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

Infective endocarditis (IE) is a severe disease with in-hospital and 5-year mortality rates of 20% and 40%, respectively.1–3 Although diagnosis of IE may be obvious in some patients, it is often more difficult in others presenting various nonspecific clinical manifestations that could delay appropriate diagnosis and urgent therapy. In patients without sustained bacteremia and valvular vegetation, diagnosis takes into account predisposing conditions (valvular lesions, intravenous drug addiction), neurological and vascular manifestations of IE.

Recently, the presence of asymptomatic cerebral microbleeds (CMBs) has been reported in 2 patients with IE.4,5 CMBs are small microhemorrhages only detectable by T2* MRI sequences.6,7 These MRI features have been previously associated with small vessel diseases and reported in patients with vascular risk factors such as hypertension, history of stroke, or cognitive impairment.8–14 Because small vessel vasculitis is frequent in patients with IE, we hypothesized that CMBs could be a manifestation of IE. While conducting a prospective study to evaluate the diagnostic and therapeutic impact of MRI at the early phase of IE (Imagerie par résonance Magnétique à la phase Aiguë de l’Endocardite infectieuse [IMAGE] Study), we observed a previously unreported frequency of microbleeds. We therefore took the opportunity to conduct a case–control study to assess the prevalence of CMBs in patients with IE and compare it with the prevalence of CMBs in a control group without diagnostic criteria of IE.

Methods

Patients

Cases
The first 60 patients with community-acquired IE included in the single-center prospective IMAGE Study, approved by the local

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From AP-HP, Departments of Radiology (I.K., A.H., J.-P.L.), Cardiology (B.I., D.M.-Z.), Neurology (J.L., P.L.), Intensive Care (M.W.), and Infectious and Tropical Diseases (C.L., X.D.), Bichat University Hospital, Paris, France; AP-HP, Department of Intensive Care, Bichat University Hospital, Paris, France; Inserm CIC 007 (X.D.), Centre d’Investigation Clinique; Inserm 738; Université Paris 7, UFR de Médecine; Paris, France; and AP-HP, Département d’Épidémiologie (X.D.), Biostatistique et Recherche Clinique Bichat University Hospital, Paris, France.
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3461
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.

Results

**Statistical Analysis**

Interobserver agreement was evaluated using the simple k coefficient (for binary variables) and weighted k 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).

**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 k 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 k 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 k 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 k 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=71]) 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 whatever 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 homogeneous 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 presence 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-

\textit{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 hemorrhagic 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 cerebrovascular disease, might be markers of microangiopathy.\(^{6-14,18}\) 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 associated 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.\(^{4}\) Additionally, 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 anticoagulation increased CMB prevalence.\(^{13,14}\) In our series, anticoagulation was associated with CMBs in patients with IE but not in control subjects. However, in sensitivity analysis restricted to nonanticoagulant-treated patients, CMB prevalence was higher in IE cases than in control subjects.

Our study suffers from limitations. Because control subjects 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
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

Figure 1. T2*-weighted gradient recalled echo images showing representative distribution and morphological patterns of CMBs in 10 patients with IE (A–B, arrows) compared with 10 control subjects (C–D, arrows).

Figure 2. Matched OR of IE associated with CMB load.

<table>
<thead>
<tr>
<th>Microbleeds</th>
<th>Cases</th>
<th>Controls</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study sample: (69 cases and 159 matched controls)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>19 (31.7)</td>
<td>5 (4.2)</td>
<td>20.12 (5.20, 77.801)</td>
</tr>
<tr>
<td>1-3</td>
<td>15 (25.0)</td>
<td>13 (10.8)</td>
<td>6.12 (2.99, 17.94)</td>
</tr>
<tr>
<td>None</td>
<td>26 (43.3)</td>
<td>102 (85.0)</td>
<td>(ref.)</td>
</tr>
</tbody>
</table>

| Non-anticoagulant-treated patients: (43 cases and 43 matched controls) |
| >3          | 10 (23.3) | 5 (7.0) | 13.75 (1.14, 134.14) |
| 1-3         | 10 (23.3) | 5 (11.6) | 4.90 (1.09, 24.62) |
| None        | 23 (53.5) | 35 (81.4) | (ref.) |
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.

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