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ORIGINAL ARTICLE

Is brain angio-MRI useful in infective endocarditis management?

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Abstract In infective endocarditis (IE), brain magnetic resonance imaging (MRI) is helpful to diagnose clinically silent neurological events. We assessed the usefulness of systematic early brain MRI in IE diagnosis and medico-surgical management. Over a period of 1 year, all patients admitted in one of the three hospitals participating in and fulfilling the Duke criteria for definite or possible IE underwent cerebral MRI within 7 days of IE suspicion. Eight panels of experts analyzed the records a posteriori. For each case, one record with and one record without the MRI results were randomly assigned to two panels, which determined the theoretical diagnosis and treatment. Paired comparisons were performed using a symmetry test. Thirty-seven brain MRIs were performed within a median of 5 days after inclusion. MRI was pathological in 26 patients (70 %), showing 62 % microischemia and 58 % microbleeds. The expert advice did not differ significantly between the two evaluations (with or without the MRI results). The therapeutic strategies determined diverged in five cases (13.5 %). Diagnosis differed in two cases (5.4 %), with an upgrading of diagnosis from possible to definite IE using MRI results. Early brain MRI did not significantly affect the IE diagnosis and medico-surgical treatment plan. These results suggest that systematic use of early brain MRI is irrelevant in IE. Further studies are necessary to define whether MRI is mandatory in IE management within a multidisciplinary approach, with particular attention paid to better timing and the subset of patients in whom this imaging examination could be beneficial.

Introduction

Despite improvements in therapy, infective endocarditis (IE) still carries a high risk of mortality [1–5]. Cerebral

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lesions are frequent, with an incidence rate ranging from 10 to 65 % [5, 6]. Recent data suggest that neurological failure is a major determinant for short-term prognosis [2]. Considering the occurrence of subclinical neurological damage [7, 8], some studies have suggested performing neuroimaging for all IE patients, even those without clinical neurological symptoms [9–12]. Moreover, neuroimaging diagnosis is recommended within a few days after IE suspicion [13, 14], given the high risk of embolism and neurological worsening during the first week of antimicrobial therapy [15, 16]. Since brain magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT), this examination appears to have greater value in detecting cerebral microlesions [17]. Most lesions that go undetected on CT and warrant systematic MRI are cerebral microbleeds (CMBs) and widespread microinfarcts [18]. Diffusion-weighted echo planar imaging (DWI) and gradient recalled echo (GRE) sequences are especially used in this field [13, 19].

Providing early and precise neurological embolic status, MRI may influence therapeutic plans [12] and lead to a faster surgical decision [9, 20]. Actually, although there is clear agreement for urgent surgery for patients with poor hemodynamic tolerance, embolic events remain a controversial indication for surgery [21, 22]. The risk factors of embolic events are well known: *Staphylococcus aureus* infection [23], even more so in a mitral location, large (>10 mm) and highly mobile vegetation, other systemic embolisms [11, 12, 15]. Several studies have shown that early surgery prevents recurrent embolic events and decreases mortality for these patients [11, 24–26]. Moreover, cardiac surgery can be safely performed after silent cerebrovascular complications [16, 27, 28]. In this way, brain MRI fit into a complete imaging check-up could lead clinicians to change the surgical strategy with regards to the indication for cardiac surgery and the timing of valve replacement [12].

Additional information provided by cerebral MRI may also impact IE diagnosis [12]. Although small ischemic lesions, such as peripheral manifestations of IE, upgrade the Duke classification, the role of CMBs remains unclear. These small hemorrhage foci have a strong association with IE [7], with a specific distribution in cortical areas [7, 19]. The value of this phenomenon as pyogenic vasculitis [20] may indicate the infection severity [19]. As an IE feature, CMBs may be considered a new minor imaging criterion [19].

Overall, few studies have analyzed the influence of microischemia and CMBs on decision-making in IE. IE guidelines are still mainly based on expert opinion [22]. The aims of this study were: (1) to evaluate the usefulness of systematic early brain MRI in IE therapeutic management and (2) to assess the brain MRI outcome on the diagnosis of IE according to the Duke modified classification.

Patients and methods

Study design

An observational prospective multicentric study was conducted at the Grenoble University Hospital and at the Annecy and Chambery General Hospitals (France). IE patients underwent brain angio-MRI within 7 days of diagnosis. Whole records, with or without the MRI results, were randomly assigned to panels of experts. Theoretical diagnosis and treatment were defined a posteriori by the panels. The protocol was approved by the local ethics committee (Comité d'Éthique des Centres d'Investigation Clinique de l'inter-région Rhône-Alpes-Auvergne, IRB number 6705).

Population

Between November 2013 and November 2014, adult patients with definite or possible IE according to the Duke criteria were eligible for the study. After confirmation of the diagnosis by an infectious disease specialist or a cardiologist and in patients with no absolute contraindications for MRI, brain MRI was quickly performed.

Inclusion criteria were as follows: definite or possible IE with at least one major Duke criterion (evidence of endocardial involvement, repeated positive blood cultures), brain MRI within 7 days of IE suspicion, and written consent.

Patients were excluded if they had undergone emergency cardiac surgery during the first 24 h after diagnosis, if they underwent surgery before MRI, or if initial IE care was provided in another hospital where more than 1 week of adapted antibiotic treatment was received.

Data collection

Data were collected at inclusion and during hospitalization. Chest, abdomen, pelvis, and brain CT as well as transthoracic and/or transesophageal echocardiographies were performed, as clinically indicated. After discharge, follow-up care was organized with an infectious disease specialist by a consultation at 3 months. In cases of missing data, the information was collected by calling the patient's general practitioner.

MRI

The following type sequences were included in a standardized protocol: axial DWI, axial FLAIR, axial T2 GRE, axial or sagittal T1, axial or sagittal T1 3D with gadolinium injection, intracranial time-of-flight MRI angiography, and with gadolinium. Cerebral MRI was reviewed by an experienced neuroradiologist.

Evaluation criterion

Eight multidisciplinary panels of three experts (an infectious diseases specialist, a cardiologist, and an intensivist) met a posteriori. The patient data, with or without MRI results, were randomly assigned to one panel of experts. Experts reviewed the patient's entire medical history, as well as the biological and imaging results. Completing a standardized questionnaire, panels established the diagnosis and the best medico-surgical treatment for each case. Treatment was supposed to be determined based on available guidelines [22]. The panels were blinded for actual care.

Statistical analysis

Continuous variables were presented as median and 25th–75th interquartile ranges (IQRs). Categorical variables were presented as numbers and percentages.

A paired comparison of the expert advice on strategies was performed using asymptomatic tests for symmetry and marginal homogeneity. The exact McNemar test was used for two-by-two tables and the exact Stuart–Maxwell test was used for three-by-three tables [29].

Statistical analysis was done with Stata 12 software. A p-value <0.05 was declared as being statically significant.

Results

Study population and MRI findings (see Tables 1 and 2)

Assessment of treatment by panels of experts (Table 3)

Analyses of the experts' advice showed eight differences in IE treatment in five patients (13.5 %).

Variations in surgical strategies concerned one indication (no surgery with the MRI results), one variation in the choice of prosthesis, and three variations in the timing of surgery. Accurately, out of the 12 patients for whom surgery was retained, the timing of surgery differed in three cases, i.e., one postponed and two earlier surgeries based on the MRI results.

Medical treatment differed in three cases: anticoagulant therapy in two cases and antimicrobial therapy in one case (addition of rifampicin with the MRI results).

Assessment of diagnosis by panels of experts (Table 3)

The IE diagnosis was upgraded in two cases (5.4 %) from possible to definite IE when the panels had knowledge of the MRI results.

Table 1 Patient characteristics and clinical features

	N = 37 or (median)	% or (IQR)
Age	71	(66–81)
Men	21	57
IE risk factors		
Prosthetic material endocarditis	11	30
Underlying heart disease	16	43
Diabetes/immunodepression/cancer	31	85
Charlson comorbidity index	(5)	(3–6)
Definite IE (Duke criteria)	26	70
Clinical presentation		
Cardiovascular or respiratory failure	13	36
Prolonged fever (>15 days)	12	32
Neurological symptoms	11	30
Neurological complications at 3 months	7	23
SOFA[a] score at admission	(2.2)	(0–3)
Intensive care transfer within 24 h of diagnosis	10	27
EuroSCORE[b]	(14)	(11–17)
Positive blood culture/valvular cultures	26	70
Microorganism identified	33	89
Staphylococci	15	41
Streptococci	15	41
Enterococci	2	5
Healthcare-associated IE	10	29
Echocardiography data		
Vegetation	30	81
Mobile vegetations	17	77
Vegetation length[c] (mm)	10	5–14
Cardiac abscess or valvular perforation	7	21
Surgical care		
Cardiac surgery	10	27
Time from inclusion to surgery (days)	(8)	(6–59)
Death at 3 months	6	16
Cardiovascular or neurologic failure	2	34
Disease recurrence	2	7

[a] Sequential Organ Failure Assessment

[b] Valvular regurgitation was assessed semiquantitatively from 0 to 4

[c] Length was considered at zero for patients without vegetation

Discussion

The experts' treatment decisions differed in 13.5 % of the cases in light of the MRI results. The experts changed the diagnosis for only two patients (5.4 %). This study is the second prospective study in this field: regarding these results and our clinical experience, early MRI seemed difficult to position within an appropriate IE management algorithm.

In the literature, this approach had already yielded advice arguing in favor of the use of MRI: a recent

Table 2 Angio-MRI data

	N = 37 or (median)	% or (IQR)
Duration from diagnosis to MRI (days)	(5)	(3–7)
MRI abnormalities	26	70
MRI lesions without neurological symptom	8	31
Ischemia	16	62
Ischemia: territorial lesion	1	6
Ischemia: punctiform lesions	15	94
Hemorrhage	4	15
Microbleeds	15	58
Microbial aneurysm	1	4
Brain abscess	1	4
Others	5	19

French trial conducted on 130 IE patients demonstrated that MRI findings changed the plans in 28 % of patients [9]. Precisely, excluding CMBs and solely based on MRI results, Duval et al. found 14 % surgical plan adjustment. In this study, the methodology differed since a pair of experts established the IE strategy 24 h before and 24 h after MRI results were received and the decisions were compared. The experts may have overestimated the usefulness of MRI because of a confirmation bias. In the present study, panels were blinded for the opinion of the other groups and the results are probably more reliable.

Certain considerations could provide explanations for these results.

Because of the risk of neurological worsening due to extracorporeal circulation, intraoperative hypotension, and anticoagulant use [9, 20], the appropriate timing for surgery remains controversial and is team-dependent. The earlier surgery policy in our referral center could explain the minor role of MRI in this study. Moreover, new European guidelines [22] incite to prevent recurrent embolisms and support the routine use of early valve replacement before the end of the first week of antimicrobial treatment in cases of isolated large vegetation (15 mm) or in the presence of a 10-mm vegetation following one or more clinical or even asymptomatic embolic events [15].

Nonetheless, making an early decision for surgery remains difficult. A multidisciplinary team should discuss the risk–benefit ratio and the period of surgery in litigious cases, with

Table 3 Main results

Difference between indication for surgery, type of prosthesis, and choice of curative anticoagulation						
	With MRI				Discordance rate	*p*-Value
Without MRI	Surgery					
			Yes	No	2.7 %	>0.99
		Yes	11	1		
		No	0	25		
	Bioprosthesis					
			Yes	No	2.7 %	>0.99
		Yes	10	1		
		No	0	26		
	Curative anticoagulation					
			Yes	No	5.4 %	>0.99
		Yes	19	1		
		No	1	16		
	High cerebral diffusion antibiotic addition (rifampicin)					
			Yes	No	3.7 %	>0.99
		Yes	0	0		
		No	1	26		
Difference regarding timing of surgery						
	With MRI				Discordance rate	*p*-Value
Without MRI		Emergency[a]	Urgent[b]	Postponed	27.7 %	>0.99
	Emergency[a]	4	2	0		
	Urgent[b]	1	3	0		
	Postponed	0	0	1		
Expert diagnosis according to Duke criteria						
	With MRI				Discordance rate	*p*-Value
Without MRI		Definite	Possible	Excluded	5.4 %	>0.99
	Definite	23	0	0		
	Possible	2	9	0		
	Excluded	0	0	3		

[a] Within 24 h after diagnosis

[b] After 48 h of antibiotic treatment

regards to the risk of fatal embolic recurrence and the risk of cardiac surgery [30]. The role of comorbidities must be considered. Thus, a randomized study comparing conventional treatment and early valve replacement revealed that, for patients with large vegetation, early surgery decreases the composite end point of death and embolic events by declining embolism. In this trial, patients were young with a low surgical risk. MRI should perhaps be more beneficial for this subgroup of patients [24].

The discovery of silent lesions might also impact diagnosis. Since the Duke criteria have some limitations in clinical practice [15], IE diagnosis is frequently delayed, inducing progression of systemic damage. The diagnosis is even more difficult because echocardiography can be negative in around 5–10 % of cases, mostly for intracardiac device IE, prosthetic valve IE, or preexistent severe valvular lesions [31]. The identification of cerebral microlesions (microinfarctions, microabscesses, and CMBs) as minor criteria in the Duke classification may allow upgrading the diagnosis. In the prospective IMAGE study, solely based on MRI results, they upgraded the IE classification in 51 % of cases from non-definite to either definite or possible IE [12]. In the present study, the diagnosis changes prompted by MRI were modest, as demonstrated by the low interobserver discrepancy.

However, using highly sensitive cerebral imaging, CMB detection should become an additional diagnosis marker, given that these non-pathognomonic IE lesions have a specific endocarditis pattern [19, 27, 32] and indicates tissue damage [33, 34]. In the same way as positron emission tomography, CMBs may represent IE activity [31]. In this study, a high brain parenchyma diffusion drug was added in one case of *Staphylococcus* endocarditis with CMBs. This reflects the fact that, sometimes, clinicians consider CMBs like microabscess. New approaches for elucidating the role of these common lesions are necessary.

Study limitations

The availability of MRI was not always guaranteed and the small sample size is the major weakness of this study. Secondly, a small number of centers in the same region may not be representative of all current cardiac surgery and antimicrobial IE strategies.

Conclusion

To date, the usefulness of early brain MRI remains unclear and should not be systematically included in an endocarditis management algorithm.

Yet, when available, it should be preferred to CT, especially for severe and/or young IE patients, for a clearer embolism risk stratification that is mainly useful in making the decision for early surgical intervention. This examination may also be indicated in cases of doubt on IE diagnosis. Other advantages of MRI must be taken to account: non-irradiation and, above all, non-iodine injection have to be considered in these frail patients who often have renal failure. With practical experience, this sensitive examination can be done even in critically unstable patients.

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Compliance with ethical standards

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