). Similarly, interobserver reliabilities on other imaging data were high with a κ coefficient (95% CI) of 0.89 (0.74 to 0.90) for recent ischemic lesions, 0.84 (0.56 to 1.00) for old ischemic lesions, 0.83 (0.75 to 0.91) for leukoaraiosis score, and 0.72 (0.41 to 1.00) for hemorrhagic lesions.

Among the control group, CMB prevalence did not differ between anticoagulant-treated (11.7% [n=7]) and nonanticoagulant-treated patients (18.3% [n=11]; P=0.39); the resulting CMB prevalence in the control group was 15.0% (95% CI, 8.6% to 22.7%). In IE cases, CMB prevalence was 57% (95% CI, 44.1% to 69.2%), significantly higher than the
control group (matched OR, 10.06; 95% CI, 3.88 to 26.07; 
\( P < 0.001 \)). A similar result was found in sensitivity analysis 
excluding anticoagulant-treated patients (matched OR, 7.00; 
95% CI, 1.59 to 30.80).

Table 2 describes the distribution of CMBs according to 
localization and signal content in cases and control subjects 
separately.

The case–control difference in CMB prevalence was found 
whether the localization (all pairwise comparisons < 0.05).

No control subject had CMBs > 5 mm, whereas CMBs > 5 mm were found among 11 IE cases (32.3%). No control subject had CMBs in cortical sulci, whereas 9 IE cases (15%) had CMBs in cortical sulci (Figure 1). In cases and control subjects, CMBs were round and well-shaped (Figure 1). For both cases and control subjects, CMB signal content was variable. Most patients, either cases or control subjects, had homogeneous CMBs (Figure 1). On the other hand, a case–
control difference in CMB prevalence was found for homo-
geneous signal content (53% versus 13%, \( P < 0.001 \)) as well 
as for heterogeneous signal content (28% versus 3%, 
\( P < 0.001 \)).

CMB number reached 90 in IE cases and 12 in control 
subjects. As shown in Figure 2, the OR of IE increased 
gradually with the number of CMBs. Among IE cases, CMB 
prevalence was associated with anticoagulant therapy (82.3% 
\[ n = 14 \] versus 47% \[ n = 20 \], \( P = 0.012 \)), valvular prosthesis 
(93.3% \[ n = 14 \] versus 44% \[ n = 20 \], \( P < 0.001 \)), and non-
Streptococcus micro-organism (66.7% \[ n = 26 \] versus 38% 
\[ n = 8 \], \( P = 0.033 \)). CMB prevalence did not differ between 
patients with definite (42% \[ n = 18 \]) or possible IE (47% 
\[ n = 8 \], \( P = 0.71 \)). Other case characteristics, including imaging 
data such as acute ischemic stroke, were not significantly 
related to CMB presence (data not shown).

**Discussion**

This study showed a previously unreported high prevalence 
of CMBs in patients with IE compared with a control group. 
The strength of the association between CMBs and IE 
increased with the number of CMBs.

To our knowledge, this is the first cross-sectional study that 
systematically analyzed MRI abnormalities including CMBs 
in IE. Minor or silent stroke is highly frequent during the 
acute phase of IE.\(^{16,17} \) In our study, CMBs were observed 
during the early phase of patient management. Although we 
cannot be sure that the presence of CMBs indicates early 
stages of infective endocarditis, the high frequency of CMBs 
suggests that they should be evaluated as new diagnostic 
markers of IE.

It is unlikely that CMBs could be signs of previous emboli 
from diseased valves before IE occurred. CMBs are hemo-

rhagic signal abnormalities that are easily differentiated from 
a 
significant bias in the association we found 
that CMBs are hemor-

rhagic signal abnormalities that are easily differentiated from 
acute or old ischemic infarcts with MRI.\(^6–8 \) In our study, 
CMBs were not associated with ischemic lesions. In patients 
with IE, CMBs were mostly homogeneous, < 5 mm, and 
predominantly located in cortical areas rather than subcortical 
areas. Although similar morphological and topographical 
differences were found in control subjects, CMBs were 
observed in cortical sulci and tend to be larger and more 
heterogeneous in patients with IE. Asymptomatic CMBs, 
common MRI features in elderly patients with cerebrovascu-
lar disease, might be markers of microangiopathy.\(^8–14,18 \) 
Similarly in IE, CMBs may reflect a subacute microvascular 
process leading in some cases to the development of mycotic 
aneurysms on distal or pial arteries. Consistently, in a 
previous report, a mycotic aneurysm was found to be asso-
ciated with a CMB located in a cortical sulcus and the number 
of CMBs was greater at follow-up MRI.\(^5 \) CMBs were also 
detected in association with a ruptured aneurysm.\(^4 \) Addition-
ally, our results suggest that CMB prevalence might vary with 
the type of micro-organism.

In non-IE patients, previous series have shown that CMBs 
are strongly associated with intracerebral hemorrhage\(^10–14,19 \) 
and that CMBs increased the risk of cerebral bleeding in 
patients under warfarin,\(^20,21 \) but it is unclear whether antico-
agulation increased CMB prevalence.\(^13,14 \) In our series, anti-
coagulation was associated with CMBs in patients with IE but 
not in control subjects. However, in sensitivity analysis 
restricted to nonanticoagulant-treated patients, CMB preva-

lence was higher in IE cases than in control subjects.

Our study suffers from limitations. Because control sub-
jects were not matched to cases by all vascular risk factors 
known to be associated with CMBs, we could not exclude a 
residual confusion bias. However, it seems unlikely that this 
would cause a significant bias in the association we found 
between IE and CMBs, in particular because control subjects 
were mainly patients admitted for acute stroke with multiple

Table 2. Distribution of CMBs According to the Localization and Signal Content in IE Cases and Control Subjects

<table>
<thead>
<tr>
<th>Location of CMBs</th>
<th>Cases (n=60)</th>
<th>Control Subjects (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Whole area</td>
<td>34 (56.7)</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>Cortical</td>
<td>30 (50.0)</td>
<td>14 (23.3)</td>
</tr>
<tr>
<td>Surface</td>
<td>27 (45.0)</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td>Sulci</td>
<td>9 (15.0)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>16 (26.7)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>White matter</td>
<td>9 (15.0)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>10 (16.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>14 (23.3)</td>
<td>5 (8.3)</td>
</tr>
</tbody>
</table>

Note: Data are no. (percentage) of subjects with at least one CMB.
vascular risk factors hence with increased CMB risk. Indeed, we found a higher prevalence of CMBs in control subjects (15%) than expected in the normal population (5% to 6%). Thus, there were no relevant differences in predictive factors of CMBs between cases and control subjects as shown in Table 1. Due to the relatively small sample size, our results should be interpreted with caution, especially for subgroup analyses. We cannot exclude the possibility that some associations could have been overlooked as well as the presence of false-positive findings, especially in the context of multiple regression analyses.

Table 1. Matched OR of IE associated with CMB load.

<table>
<thead>
<tr>
<th>Microbleeds</th>
<th>Cases (n(%))</th>
<th>Controls (n%)</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study sample</td>
<td>(80 cases and 92 matched controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>19 (31.7)</td>
<td>5 (4.2)</td>
<td>20.12 (5.20, 77.80)</td>
</tr>
<tr>
<td>1-3</td>
<td>15 (25.0)</td>
<td>13 (10.8)</td>
<td>6.12 (2.89, 17.94)</td>
</tr>
<tr>
<td>None</td>
<td>26 (43.3)</td>
<td>162 (85.0)</td>
<td>(ref.)</td>
</tr>
<tr>
<td>Non-anticoagulant treated patients (63 cases and 64 matched controls)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>10 (23.3)</td>
<td>3 (7.0)</td>
<td>13.75 (1.41, 134.14)</td>
</tr>
<tr>
<td>1-3</td>
<td>10 (23.3)</td>
<td>5 (11.6)</td>
<td>4.90 (1.08, 24.63)</td>
</tr>
<tr>
<td>None</td>
<td>23 (53.5)</td>
<td>35 (81.4)</td>
<td>(ref.)</td>
</tr>
</tbody>
</table>
comparisons. Finally, our control group did not include patients with cardiac prostheses. Extrapolation to this population would require further studies.

In conclusion, this study shows a particularly high frequency of cerebral microbleeds in infective endocarditis as compared with a hospital age-/gender-matched group. The strength of this association raises the question of the additional diagnostic value of CMBs for IE, which needs to be addressed by further specifically designed studies.

Appendix

IMAGE Study Group


Independent Committee

F. Bricaire, A. Cohen, and Y. Cordoliani.

Monitoring and Statistical Analysis


Working Group and Clinical Investigators


Sponsor

Assistance Publique, Hôpitaux de Paris, Direction de la Recherche Clinique, N. Best, and O. Chassany.

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Disclosures

None.

References

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