



Infective endocarditis neurological complications: a serie of cases and literature review

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Abstract: After hemodynamic complications, neurological consequences from infective endocarditis are the second leading cause of death. The majority of these are caused by hemorrhagic or ischemic cerebrovascular events. In almost 40% of cases, they are the first to appear or show up within the first week of admission. In about 70% of patients, they take place prior to receiving antibiotic therapy. The most frequent neurologic consequence is a stroke. Hemorrhagic consequences can result from an ischemic stroke that has hemorrhagic transformed, or from vascular necrosis that ruptures an artery and can progress to mycotic aneurysms. Treatment is based on treating the symptoms and the underlying cause, using early antibiotic therapy tailored to the type of germ and whether or not a valve prosthesis is present. The timing of cardiac surgery following a neurological event should be discussed in light of any associated brain damage; however, a number of recent studies have shown that valve replacement surgery is feasible without significant risk during the acute phase of an ischemic stroke, with the exception of large ischemic lesions or significant cerebral hemorrhage. Nonetheless, cooperation with a neurovascular pathology-focused neurologist is crucial. We have outlined the epidemiological, physiopathological, clinical, paraclinical, outcome, and therapeutic aspects of infective endocarditis complicated by brain injury through our series of 19 patients and in light of data from the literature.

I. INTRODUCTION

Infective endocarditis (IE) is a serious septicemia frequently complicated by neurological damage which represents the 2nd cause of mortality after hemodynamic complications [1]. These are most often cerebrovascular complications secondary to the migration of fragments of vegetation (complete or transient ischemic strokes, cerebral hemorrhages), infectious complications (cerebral abscesses, meningitis) and non-specific complications (encephalopathies, convulsions, headaches) [1]. These neurological events are frequently subclinical. They are symptomatic in 15 to 30% of cases, they must be sought for any sign of neurological focalization or disturbance of consciousness [2]. Stroke is the second leading cause of death after congestive heart failure. The prognosis is strongly influenced by the type of cerebromeningeal lesions and the resulting clinical manifestations. Thus, it is essential to diagnose these complications, to know their prognosis, to know how to predict them, to prevent them and to adapt our care according to their presence [1]. Cerebral mycotic aneurysm represents the cause of most cerebral hemorrhages [2]. Early diagnosis and adequate antibiotic therapy are of major importance to prevent the occurrence of neurological embolization [3]

II. RESEARCH METHODOLOGY

We conducted a retrospective study of infective endocarditis (IE) complicated by neurological localisations over a period of 4 years (2017-2020), within the cardiology department B of the Ibn SINA Maternity hospital center in RABAT, MOROCCO. We collected all the medical records of patients with IE during this period, and we gathered information only from patients presenting IE with neurological complications. According to the new Duke criteria, all patients in our study presented definite IE. Neurological complications were classified into: ischemic stroke, hemorrhagic stroke, meningitis and brain abscess. Cardiac imaging and neuroimaging data were recorded.

Inclusion criteria: Patients, men and women of all ages, hospitalized for a neurological event secondary to infective endocarditis.

Exclusion criteria:

- Patients hospitalized for infective endocarditis without neurological embolic complications
- Patients hospitalized for a neurological event secondary to a non-endocarditic cause

The retrospective analysis was carried out by collecting data from the register of cardiology department B and the clinical files of the patients. It was reported; on operating sheets; the different anamnestic, clinical, paraclinical, therapeutic and evolving parameters of patients.

III. RESULTS

1- Age and sex:

We collected 114 cases of IE, 19 of which (16.6%) were complicated by neurological involvement. The average age is 44 years (a maximum of 68 years and a minimum of 19 years) with a male predominance of 68.4%.

2- Clinical presentation

Most patients presented poor oral dental condition and 3 patients reported recent dental care. When it is identified, the entry point is cutaneous (4 patients), digestive (1 patient) and urinary (1 patient).

An infectious syndrome with deterioration of general condition was common at admission. 7 patients presented disorder of consciousness (1 abscess, 1 subarachnoid hemorrhage, 1 ruptured mycotic aneurysm and 4 strokes). Hemiparesis was found in 4 patients, hemiplegia with dysarthria in 5 patients and notion of convulsive seizure in one case. Heart failure was noted in 3 patients. Four cases of IE had the neurological complication during the first week of antibiotic therapy and 2 cases during the second week. The neurological complication had already occurred before hospitalization in 13 cases (68.4%). In 73.6% of cases (14 patients) the neurological complication was present before the start of antibiotic therapy with an average of 34 days.

In three cases (15%), the complication occurred during the first 2 weeks of antibiotic therapy. 2 patients in our study were neurologically asymptomatic.

3- Bacteriology

Blood cultures were positive in 68% of cases (13 patients), with identification of a streptococci in 6 patients, a staphylococcus in 7 patients (table 1)

Blood culture was negative in 6 patients, one of whom had candida albicans on a mouth swab as well as on his ECBU.

4- Cardiac Doppler ultrasound:

100% of AEs concerned the left heart. In this series of patients, the oslerian graft occurred on a native valve in 73.6% of cases (14 patients), and on a prosthetic valve in 2 cases. The notion of congenital heart disease was found in 3 cases.

The vegetations were visible in most patients (89.4%). In 71.4% of cases they were mobile with an average of 15.4mm in diameter. The mitral location was the most frequent (14 cases = 73.6%), and the aortic location in 2nd position (11 cases = 57.8%) (Fig 1A, B, C). Vegetations were also found on the cords, the interventricular septum, the tricuspid valve and the initial aorta in one case each.

Local complications were marked by valvular perforation in 4 patients, an abscess in 4 cases, CIV and cord rupture in one patient case. Mitral regurgitation was noted in 68% of cases (13 cases), and aortic regurgitation in 42% of cases (8 cases) (Fig 1D). Most patients did not present left ventricular dysfunction (17 cases).

5- Brain imaging:

All our patients underwent CT brain. A brain MRI was performed in 5 patients (26%), and revealed 3 cases of ischemic stroke with microbleeding in 2 patients and 2 cases of cerebral mycotic aneurysm.

Ischemic stroke was found in 68% of cases (13 cases) with the notion of hemorrhagic transformation in 4 patients (Fig 2A).

A cerebral mycotic aneurysm was observed in 26.3% of cases (5 patients). 4 patients presented a ruptured cerebral mycotic aneurysm (the right sylvian artery: 2 cases, branch of the right middle cerebral artery: 1 case), and unruptured right parasagittal cerebral microaneurysms in a single case (Fig 2C, D). Only one patient presented proximal vasculitis of the left sylvian trifurcation and the anterior cerebral artery with subarachnoid hemorrhage (Fig 2B).

A brain abscess was discovered in 21% of cases (4 cases): frontal abscesses (2 cases), left parietal and temporal (1 case) and occipital (1 case) microabscesses (Fig 2E)

6- Treatment

a- Antibiotic treatment:

All patients received antibiotic therapy as soon as the diagnosis was suspected and after blood cultures were taken. The average treatment duration is 6 weeks. In only one case, the combination of antifungal and antibiotic therapy was necessary given the clinical, biological and radiological context of the patient.

b- Surgical treatment:

No surgical treatment is carried out urgently (within a few days <7 days) nor in extreme urgency (within 24 hours).

Uncomplicated patients underwent surgery after completing the recommended duration of antibiotic therapy (5 patients). They were transferred to the cardiovascular surgery structures immediately after the end of the antibiotic treatment. 4 patients underwent double mitro-aortic replacement with tricuspid plasty and only one patient had an aortic valve replacement with CIV closure.

Three patients underwent surgical treatment for an uncontrolled infection after three weeks of antibiotic therapy with a significant embolic risk and 2 patients for severe acute valvular regurgitation.

Neurologically, a patient who presented a ruptured mycotic aneurysm without indication for cardiac surgery underwent neurosurgical insertion of a clip.

7- Evolution

The evolution of our patients was marked by the clinical-biological improvement which was obtained in 11 patients.

Intrahospital mortality before surgery was 42%, which illustrates the very poor prognosis of the pathology. 3 patients died from septic shock secondary to an uncontrolled infection, 3 patients from cerebral involvement and 2 patients from intracerebral hemorrhage.

All patients who underwent cardiovascular intervention progressed well. The notion of relapse was not noted in any case.

IV. DISCUSSION

The main central nervous system complications of IE are ischemic embolic stroke, cerebral hemorrhage, meningitis, and brain abscesses.

These complications result from two mechanisms: embolism of a vegetation in the cerebral circulation which causes a suppurative lesion if the embolus is septic or a purely ischemic lesion if the embolus is non-septic [4]. The second mechanism is secondary to the toxin or immunological effects induced by germs, sepsis, the neurotoxicity of certain antibiotics thus leading to encephalopathy of variable severity, ranging from confusional syndrome to coma, particularly in IE caused by *Staphylococcus aureus* [5].

The incidence of clinically expressed neurological complications varies depending on the series between 10 and 35%, these differences being undoubtedly explained by recruitment biases. The most recent data from the international collaborative group ICE report an incidence of cerebral embolic events of 17%, among 2791 patients included in the cohort [2]. This incidence is much higher in patients admitted to intensive care for IE, reaching 37% in a series of 228 patients [6]. In a prospective study recently conducted in France, this incidence even exceeds 60%. In our series, the frequency of neurological complications was 14.8%.

Neurological complications are clinically inaugural in more than 40% of cases or appear in the first week following admission in approximately one in three cases [3]. They occur before any antibiotic therapy in more than 70% of patients according to the study by Heiro et al [5], which is similar to the figures from our study (66.6%). The inaugural nature explains the relative stability in the frequency of neurological manifestations for several decades, to the extent that it is then very difficult to prevent them [7]. They generally occur in a context of left IE, isolated right IEs are not complicated by cerebral embolic events [8,9]. None of our patients presented right-sided IE.

Neurological complications do not appear to be more frequent in patients with prosthetic valve IE; they mainly concern “late” AEs occurring one year after valve replacement, which was the case in only one patient in our series [10,11].

Bleeding complications are more common with mechanical prostheses than with bioprostheses due to effective anticoagulation [13]. Thus, the risk of hemorrhagic transformation of ischemia seems particularly high in patients on effective anticoagulation at the time they develop an IE [14].

In a study by Thuny and al. [15] cerebral tomography revealed 22% of embolic neurological events, 4% of which were silent. These complications appear more frequent in studies that used brain magnetic resonance imaging (MRI) given the greater sensitivity of diffusion sequences compared to CT. Thus, the MRI study by Snygg-Martin et al. [16] reveals 65% of neurological events, 30% of which are silent, associated with the diagnosis of infective endocarditis. In our series, 33.3% of neurological complications were diagnosed on brain MRI.

Across the literature, approximately half of the neurological complications of AEs are ischemic stroke linked to emboli from vegetations. In our study, they represented 66.6% of neurological complications. Symptomatic ischemic stroke is reported in 10 to 35% of AEs. The clinical consequences depend on the size of the embolus and the affected territory. Thus, more than 40% of embolic events in the central nervous system affect the territory of the middle cerebral artery [11,17]. In a study by Pruitt AA et al, the incidence of cerebral emboli was more frequent in cases of left mitral than aortic endocarditis [18]. *Staphylococcus aureus*, *Streptococcus gallolyticus* (formerly *Streptococcus bovis*) represent the bacteria most frequently found in IE with cerebral embolization [19], as well as mycoses which are responsible for large vegetations [20]. A patient in our series presented multiple ischemic stroke with a voluminous vegetation on transthoracic echocardiography with a cauliflower appearance on the mitral valve.

10 to 30% of neurological complications are intracranial hemorrhages [3,5,11,21]. They are secondary; either the hemorrhagic transformation of an ischemic stroke which represents the leading cause of mortality from intracranial hemorrhage [22] and is directly linked to the size of the infarct [23]; or the rupture of a vessel by necrotizing arteritis which often occurs in a context of acute IE due to *staphylococcus aureus* [3]. It is clinically characterized by neurological focalization signs of sudden onset and which can be preceded by transient or established embolic events [24,25]. The progression of necrotizing arteritis can lead to mycotic aneurysms which can subsequently rupture.

Rupture of a mycotic aneurysm (MA) is a rare entity that represents less than 10% of neurological complications of IE [21,26]. They can be asymptomatic and discovered incidentally. AMs most often develop distal to the cerebral arteries, particularly at the level of the bifurcations of the MCA [27]. In 18 to 25% they are multiple and bilateral [27,28]. Posterior location is very rare and only a few cases have been recorded [27]. In a series of 17 patients with 29 AM, only one patient had an aneurysm in the superior cerebellar artery [27].

Meningitis complicates 2 to 20% of AEs [10,13,25]. Any *Staphylococcus aureus* meningitis occurring outside of a neurosurgical context should raise suspicion of an AE. During IE, the passage of germs into the cerebrospinal fluid occurs through a vascular breach by necrotizing arteritis, by rupture of an aneurysm or a micro-abscess. In these cases, the CSF is not purulent, and the presence of germs is often fleeting.

V. CONCLUSION

Neurological accidents constitute a frequent and often serious complication of IE. Although they are often indicative of the disease, some of them can be prevented by initiating rapid antibiotic therapy and performing urgent valve surgery in patients at very high risk. Their occurrence can have numerous consequences, particularly on the indication and timing of valve replacement surgery. Contrary to popular belief, a stroke does not contraindicate valve surgery if it is recommended, except in cases of significant cerebral hemorrhage or extensive ischemic lesions. In all cases, collaboration with a neurologist specializing in neurovascular pathology is essential.

COMPETING INTERESTS

The authors declare no competing interest.

Tables and figures

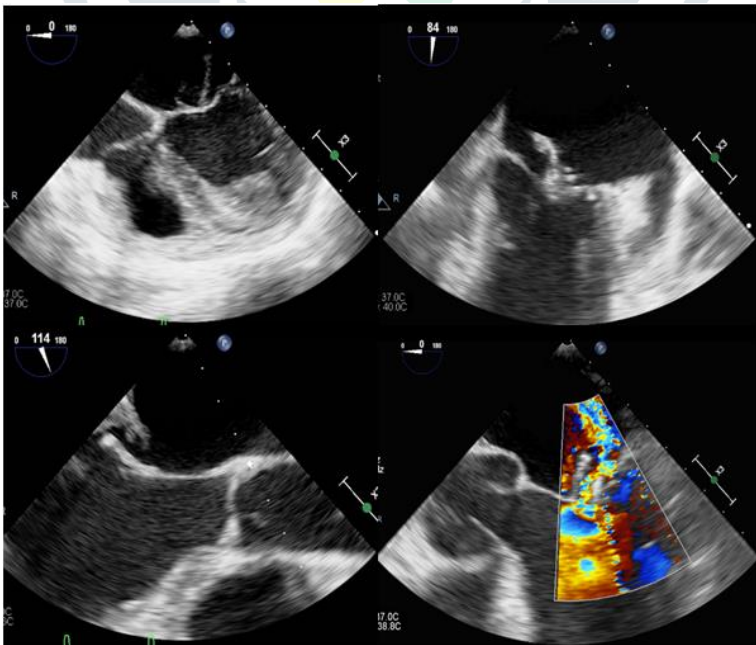
Table 1: bacteriological profile of our series

	streptococcus mitis multisensible	Streptococcus sp�cie	streptococcus anginosus and streptococcus acidominimus	Streptococcus agalaciae (streptocoque group B)	staphylocoque coagulase n�gatif	Staphylococcus aureus	Untyped Streptococcus
Number of patients	1	2	1	1	4	3	1

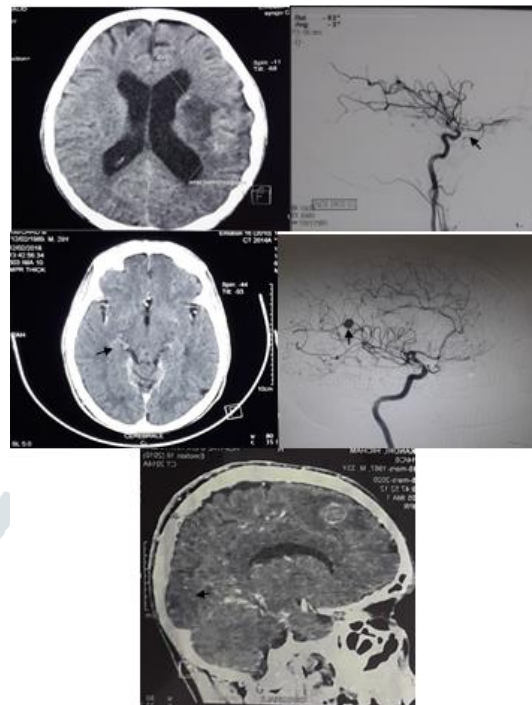
Table 2: evolution of patients in our series

Evolution of patients	Number of patients
Good progress under antibiotic therapy alone	5
Good progress under antibiotic therapy with cardiac surgery	5
Death before cardiac surgery	5
Relapse of IE	0
Neurosurgical procedure	1
Clipping of a ruptured cerebral AM	

Figure 1: Echocardiographic images of IE cases in our series.



- A: Echocardiographic image showing 2 mobile vegetations on the mitral valve, the largest measuring 18 mm
- B: Echocardiographic image showing one of the mobile vegetations on the mitral valve, the largest measuring 17mm
- C: Echocardiographic image showing a 7mm mobile vegetation on the aortic valve
- D: Cardiac color Doppler image showing significant mitral regurgitation on IE of the mitral valve

Figure 2: Brain imaging of neurological complications of IE cases in our series

- A: CT image of a left temporoparietal ischemic stroke with hemorrhagic infarction.
- B: Angiographic appearance of proximal vasculitis predominant in the left ICA.
- C: CT image of right parasagittal microaneurysm
- D: Angiographic appearance of a distal cerebral aneurysm on the right Sylvian artery.
- E: CT image of a right frontal brain abscess.

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