Brain MRI Findings in Neurologically Asymptomatic Patients with Infective Endocarditis


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ABSTRACT

BACKGROUND AND PURPOSE: Neurologic complications in infective endocarditis are frequent and affect patient prognosis negatively. Additionally, detection of asymptomatic lesions by MR imaging could help early management of this condition. The objective of our study was to describe MR imaging characteristics of cerebral lesions in a neurologically asymptomatic population with infective endocarditis.

MATERIALS AND METHODS: One hundred nine patients at the acute phase of a definite or possible infective endocarditis according to the Duke modified criteria and without neurologic manifestations according to the NIHSS were prospectively included. Each patient underwent cerebral MR imaging and MRA within 7 days of admission.

RESULTS: MR imaging showed abnormalities in 78 patients (71.5%). Acute ischemic lesions (40 patients, 37%) and cerebral microbleeds (62 patients, 57%) were the most frequent lesions. Eight patients had an acute SAH, 3 patients had brain microabscesses, 3 had a small cortical hemorrhage, and 3 had a mycotic aneurysm. Acute ischemic lesions mostly appeared as multiple small infarcts disseminated in watershed territories (25/40, 62.5%) and as lesions of different ages (21/40, 52.5%). Cerebral microbleeds were preferentially distributed in cortical areas (362/539 cerebral microbleeds, 67%). No significant correlation was found among lesions, in particular between acute ischemia and cerebral microbleeds.

CONCLUSIONS: Occult cerebral lesions, in particular cerebral microbleeds and acute ischemic lesions, are frequent in infective endocarditis. The MR imaging pattern of acute small infarcts of different ages predominating in watershed territories and cortical cerebral microbleeds may represent a surrogate imaging marker of infective endocarditis.

ABBREVIATIONS: CMB = cerebral microbleed; IE = infective endocarditis; IMAGE-Endocarditis = Resonance Magnetic Imaging at the Acute Phase of Endocarditis

Infective endocarditis is associated with symptomatic neurologic complications in 20%–40% of cases. Among symptomatic complications, ischemic stroke is the most common manifestation, whereas hemorrhagic stroke, brain abscess, cerebral hemorrhage or SAH, and mycotic aneurysms are less frequent. Symptomatic cerebral complications are one of the main prognostic factors in infective endocarditis (IE) because they are significantly associated with a 3-month mortality rate. Symptomatic neurologic complications are difficult to predict and prevent because they mostly occur in the early phase of IE and have been reported as the presenting symptom of the disease in up to 47% of cases.

Asymptomatic cerebral lesions revealed by systematic cerebral CT and/or MR imaging have been recently reported, but their impact on patient care and prognosis has not been completely assessed. Our group showed that detection of cerebral asymptomatic lesions influenced diagnostic decisions in cases of suspected IE.

The purposes of the present study were to extensively describe MR imaging characteristics of cerebral lesions in a neurologically asymptomatic population at the acute phase of IE, to prospectively report their respective frequencies, and to assess correlations between different MR imaging features.

MATERIALS AND METHODS

Patients

One hundred fifty consecutive patients included in the previously published IMAGE-Endocarditis study prospectively underwent...
brain MR imaging for clinically suspected IE according to the Duke modified criteria (On-line Tables 1 and 2)\(^1\)\(^6\) between June 2005 and September 2008.

Among them, 41 patients were excluded because MR imaging was not interpretable or not hardware-archived (n = 15), because the diagnosis of IE was finally excluded (n = 10), or because they had acute neurologic symptoms related to IE at the clinical examination performed before MR imaging (n = 16, NIHSS > 0). Consequently, the population study consisted of 109 patients with definite (n = 84) or possible (n = 25) IE. The local ethics committee approved the study. All patients gave written informed consent.

**Brain Imaging Protocol**

MR imaging was performed on a single Signa HDx 1.5T system (GE Healthcare, Chalfont St. Giles, UK) within 7 days after inclusion in the IMAGE study. We used a standardized protocol, including T1WI, DWI, FLAIR, and T2* sequences.

DWI was acquired with a single-shot EPI spin-echo sequence with TR/TE/TI, 8000/87.6 ms; FOV, 26 × 26 cm\(^2\); matrix, 128 × 128; NEX, two; 5-mm section thickness; and 0.3-mm section gap. The trace images were calculated from 3 diffusion-weighted acquisitions with gradients sequentially applied along each of the 3 orthogonal axes (b = 1000 s/mm\(^2\)). The acquisition parameters of FLAIR were as follows: TR/TE/TI, 8002/158.2/2000 ms; matrix, 320 × 192; NEX, 1; with all other parameters being identical. For the T2* sequence, the parameters were the following: TR/TE, 750/17.3 ms; flip angle, 20; FOV, 24 × 19.5 cm\(^2\); matrix, 416 × 224; NEX, one; 5-mm section thickness; 0.5-mm section gap.

After intravenous injection of contrast medium (gadoterate meglumine, Dotarem; Guerbet, Alnauy-sous-Bois, France), we performed an elliptic centric MRA (TR/TE, 8.6/3 ms; FOV, 24 × 18 cm\(^2\); matrix, 512 × 416; NEX, 0.75; 0.8-mm section thickness; −0.4-mm section gap) and a 3D T1 sequence (TR/TE, 13.1/5.3 ms; FOV, 25.6 × 20.5 cm\(^2\); matrix, 256 × 256; NEX, 0.5; 1.2-mm section thickness; −0.6-mm section gap).

**MR Imaging Analysis**

A standardized form, first tested on an independent sample to collect relevant information, was used to interpret the MR imaging. The 60 initial MR images were reviewed by 2 readers (A.H. and I.K.), with, respectively, 3 and 10 years of experience in neuroradiology, blinded to each other and to patient characteristics. In case of a discrepancy, diagnosis was obtained by consensus. After satisfactory concordance was reached, the remaining MR images (n = 49) were assessed by 1 reader (A.H.).

Acute ischemic lesions were classified as territorial infarcts and small cortical or subcortical lesions. We additionally defined 3 topographic patterns of ischemic lesions: 1) a single lesion including either a territorial infarct, a small cortical lesion, or a small subcortical lesion; 2) multiple lesions associating a territorial infarct and 1 or several small cortical and/or subcortical lesions; and 3) multiple small cortical and/or subcortical infarcts distributed in the watershed territories. The infarct age was defined by using an ADC map, FLAIR, and postcontrast 3D T1 sequences as either “recent,” including acute ischemia (<8 days) with low ADC and subacute ischemia (<3 months) with normalized ADC and contrast enhancement, or “chronic” (>3 months) with high ADC and no contrast enhancement.

Cerebral microbleeds were defined as round T2* hypointensities with a diameter ≤10 mm. We collected their number, size (≤5 or 5–10-mm), localization (cortical including meningeal location, subcortical, or posterior fossa), and signal (homogeneous or heterogeneous).

SAH was defined as linear FLAIR hyperintensities or T2* hypointensities following the shape of cortical sulci. We collected their localization (adjacent to a cerebral microbleed [CMB], acute ischemic or hemorrhagic lesion, isolated), number (single or multiple), and age (acute or chronic).

Parenchymal hemorrhage was detected by T2* and FLAIR sequences. Additionally, a T1 sequence was used to evaluate the age of bleeding.

Cerebral abscess was defined as an expansive lesion with central restricted ADC, peripheral edema, annular enhancement ± T1 hyperintensity, and T2* hypointensity of the abscess capsule. We collected the number (single or multiple), size, and adjacent abnormalities (ischemic lesion or CMB).

Mycotic aneurysms were searched by using a postcontrast 3D T1 sequence and MRA. They were defined by using angiographic criteria described elsewhere.\(^17\)\(^18\) Briefly, each aneurysm had to be either distal (ie, involving segments 2, 3, or 4 of the middle or posterior cerebral artery) or proximal in association with at least 2 other criteria: change in size or morphology on consecutive angiographies, presence of another intra- or extracranial mycotic aneurysm, rupture of the aneurysm, arterial occlusion or stenosis adjacent to the aneurysm, or cerebral infarction at the level of the aneurysm.\(^17\) We added a fusiform shape in angiographic features as a diagnostic criterion.\(^18\) We also collected their number (single or multiple), size, arterial localization, and adjacent abnormalities (ischemic lesion, CMB, SAH, or parenchymal hemorrhage).

Leukoaraiosis was graded with the modified score of Fazekas et al.\(^19\)

**In-Hospital Outcome**

Neurologic examination was performed during the follow-up in the patients who underwent cardiac surgery, to rule out the occurrence of symptomatic neurologic complications.

**Statistical Analysis**

Interobserver agreement was evaluated by using a simple \(k\) coefficient (for binary variables) and a weighted \(k\) coefficient (for ordinal variables).

We described MR imaging data as proportional and effective for qualitative variables and as mean and SD for continuous variables.

We used a \(\chi^2\) test (or Fisher exact test for a sample size of <5) to assess associations between cerebral lesions. Statistical testing was done at the 2-tailed \(\alpha\) level of 0.05. Data were analyzed with the SAS package, Release 9.3 (SAS institute, Cary, North Carolina).

**RESULTS**

**Patients**

Clinical characteristics of patients are summarized in Table 1. The mean age was 59 years, 76% were men, and oral streptococci (25%) and *Staphylococcus aureus* (24%) accounted for half of the cases.
Acute ischemic lesions (pattern 1) classified as a single territorial (87.5%), while 8 patients (8/40; 20%) had a single acute ischemic lesion 3) with multiple acute small lesions distributed in junctional cortical and subcortical arterial territories (n = 25/40; 62.5%), while 8 patients (8/40; 20%) had a single acute ischemic lesion (pattern 1) classified as a single territorial (n = 3), and small cortical and/or subcortical infarcts). All 40 patients presented with supratentorial lesions, and 16 patients (29%) had several acute lesions. Acute ischemic lesions were found in 5 patients with pattern 2 (5/21; 24%) and in 16 patients with pattern 3 (16/21; 76%) (Fig 2).

### Brain Microabscesses

At least one microabscess was found in 40 patients (37%) in the subcortical white matter and basal ganglia (29 patients, 74%) or in the posterior fossa (27 patients, 65%). Sixty-five CMBs (12% of all CMBs) had a heterogeneous signal on T2* sequences. Thirty patients (48.5%) presented with at least 1 CMB with a heterogeneous signal. Twenty-one CMBs (4% of all CMBs) were greater than 5 mm, and 13 patients (20%) had at least 1 CMB of greater than 5 mm. Twenty-one of the 21 CMBs larger than 5 mm (95%) were heterogeneous in signal.

CMBs and ischemic lesions were located in different areas. No CMB was found in watershed territories. Furthermore, no statistical association was found between CMBs and acute ischemic lesions (P = .61), whatever the pattern (P = .68 for pattern 1, P = .11 for pattern 2, and P = .08 for pattern 3). CMBs were not associated with older age (mean age, 58.2 ± 2 for patients with CMBs versus 60.1 ± 2.2 for patients without CMBs; P = .5).

### Acute SAH

Small SAHs were found in 8 patients (7%), adjacent to a mycotic aneurysm in 1. Six patients with SAH (75%) had CMBs, but no statistical association was found (P = .17).

### Small Cortal Parenchymal Hemorrhage

Small cortical parenchymal hemorrhages were found in 3 patients (3%). Two were heterogeneous in signal, appearing hyper- and isointense in T1 and hyper- and hypointense in T2 sequences, consistent with subacute hemorrhage. One of the cortical hemorrhages occurred in a patient with a contralateral mycotic aneurysm. The third patient had a cortical hemorrhagic transformation of subacute ischemia.

### Brain Microabscesses

Three patients (3%) had brain microabscesses that were associated with multiple ischemic lesions and multiple CMBs in 2 patients. One patient had a mycotic aneurysm adjacent to the microabscesses. In 1 patient, microabscesses were also associated with another patient with a mycotic aneurysm adjacent to the microabscesses. In 1 patient, microabscesses were also associated with...
adjacent leptomeningeal enhancement on postcontrast T1 sequences, consistent with meningitis.

**Mycotic Aneurysm**

Three mycotic aneurysms were found in 3 patients (3%), all in distal branches of the middle cerebral artery M3 (n = 1) or M4 (n = 2), confirmed by conventional angiography in 2 cases. They were saclike (n = 2) or fusiform (n = 1). These small aneurysms (1.8, 3, and 3.4 mm in the widest diameter \[mean, 2.4 \pm 0.9 \text{ mm}\]) were detected by postcontrast T1 sequences and postcontrast MRA.

For 2 patients, the mycotic aneurysms also appeared as round susceptibility magnetic artifacts in T2* sequences and DWI. One patient had an acute ischemic lesion systematized to the left superficial Sylvian territory near the mycotic aneurysm, and 1 patient had both acute SAH and microabscesses adjacent to the mycotic aneurysm. In the third patient, the mycotic aneurysm was distant from a contralateral small cortical hemorrhage.

**Old Ischemic Lesions and Leukoaraiosis**

Twenty-nine patients had old ischemic lesions (26.5%), and 42 patients (38.5%) had leukoaraiosis (punctuate, 24 [57%]; early confluent, 15 [36%]; confluent, 3 [7%]).

**In-Hospital Outcome**

Forty-nine patients (45%) underwent cardiac surgery at the acute phase of IE. Among them, 29 (59%) had CMBs, 20 (41%) had acute ischemic lesions, and 15 (30.5%) had both on MR imaging performed before surgery. None of these patients experienced clinically symptomatic cerebral complications after a mean follow-up of 20.3 \(\pm\) 19.4 days.

**DISCUSSION**

In the present prospective study, we report a very high frequency of asymptomatic acute cerebral lesions detected in 71.5% of patients assessed by MR imaging. To the best of our knowledge, the present study is the largest prospective series reporting a comprehensive MR imaging description of asymptomatic cerebral lesions at the acute phase of IE and the first prospective one reporting CMBs in IE. The high prevalence of brain MR imaging lesions reflects both the poor sensitivity of neurologic examinations at the acute phase of IE and the embolic potential of valvular vegetation, larger than that attested to by clinical examination only.

To date, 2 previous prospective studies reported systematic MR imaging findings in patients with IE. In 1 study, the authors evaluated the incidence of cerebrovascular complications by systematic MR imaging in 60 patients with IE. They found that 65% of patients had cerebral lesions. Among them, 30% of patients had silent lesions at MR imaging. In another study of 40 patients, subclinical brain embolisms were reported in up to 48% of patients with left-sided IE. None of those studies reported CMBs or provided an extensive description of MR imaging findings. In the present study, CMBs were the most frequent cerebral abnormalities, in more than half of patients. Although none of the patients had undergone brain MR imaging before the onset of IE, different circumstances suggest a causal relationship between CMBs and IE. First, we reported, in a case-control study including part of the patients in our series, a specific association between CMBs and IE with an odds ratio of 10.06 (95% confidence interval, 3.88–26.07). Moreover, the strength of the association between CMBs and IE increased with the number of CMBs, indicating a causal link. Furthermore, several other reports recently highlighted the occurrence of CMBs in IE.

In IE, characteristics of CMBs seem slightly different compared with CMBs usually described in elderly patients and in cerebrovascular disease; this difference may suggest varying un-
derlying pathologic processes. In patients with IE, CMBs were mostly located in superficial areas and were obviously large and heterogeneous in signal. In a retrospective study of 11 patients, 7 had CMBs, with an increasing number of CMBs in 5 of them in subsequent MRI, suggesting an active process. In a patient in our series, a mycotic aneurysm confirmed angiographically was directly superimposed on a large and heterogeneous cortical CMB. In addition, higher blood inflammatory marker levels (high-sensitivity C-reactive protein, interleukin 6 and 18) have been reported in patients with CMBs compared with those without them, independent of cardiovascular factors, raising the hypothesis that inflammation might be important in the pathogenesis of CMBs. Hence, CMBs in IE may result from a subacute inflammatory microvascular process. The occurrence of intracranial hemorrhage in IE has been recently associated with CMBs, inflammatory microvascular process. The occurrence of intracranial hemorrhage in IE has been recently associated with CMBs, suggesting a vascular vulnerability. In our series, we did not find an association between CMBs and mycotic aneurysms or parenchymal hemorrhage, which may be explained by the fact that our patients were asymptomatic, with few hemorrhagic lesions. In addition, anticoagulation therapy was reduced in patients with >3 CMBs undergoing anticoagulation; this result may partly explain a lack of symptomatic intracranial hemorrhage in our patients with CMBs who underwent cardiac surgery.

Acute ischemia was the second most frequent lesion, found in 36.7% of patients. Multiple watershed ischemic lesions were quite frequent, found in more than half of patients. Additionally, lesions of different ages with coexisting acute and subacute small infarcts were more numerous in those patients. Different patterns of ischemic lesions in IE visualized by using DWI have been previously reported in 367 cases and noninfective endocarditis cases with neurologic symptoms. In this retrospective study, larger ischemic lesions were more prevalent; this feature was consistent among a population of symptomatic patients.

In our study, CMBs and ischemia had different anatomic locations, which may support the different pathophysiology of these 2 types of lesions. The superficial (ie, cortical or meningeal) localization of CMBs in our patients may reflect a preferential mode of entry through the blood-brain barrier at the cortico-pial junction, whereas ischemic lesions result from an artery-to-artery embolic mechanism. CMBs are described as being persistent or transient. Cortical CMBs and multiple small watershed infarcts were the most frequent patterns observed in our large prospective series and could be used as a surrogate diagnostic marker in IE. Indeed, the diagnosis of IE remains difficult at the acute phase despite the use of the Duke criteria. Adding new imaging minor criteria may help in earlier diagnosis and appropriate therapeutic management. Our group recently reported that cerebral and abdominal imaging modified the diagnostic classification of IE and therapeutic plans. Duval et al showed that for 36 of 130 patients (28%), the Duke classification for IE diagnosis and treatment options was modified on the basis of MR imaging findings. Jung et al found that both cerebral and abdominal MR imaging findings affected diagnosis but only cerebral MR imaging affected clinical management plans.

In clinical practice, unenhanced brain CT is mostly used for screening cerebral complications in IE because of its availability and rapidity. In case of suspected mycotic aneurysms, CT angiography has been reported to be comparable with 2D DSA for the detection of cerebral aneurysms. We chose MR imaging as the first-line imaging technique because of a better sensitivity in the detection of small parenchymal or meningeal complications and a high performance in the diagnosis of aneurysms. Additionally, MR imaging was preferentially used to avoid the substantial CT angiography contrast load, which can be of concern in patients with acute cardiac and/or renal failure in IE and/or in those receiving renal toxic drugs such as aminoglycosides.

Our study has several limitations. First, no follow-up imaging was systematically performed in our study. Therefore, the evolution of the detected lesions and the impact of cardiac surgery and anticoagulation of the extracorporeal circulation on their occurrence and/or evolution could not be assessed. Second, because no systematic conventional angiography was performed, some mycotic aneurysms could have been undiagnosed. However, minimally invasive techniques now have a more important role in the diagnosis of cerebral aneurysms. Indeed, MRA is highly accurate for the detection of cerebral aneurysms with the sensitivity of postcontrast MRA and 3D time-of-flight MR angiography reported to be, respectively, 95%–100% and 82%–96%. Finally, some patients considered neurologically asymptomatic may have had subtle neurologic manifestations that could be masked by cardiovascular deficiency and septic syndrome in the context of acute IE. Indeed, in the study of Singhal et al of 36 patients with endocarditis with neurologic symptoms, 75% with small disseminated acute ischemic lesions on DWI had nonspecific encephalopathy symptoms. In our study, the absence of focal neurologic symptoms was verified by a standard neurologic examination (NIHSS), but without further analysis of neurocognitive functions.

**CONCLUSIONS**

Systematic MR imaging detects asymptomatic cerebral lesions in IE with a high prevalence. The radiologic description of cerebral lesions highlighted cortical CMBs and small watershed ischemic lesions as the most frequent pattern in this population. Further prospective studies are needed to evaluate the diagnostic accuracy of such MR imaging findings as surrogate criteria for IE diagnosis. Moreover, follow-up of patients is needed to assess the clinical relevance of brain MR imaging lesions to neurocognitive-func
tional disorders, quality of life, and prognosis.

