Management of infectious endocarditis with mycotic aneurysm evaluated by brain magnetic resonance imaging†

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Background: Cerebral complications of infective endocarditis (IE) are a common and serious cause of morbidity and mortality. Mycotic aneurysms are a particularly serious complication and often lead to subarachnoid or intracerebral hemorrhage. Various imaging techniques, including brain magnetic resonance imaging (MRI), have been used to detect mycotic aneurysms. However, the clinical importance of detection by MRI has not been fully established.

Aims: The aim of this study was to evaluate the incidence and characteristics of mycotic aneurysms detected by MRI in patients with active IE, and to determine whether MRI findings were associated with outcomes.

Methods: We retrospectively reviewed the records of 56 patients with active IE who underwent brain MRI between January 2000 and December 2010. MRI findings included black dots, hypointense spots, and contrast enhancement around black dots. Six patients who did not undergo MRI were excluded. The remaining patients were classified into four groups according to the presence and characteristics of black dots: Group A (n=13): cerebral hemorrhage, cerebral infarction, abscess and encephalitis; Group B (n=7): simple or multiple black dots; Group C (n=15): single or multiple black dots alone; Group D (n=15): no abnormal MRI findings. None of the 12 patients who successfully underwent elective open heart surgery in Groups B and C developed postoperative cerebral complications.

Results: Six patients who had not undergone MRI were excluded. The remaining patients were classified into four groups according to preoperative brain MRI findings—Group A (n=13): cerebral hemorrhage, cerebral infarction, abscess and encephalitis; Group B (n=7): simple or multiple black dots; Group C (n=15): single or multiple black dots alone; Group D (n=15): no abnormal MRI findings. None of the 12 patients who successfully underwent elective surgery in Groups B and C developed postoperative cerebral complications.

Conclusions: Brain MRI is an important tool for the detection of asymptomatic intracranial abnormalities associated with IE and evaluation of the preoperative bleeding risk of patients. Patients with contrast enhancement around black dots are at high risk for bleeding, and performing open heart surgery in such patients whenever possible after improvement in inflammatory findings reduces the potential risk of cerebral hemorrhage.

Keywords: Infective endocarditis, Magnetic resonance imaging, Mycotic aneurysm

INTRODUCTION

Infective endocarditis (IE) is a serious disease with a mortality rate of 16–25% [1, 2], and a high rate of symptomatic cerebrovascular disorder complications (20–24%) has been reported [3]. Cerebrovascular disorders are the main cause of death from IE, as well as heart failure, and the mortality rate further increases when IE is complicated by cerebrovascular disorders.

The use of brain magnetic resonance imaging (MRI) for IE patients has recently been reported [4–7]. The incidence of asymptomatic cerebral infarction on brain MRI was high (30–50%), and ~80% of IE cases were complicated by cerebral infarction, including asymptomatic infarction [8, 9]. In addition, hypointensive spots on T2*-weighted imaging have been attracting attention: these spots have been noted in many IE patients [5, 6, 10] and have been suggested as being indicative of the presence of mycotic aneurysm in others [11, 12].

Bearing in mind that these hypointensive spots (called black dots in our study and also denoted as black dots by Duval et al. [6] and Klein et al. [11]) are a feature of thrombosed mycotic aneurysm (Fig 1(A)) in IE patients, we have noted a high incidence of symptomatic cerebral and subarachnoid hemorrhage after surgery in patients in whom encephalitis surrounding the spot was enhanced on gadolinium contrast imaging and those with inflammatory findings indicative of meningitis. From 1996 to 1999, we found that cases with contrast enhancement consistent with the black dots on gadolinium contrast imaging (Fig 1 (B)) are likely to be accompanied by inflammation, such as encephalitis and meningitis, around the black dot and to develop subarachnoid and cerebral hemorrhage. We also found that black dots only were noted on MRI in 3 of the 15 active IE patients, and black dots plus contrast enhancement in 2. After open heart surgery, symptomatic cerebral or subarachnoid hemorrhage...
occurred in 1 of the 3 patients with black dots only (33.3%) and in 2 of the 2 patients (100%) with black dots plus contrast enhancement. Since 2000, we have applied the following treatment strategy for patients with conservative treatment-applicable diseases, such as circulatory and infectious diseases and thrombosis: surgery is performed after mycotic aneurysms are identified on brain MRI and accompanying inflammatory findings are improved by conservative treatment with appropriate antibiotics.

In patients with IE with cerebral complications, the optimal timing of open heart surgery has been controversial with regard to the postoperative exacerbation of the cerebral disorder [13–19]. On the other hand, there has been no previous report regarding the timing of surgical intervention based on the evaluation of cerebral complications on brain MRI. In this study, focusing on the evaluation of asymptomatic intracranial abnormalities, particularly, mycotic aneurysms detectable by MRI, we investigated and evaluated the timing of surgical intervention.

**MATERIALS AND METHODS**

Fifty-six patients (35 men, 21 women, mean age 56 years) diagnosed with active IE based on the Duke criteria between January 2000 and December 2010 were evaluated retrospectively. The symptoms were fever in 43 patients, neurological abnormality in 9, systemic malaise/appetite loss in 5, respiratory distress in 12 and other symptoms in 12. The affected valve was the aortic valve (A) in 18 patients, mitral valve (M) in 21, tricuspid valve (T) in 2, A + M in 11, A + T in 1 and prosthetic valve endocarditis in 3. The bacterium detected by blood culture was *Staphylococcus* in 14 patients, *Streptococcus* in 15, *Candida* in 1, methicillin-resistant *Staphylococcus aureus* in 3 and others in 5 patients; no bacterium was detected in 18 patients (Table 1).

MRI was performed using a clinical whole-body imager operating at 1.5 T (Singa HDxT; GE Healthcare, Milwaukee, WI, USA). Axial T2-weighted fast spin echo imaging (repetition time (TR) 2800 ms; echo time (TE) 100 ms; coronal T1-weighted imaging (TR 400 ms; TE 9 ms)), diffusion-weighted echo planer imaging (DWI) (b = 1000; TR 10,000 ms; TE 85 ms) and three-dimensional time-of-flight magnetic resonance angiography (3D-TOF MRA) were available for all patients. Most of the patients were scanned within 5 days of admission. Axial, coronal and sagittal MRI after intravenous administration of gadopentetate dimeglumine (0.2 ml/kg) and axial T2*-weighted gradient echo MRI (TR 580 ms; TE 28 ms; flip angle 20°; acquisition matrix: 256 × 192; number of signal average: 2; section thickness: interleave and field of view: 22 cm²) were performed in all patients except 1 patient with renal dysfunction.

Patients in whom black dots and a contrast-enhancement effect around the spots were noted on gadolinium contrast brain MRI underwent re-evaluation every 7–10 days. The same 2 radiologists evaluated the presence or absence of the contrast enhancement and the size reduction of the black dots.

### Table 1: Preoperative characteristics of 56 patients with infective endocarditis

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>43</td>
</tr>
<tr>
<td>Neurological abnormality</td>
<td>9</td>
</tr>
<tr>
<td>General fatigue/appetite lost</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
</tr>
<tr>
<td>Affected valves</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>18</td>
</tr>
<tr>
<td>Mitral</td>
<td>21</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>2</td>
</tr>
<tr>
<td>Aortic + mitral</td>
<td>11</td>
</tr>
<tr>
<td>Aortic + tricuspid</td>
<td>1</td>
</tr>
<tr>
<td>PVE (post AVR (2), DVR + TAP (1))</td>
<td>3</td>
</tr>
<tr>
<td>Causative microorganism</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>14 (25)</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>15 (27)</td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>1 (2)</td>
</tr>
<tr>
<td>MRSA</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Undetected</td>
<td>18 (32)</td>
</tr>
</tbody>
</table>


Figure 1: (A) Axial T2*-weighted image shows black dot (arrow). Axial contrast-enhancement. (B) T1-weighted image shows abnormal enhancement is consistent with black dot (arrow).
In the treatment of infection, 1 or 2 effective agents were selected for patients in whom bacteria were detected on the blood culture test. For patients in whom no bacterium was detected, antibiotics were selected following the IE treatment guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) or the Japanese Circulation Society.

Surgery was also performed following these definitions in patients when other lesions, such as cerebral haemorrhage and cerebral infarction, were observed. Conservative treatment was performed as much as possible. Open heart surgery was conducted when the lesion had improved on brain MRI.

Emergency operation was defined when performed for severe congestive heart failure or cardiogenic shock due to acute valvular regurgitation or severe prosthetic dysfunction (dehiscence or obstruction) or ≥1 cm mobile vegetation on echocardiography within 24 h after admission. An urgent operation was defined as that performed in patients in whom observation by MRI was necessary but who had haemodynamic instability, poor control of infection or thrombosis during conservative treatment. An elective operation was defined as that performed when the black dots shrank or disappeared and/or the contrast-enhancing effect was lost.

RESULTS

Excluding 6 patients who did not undergo MRI due to poor systemic condition before surgery, pacemaker implantation and other reasons, 50 patients were divided into the following four groups based on the findings on the first brain MRI: Group A (n = 13), haemorrhage, infarction, abscess and encephalitis were observed; Group B (n = 7), black dots were noted in addition to haemorrhage and infarction; Group C (n = 15), only black dots were noted; Group D (n = 15), no abnormal findings were noted. A summary of patients’ clinical course before and after receiving brain MRI is shown in Figure 2.

Table 2: Death cases following brain MRI

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Group</th>
<th>Cause of death</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>A</td>
<td>SAH, CH</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>B, C, E (+)</td>
<td>SAH, CH</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>M</td>
<td>C, C, E (-)</td>
<td>SAH, CH</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>C, C, E (-)</td>
<td>VF</td>
<td>1</td>
</tr>
</tbody>
</table>

Duration: duration from first MRI to death. C–E: contrast enhancement; MRI: magnetic resonance imaging; SAH: subarachnoid haemorrhage; CH: cerebral haemorrhage; VF: ventricular fibrillation.

In Group A, neurological abnormalities were noted on admission in 3 patients (paresis, abnormal visual field and transient ischaemic attack, respectively). Urgent operation was performed in 4 patients, and surgery was conducted a mean of 1.8 days after the first MRI. Elective operations were conducted in 8 patients, and surgery was conducted a mean of 41 days after the first MRI (Fig. 2). One patient died while waiting for surgery due to subarachnoid and cerebral haemorrhage 6 days after the first MRI (Table 2).

In Group B, neurological abnormalities were noted on admission in 3 patients (paresis, disturbance of consciousness and atomic seizure, respectively). Contrast enhancement around black dots was noted in 5 of the 7 patients. Subarachnoid and cerebral haemorrhage occurred in 1 patient with black dots plus contrast enhancement during waiting; this patient died 24 days after the first MRI (Table 2). Of the other 4 patients, urgent surgery was performed in 1, and elective operations were conducted in the other 3 after the contrast enhancement disappeared. Elective surgery was performed a mean of 59 days after the first MRI. No contrast enhancement was noted in 2 patients: these patients underwent urgent and elective operations, respectively (Fig. 3).
In Group C, neurological abnormalities were noted on admission in 3 patients (vertigo and disturbance of consciousness in 2). Six of 15 patients were positive for black dots plus contrast enhancement. Urgent operations were performed in 2 of these 6 patients, and surgery was conducted 3 and 15 days after the first MRI, respectively. Elective operations were performed in 4 patients, and surgery was conducted a mean of 55 days after the first MRI. Nine patients were black dot-positive but contrast enhancement-negative (contrast imaging was not performed in 1 patient because of renal dysfunction), and urgent surgery was necessary for 3 patients. Elective operations were conducted in 4 patients, and surgery was conducted a mean of 15 days after the first MRI. Two patients died during waiting. Both were positive for black dots but negative for contrast enhancement: 1 died of subarachnoid and cerebral haemorrhage 24 days after the first MRI. In the other, ventricular arrhythmia occurred 1 day after the first MRI (Table 2).

In Group D, no neurological abnormality was noted in any patient. Urgent operation was performed in 5 and elective operations in 10 patients. Elective surgery was performed a mean of 20 days after the first MRI (Fig. 2). A summary of the clinical results in patients with black dot on brain MRI is shown in Fig. 3.

Regarding excluding 6 patients, no neurological abnormalities were noted. Emergency operation was performed in 3 patients. Urgent and elective operations were performed in 2 and 1, respectively.

Intracranial abnormalities were detected at a high rate [35 of the 50 patients (70%) in Groups A, B and C] on brain MRI. In addition, black dots were noted in 22 of the 50 patients (44%) in Groups B and C, and contrast enhancement was noted around the black dots on gadolinium contrast imaging in 11 of the 22 patients (50%).

Surgery was performed in 52 patients excluding 4 who died while waiting: aortic valve replacement (AVR) in 17 patients; mitral valve replacement (MVR) in 6, tricuspid valve annuloplasty (TAP) in 1, mitral valve plasty (MVP) in 12, AVR + MVR in 2, AVR + MVP in 6, AVR + TAP in 1, Bentall procedure in 2, Bentall + TAP in 1, Bentall + MVP in 1 and others in 3. Combined surgery was performed in 11. The mean operation, cardiopulmonary bypass and aortic cross-clamp times were 304, 133 and 101 min, respectively.

One patient (1.9%) who underwent urgent surgery in Group C died of disseminated intravascular coagulopathy and multiple organ failure. Regarding postoperative neurological abnormality, cerebral infarction occurred in 1 patient who was conducted elective surgery in Group A, transient convulsion occurred after surgery in the patient in whom no contrast enhancement was noted and an urgent operation was performed, and subdural haematoma was detected on postoperative computerized tomography (CT) in Group B. Postoperative result are summarized in Table 3.

**DISCUSSION**

We perform brain MRI in patients diagnosed with active IE routinely as far as possible. The frequency of asymptomatic cerebral infarction on MRI was high (30–50%); a complication rate of ~80% for cerebral infarction in IE cases including asymptomatic
lesions has been reported [8, 9]. In our study, intracranial abnormalities were noted in 70%, and black dots were present in 44%. These findings showed that cerebral disorder was detected in IE at a high rate on MRI as reported previously [8, 9].

It has recently been reported that brain MRI detects intracranial abnormalities in IE with a greater sensitivity than CT, and brain MRI should be performed at an early stage to develop a therapeutic strategy [4, 6, 20]. We consider that brain MRI is important for IE patients based on our experience: we performed open heart surgery in 5 active IE patients with black dots on brain MRI, and subarachnoid and cerebral haemorrhage occurred after surgery at a high frequency (3/5, 60%), i.e. open heart surgery in the presence of black dots on brain MRI has a high risk of intra- and postoperative complications, such as devastating cerebral haemorrhage. It is generally thought that open heart surgery for IE with cerebrovascular disorder complications may aggravate neuropathy due to hypotension, cerebral oedema and a heparin-induced haemorrhagic condition during extracorporeal circulation, for which the optimal timing of surgery is important to avoid the postoperative aggravation of neuropathy. The timing of surgery for patients with cerebral complications is still controversial: some reports recommend early surgery [13–15], whereas others recommend elective surgery [16–18]. However, there has been no report in which the timing of surgical intervention for IE was decided based on the presence and evaluation of black dots in addition to haemorrhage and infarction, although the importance of MRI has been reported.

Black dots observed on T2*-weighted imaging have been expressed as microbleeds and have been noted as a risk factor for cerebral haemorrhage in the elderly and hypertensive patients [21]. We differentiated black dots observed in patients with IE with regard to the location: these spots are present on the brain surface, on which infectious cerebral aneurysm is likely to occur, being different from previously reported microbleeds. We considered them as showing the possibility of existing thrombosed aneurysms reflecting hemosiderin deposition. A high incidence of black dots on MRI in IE patients [6, 10, 22] and the presence of cerebral aneurysms at the corresponding sites [11, 12] have recently been reported. It has also been reported that microbleeds are urgent indicators of cerebral haemorrhage in IE patients, involving vascular vulnerability [22]. Based on these reports, black dots may suggest the presence of mycotic aneurysm. On the other hand, no aneurysm consistent with the black dots was observed on simultaneously performed angiography or MRA in this study. One reason may be the non-detectability of the dots as aneurysms because of the small size of the black dots or because the aneurysm was thrombosed. Since we did not pathologically evaluate these findings, further investigation is necessary.

More importantly, it was suggested that cases with contrast enhancement consistent with the black dots on gadolinium contrast imaging (Fig. 1B) are likely to be accompanied by inflammation, such as encephalitis and meningitis, around the aneurysm and to develop subarachnoid and cerebral haemorrhage. We have described cases with postoperative brain haemorrhage from 1996 to 1999 in the introduction. One cause may have been the application of open heart surgery without recognizing black dots as a risk of cerebral haemorrhage at that time. Although the number of patients was small, cases with gadolinium contrast enhancement around black dots were accompanied by inflammation, such as encephalitis and meningitis, compared with cases without contrast enhancement, suggesting the increased vulnerability of vascular tissue. Based on these findings, since 2000, we have performed gadolinium contrast imaging in addition to brain MRI in patients with active IE as far as possible, and when black dots accompanied by contrast enhancement are noted, open heart surgery is not performed until the enhancement disappears on repeated MRI. The symptomatic mycotic aneurysm and surrounding inflammatory findings on gadolinium contrast imaging that we noted carefully have been reported before [4], but no report has suggested that these findings provide important information to inform the timing of surgery. Our study demonstrated that no postoperative severe cerebral complications occurred in patients who underwent elective open heart surgery following the therapeutic strategy, and thus the incidence was markedly decreased.

MRI was performed a mean of 3.8 times (2–6 times)/patient until inflammatory findings were improved in patients considered as a high-risk group, and surgery was performed a mean of ~50 days after the first MRI. It has been reported that mycotic aneurysm was resolved or improved within 4–6 weeks by antibiotic treatment [23, 24], which is consistent with the disappearance of black dots or improvement of inflammatory findings in our study, suggesting that these events may serve as a rough standard of the duration of conservative treatment. We are aware that these results are controversial: it is not certain how many times the MRI should be repeated, and the duration of ~50 days from first MRI to operation may be too long. Further investigation regarding these points is necessary.

Surgery could not be performed in 3 of 4 patients due to the occurrence of cerebral and subarachnoid haemorrhage during the repeated MRI period, and haemorrhage occurred 6–24 days after the first MRI. Recent review reported that morbidity and mortality due to spontaneous mycotic aneurysm rupture was 12−32% [25]. The incidence was 6% (3/50) in this series. We thought this occurrence was inevitable and it is difficult to predict the occurrence of haemorrhage in these patients, and this remains to be overcome. Moreover, emergency and urgent surgeries were inevitably performed because conservative treatment was difficult due to the haemodynamic condition, infection or thrombosis in 11 of 50 patients (31%) in Group A, B and C. Although no serious cerebral complications occurred in these patients, it may be necessary to investigate how to avoid postoperative cerebral complications in these patients because open heart surgery may have to be performed before improvement of the MRI findings in patients included in the high-risk group on MRI. We believe that when dealing with these patients, the optimal timing of surgery is of concern. A recent review paper [25] suggested that the risk of postoperative neurological deterioration is dependent more on the severity of cerebrovascular complication than the timing of surgery. In this series, 4 of 11 patients, specifically urgent cases in Group A, B and C revealed neurological complication preoperatively. These symptoms were TIA, failure of eye sight in Group A, disturbance of consciousness in Group B of contrast enhancement (+) and dizziness in Group C of contrast enhancement (−). All cases did not have severe neurological damage postoperatively. According to the European Society of Cardiology (ESC) guideline, surgery can be performed early after neurological complications if the neurological damage is not as severe as intracranial haemorrhage, coma and stroke with severe damage. Our results are in accordance with this guideline. Based on the results of this study, we have recently found that a black dot without contrast enhancement in itself is not high risk compared with that with contrast enhancement.
Limitations of the study

There are some limitations of this study. The number of cases was very small because the study was performed at a single institution. Moreover, this was a retrospective study and therefore not controlled. In this series, endpoints were not clearly defined. It is very important to evaluate if this study or strategy is reliable or not. Further evaluation may be necessary. Regarding the MRI findings, the relationship between the black dots and mycotic aneurysm was not sufficiently shown. These points remain to be evaluated.

CONCLUSION

In summary, to evaluate cerebral complications in IE, it is important to investigate their presence with brain MRI even for asymptomatic patients. In addition, serious cerebral complications, such as cerebral and subarachnoid haemorrhage, may be avoided in patients showing black dots/mycotic aneurysms or surrounding contrast enhancement on brain MRI by performing elective surgery after the disappearance of these findings.

Prognostic assessment on admission is of utmost important. Brain MRI is one of the important tools that can assist clinical decisions and help to avoid devastating brain complications after open surgery. We realize that this study design has some problems and limitations. We also cannot conclude whether our operative strategy of applying elective surgery based on brain MRI, is a generalizable one. However, we believe that this approach is a benchmark for the treatment of IE patients.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr P. Tornos (Barcelona, Spain): I understand that you use MRI in all patients with infective endocarditis irrespective of whether they have neurological symptoms or not, is that correct?

Dr Kin: Yes.

Dr Tornos: To my knowledge, there have been other groups that have used systematic MRI in patients with infective endocarditis and, as far as I know, the reasons for surgery do not consider the findings on MRI if the patient is asymptomatic and if the patient’s MRI does not show bleeding complications. In your presentation it seems that these black dots, and I really do not know exactly what they mean, have a prognostic significance. What do you think that these black dots are due to? Do you think that they are really mycotic aneurysm? Have you ever performed angiography just to really better define this lesion?

Dr Kin: A good comment and a good question. This is one of our study limitations. Some authors reported that hypointense spots have been expressed as microbleeds and also have been expressed as a risk factor for cerebral haemorrhage in elderly and hypertensive patients. So we differentiated hypointense spots observed in patients with IE with regard to their location and the background of the patient. We have strongly believed that a black dot is a mycotic aneurysm in a patient with infective endocarditis. However, no aneurysms consistent with the black dots were observed on simultaneously performed MR angiography in this study. Perhaps the reason for
the non-detectability of black dots as aneurysm is because of the small size or we think this aneurysm was thrombosed.

Your recent review paper stated that conventional angiography remained the gold standard and should be performed when non-invasive techniques are negative or suspicion remains. However, we did not perform angiography in this study. So one reason is that in this study a large mycotic aneurysm was not detected in the MRI study. If a large mycotic aneurysm had been detected, we would have to do the angiography. However, for that reason we did not. And also if the size is small, I think there is no indication to treat the patient with mycotic resection or crimping. So that is my answer.