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CENTRAL NERVOUS SYSTEM INFECTIONS (K BLOCH, SECTION EDITOR)

Neurologic Complications of Infective Endocarditis: Recent Findings

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Abstract
Purpose of Review The purpose of this paper is to provide recent insights in management of neurologic complications of left-sided infective endocarditis (IE).
Recent Findings Cerebral lesions observed in IE patients are thought to involve synergistic pathophysiological mechanisms including thromboembolism, sepsis, meningitis, and small-vessel cerebral vasculitis. Brain MRI represents a major tool for the detection of asymptomatic events occurring in the majority of patients. The latter can impact therapeutic decisions and prognosis, especially when cardiac surgery is indicated. In patients presenting with neurologic complications, surgery could be safely performed earlier than previously thought.
Summary Symptomatic cerebral ischemic or hemorrhagic events occur in 20–55% of IE patients, whereas asymptomatic events are detected in 60–80% of patients undergoing systematic brain MRI. Management of such patients requires an experienced multidisciplinary team. Recent studies suggest that early cardiac surgery, when indicated, can be performed safely in patients with cerebral ischemic events. Other important issues include the appropriate use of anti-infective and anti-thrombotic agents, and endovascular treatment for mycotic aneurysms. Altered mental status at IE onset, which is associated with brain injury, is a major determinant of short-term outcome.

Keywords Infective endocarditis · Ischemic stroke · Brain hemorrhage · Neuroimaging · Cardiac surgery · Cerebral vasculitis

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Introduction

Infective endocarditis (IE) is a severe disease associated with high mortality rates. Neurologic complications are the most frequent extra-cardiac complications of left-sided IE, occurring in 20 to 55% of patients [1, 2]. They contribute to a poor prognosis, including an increased mortality and morbidity from disabling sequelae [1, 3]. Neurologic complications may impact diagnosis and therapeutic plans, particularly in patients requiring emergent cardiac surgery.

Many questions on the pathophysiology and natural history of neurologic events during left-sided IE are still unanswered. Cerebral embolism from vegetations may not be the only mechanism involved in cerebrovascular complications.

The initial management of patients with IE includes early identification of patients at risk for developing new or recurrent neurologic events, an accurate evaluation of those complications with appropriate neuroimaging tools, and the identification of optimal timing of cardiac surgery, when indicated [4••]. Additional important points include the management of anti-infectious agents, anti-thrombotic agents (anti-coagulants, anti-

platelet therapy), and endovascular therapy in acute brain infarction, and specific therapy for mycotic aneurysms. A multidiscpilinary management by an expert team is of paramount importance to improve outcomes in such patients [4••, 5].

The aim of this review is to provide recent insights and perspectives in management of neurologic complications of endocarditis.

Epidemiology and Outcomes of Neurologic Events in IE

The prevalence of neurologic complications reported in different studies depends on the severity of illness, and on the inclusion of non-symptomatic events detected only by systematic brain imaging. Recent studies conducted in patients admitted to the ICU with severe IE reported a prevalence of 55% of neurologic complications at admission [2, 6]. Recent studies conducted with use of systematic brain MRI at hospital admission reported an incidence of neurologic complications in up to 80% of patients [7]. The main risk factors for neurologic events in severe IE patients include infection with *Staphylococcus aureus*, large vegetations measured on echocardiography (> 10 mm), mitral valve involvement, and non-neurologic embolic events [1, 2, 8].

Cerebrovascular events (i.e., brain infarction, transient ischemic attack, intracranial hemorrhage, cerebral microbleeds (CMB), and subarachnoid hemorrhage) represent more than 65% of neurologic complications [2, 8]. Brain infarction is the most frequently observed complication, occurring in 60 to 80% of cases. Although embolic complications can be the presenting symptom of IE, these often occur during the first week of antibiotic therapy. In contrast, infectious complications, i.e., abscesses and meningitis seem to be less common, occurring in 1 to 20% of cases [9, 10] (Fig. 1d). A recent cohort study compared patients with primary bacterial meningitis to patients with bacterial meningitis secondary to IE. Brain ischemic (38 vs 22%) and hemorrhagic (13 vs 2%) events were significantly higher in patients with coexisting IE and meningitis. They had less favorable outcomes, with increased disability (62 vs 39%) and mortality (29 vs 18%) rates [9].

More than two-thirds of patients admitted to the ICU with neurologic manifestations of IE either die or have residual neurologic sequelae [2]. Altered mentation at IE onset represents a major predictor of mortality in IE, irrespective of its underlying mechanism [11•]. Symptomatic brain infarction and hemorrhage are determinants of poor outcome and mortality, unlike silent neurologic events [8, 12]. Non-neurological predictors of poor prognosis include septic shock and multiorgan failure, vegetation size ≥ 15 mm, and prosthetic mechanical valve IE [11•, 13]. Early cardiac surgery is independently associated with improved outcome, irrespective of severity at ICU admission. A recent randomized controlled study conducted in patients with acute left-sided IE and severe valve regurgitation found that early surgery, performed within 48 h, was associated with a significant reduction in the composite endpoint of embolic events or death at 6 weeks [14].

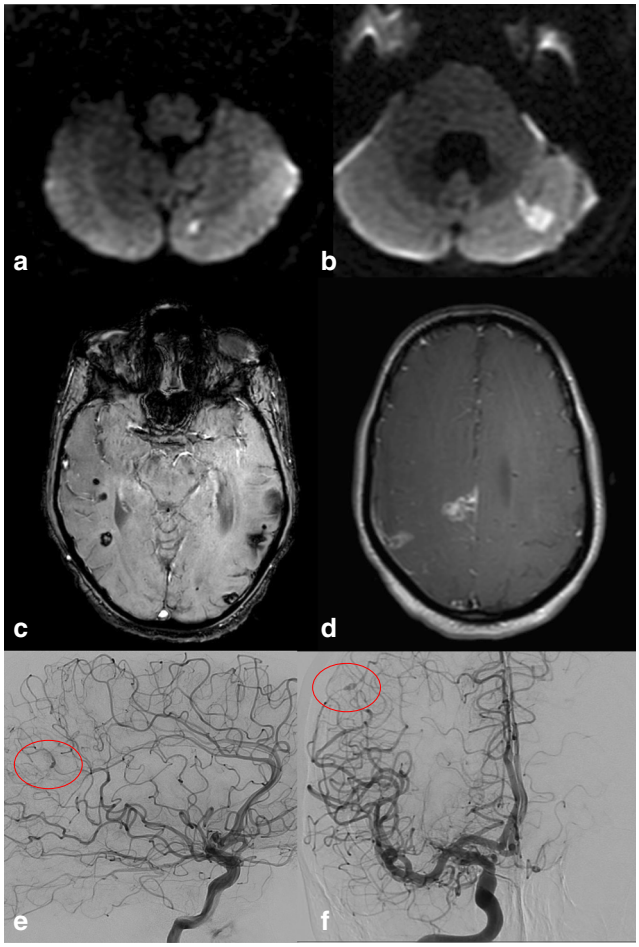

Fig. 1 Ischemic, hemorrhagic, and infectious cerebral complications in a 40-year-old patient with mitral valve endocarditis due to *Streptococcus salivarus*. **a** and **b** Diffusion-weighted MRI showing multiple hyperintensities corresponding to recent cerebellar infarctions. **c** Susceptibility-weighted imaging showing hypointensities corresponding to deep and superficial microhemorrhages (or cerebral microbleeds), associated with subarachnoid hemorrhages due to a ruptured mycotic aneurysm (non-visible on MR angiography), and hemorrhagic transformation of an ischemic lesion. **d** Gadolinium-enhancing T1 lesions corresponding to cerebral abscesses. **e** Mycotic micro-aneurysm located in a distal segment of the left middle cerebral artery. **f** Mycotic micro-aneurysm located in a distal segment of the right middle cerebral artery

The onset of neurologic complications in IE patients remains a serious issue, whose management and diagnosis are challenging.

Pathophysiology of Neurologic Complications of IE

Septic embolism from vegetations is commonly accepted as the main mechanism responsible for the observed brain lesions in IE.

In fact, others hypotheses are debated, including cerebral small-vessel vasculitis, mediated by autoimmune or *vasa vasorum* embolic processes occurring after the embolic phase [15–17]. The radiological brain lesion pattern in IE patients is similar to those observed in cerebral vasculitis, e.g., central nervous system primary vasculitis [18–21]. The latter is described as the coexistence of cortical CMB, microabscesses, and small ischemic lesions, located in multiple vascular territories and of different ages. However, this non-specific pattern is observed in other small-vessel diseases. Arterial wall enhancement detected on cerebral imaging might strongly support the vasculitis hypothesis, and future imaging studies in existing animal models of infective endocarditis would be of interest.

Interestingly, central nervous system primary vasculitis is thought to be triggered by infections, and secondary CNS vasculitis is most commonly associated with infections. Moreover, it has been reported that, in *S. aureus*-related IE, uncontrolled sepsis is risk for developing diffuse vasculitis [22]. Systemic inflammation related to bacteremia in IE may act as the trigger of small-vessel cerebral vasculitis and subsequent neurologic complications. Post-mortem histopathological cerebral studies in IE patients and experimental studies on brain lesions in pigs with IE support this hypothesis, reporting the same lesion pattern with extensive pyogenic arteritis associated with septic emboli [23–26].

Hemorrhagic lesions may involve other complex mechanisms. One third of brain hemorrhages are actually hemorrhagic transformation of ischemic lesions. Regarding CMB, recent clinical data from MRI studies report their presence in more than 50% of IE cases [7, 15]. Physiopathology hypotheses for CMB include endothelial injury and blood-brain barrier leakage after septic embolism leading to small-vessel rupture, coagulopathy and erythrocytes stasis, and vasculitis with segmental arterial wall disorganizations of the small cerebral arteries [27, 28]. Interestingly, CMB are also described in patients with mechanical valves (without IE), supporting a possible link between CMB and thromboembolism from valvular lesions, without any associated infection [29].

Few data are available on the pathophysiology of meningitis occurring in the setting of IE. Above-mentioned studies suggest that meningitis in IE patients may increase the risk of cerebral ischemic and hemorrhagic events. Brain infarction is a well-described complication of bacterial meningitis, whereas hemorrhages are rarely observed [9, 10]. However, some studies suggest a higher risk of cerebral bleeding in patients on anti-coagulant therapy presenting with IE and secondary meningitis [30]. Interestingly, cerebral vasculitis, responsible for ischemic and hemorrhagic lesions, is associated with infectious diseases including meningitis and IE. Bacteremia, valvular infection, and meningeal reaction in IE patients, may all trigger cerebral vasculitis.

All these findings support the hypothesis of a synergistic combination of thromboembolism from valvular damage, meningitis, and small-vessel cerebral vasculitis triggered by additional sepsis, to generate a distinctive pattern of neurological lesions in IE.

Brain MRI Brings New Perspectives in Management of IE

The prevalence of neurologic complications is difficult to estimate because of asymptomatic events. In the literature, symptomatic neurologic events are observed in 10 to 40% of patients with IE [1, 7]. Conversely, asymptomatic events detected on brain MRI are present in 60 to 80% of patients. Consequently, about one third of embolic events would be clinically silent [17, 31, 32•, 33].

The most frequent observed patterns on brain imaging include acute ischemic lesions and CMB [2, 15] (Fig. 1a, b, c). To identify such complications, brain CT scan is often the initial imaging because it is easily available and highly sensitive for the detection of brain hemorrhages and large ischemic stroke [34]. However, ischemic lesions in IE are characterized by small, multiple, and disseminated infarctions. Recent studies highlighted the superiority of MRI, which is more sensitive than CT in IE patients with neurologic symptoms. This holds true for both the detection of clinically symptomatic events (100 versus 81% of patients, respectively), and of additional asymptomatic events (50 versus 23% of patients, respectively). In two prospective studies, MRI results impacted diagnosis or therapeutic plans in up to 28% of patients [7, 31]. In fact, the use of systematic brain MRI in IE may improve prognostic assessment and aid in decision making, especially for cardiac surgery indication and timing [32•].

Embolic events are significantly associated with worsened long-term mortality [11•]. A few studies suggest that patients with symptomatic and asymptomatic embolism had similar long-term mortality [33, 35]. Conversely, others found higher survival rates in patients with asymptomatic embolism than in patients with symptomatic events or without neurologic complications. These results are thought to be related to a higher rate of surgery in patients with asymptomatic embolism, suggesting a protective role of valve replacement, guided by systematic MRI [32•]. Taking into account recent literature, the detection of asymptomatic events may induce substantial changes in prognosis assessment and therapeutic decisions. The current guidelines of the European Society of Cardiology recommend routine brain imaging and valve replacement in all patients presenting embolic event (symptomatic or silent) with large vegetations persistence [4••].

Systematic brain MRI in IE patients represents a necessary approach for future studies, to assess the determinants of neurologic complications. A recent study found that each millimeter increase in vegetation length was associated with a 10% increase in the rate of ischemic lesions detected on brain MRI [36].

Right Timing of Cardiac Surgery in Patients with Neurologic Complications

Valve replacement surgery is required in about 50% cases during the acute phase of IE and is associated with a reduction of embolic events and mortality rates [14]. Current indications for cardiac surgery include heart failure (severe acute regurgitation or obstruction with refractory pulmonary edema or signs of poor hemodynamic tolerance), uncontrolled infection (locally uncontrolled infection, persistent fever or positive blood cultures > 7 days, or difficult-to-treat pathogens), and prevention of embolism (in patients with large vegetations, after one or more embolic events despite appropriate antibiotic therapy or other predictors of complicated course).

In patients with neurologic complications, the optimal timing of surgery remains controversial. On the one hand, cardiopulmonary bypass and anti-coagulation required during valve replacement can be responsible for neurologic deterioration, as a consequence of infarct or hematoma growth, hemorrhagic transformation, or new ischemic and/or hemorrhagic lesions [37]. On the other hand, IE patients with a delayed surgery strategy are exposed to heart failure and recurrent cerebral embolism that are associated with increased morbidity and mortality.

In older studies, early surgery (i.e., performed within 2 to 4 weeks following IE diagnosis) performed in patients with moderate to severe brain infarction, or brain hemorrhage, was associated with perioperative neurologic deterioration and higher mortality [8]. Recent cohort studies suggest that early surgery (i.e., performed within 1 week following diagnosis) in IE patients with ischemic stroke is not associated with increased perioperative complications or mortality [38, 39•]. Studies conducted with systematic brain MRI before surgery suggest that brain infarction is present in 55 to 63% of patients [16, 37]. Preoperative acute ischemic lesions detected on MRI did not predict postoperative complications, which occurred in < 4% of cases. In sicker patients requiring ICU admission, no association between timing of surgery and mortality could be determined [11•, 37, 40•]. In the same way, the risk of postoperative neurological deterioration resulting from the exacerbation of hemorrhagic lesions seems relatively low, even in IE patients who underwent valve surgery within 2 weeks of hemorrhage onset [41•, 42].

Above-mentioned conclusions need to be carefully analyzed, considering the variability in early surgery timing definitions (7 days or 14 days), and the retrospective nature and small samples of some studies [37, 40•]. Although statistically insignificant, a recent retrospective study found that early surgery (i.e., performed within 2 weeks following neurologic event) was associated with lower mortality rates in patients with brain infarction, unlike those with brain hemorrhage, who had higher mortality rates [43]. For these reasons, experienced multidisciplinary team (intensivists, cardiac surgeons, cardiologists, infectious diseases specialists, neurologists, neurosurgeons) should assess individual benefit-risk to determine the right timing of cardiac surgery in IE patients with neurologic complications, through the help of the current guidelines. The latter include the 2015 recommendations from the European Society of Cardiology (ESC), the American Heart Association (AHA), and the Society of Thoracic Clinical Practical Guidelines [4••, 44, 45••]. Except for patients with imminent risk of death, delay of 4 weeks is recommended for major neurological injury due to ischemic stroke, or hemorrhagic strokes. No delay for surgery can be considered if neurologic events are minor or asymptomatic, to manage heart failure, uncontrolled infection or abscess, high risk of embolism, or recurrent systemic embolism or stroke.

Imaging and Specific Therapies for Mycotic Aneurysms

Hemorrhages account for 12 to 30% of neurological complications observed in IE patients [1, 2, 8]. They may be the consequence of ruptured infectious intracranial aneurysms (mycotic aneurysms) (MA). In a recent meta-analysis, 72% of patients with MA had hemorrhages (subarachnoid (22%), intraparenchymal (28%), and intraventricular (5%) hemorrhage) [46]. MA correspond to arterial dilatations caused by septic emboli. Bacterial invasion of the arterial wall, local inflammatory responses, and pulsatile pressure on the vessel wall lead to aneurysmal dilatation. MA are observed in 2 to 4% of IE patients, and detected in 5 to 15% of those with neurologic symptoms [33, 47]. In fact, their overall prevalence remains difficult to quantify because the diagnosis of asymptomatic unruptured MA, located in small distal vessels, is sometimes challenging.

Brain vascular imaging is indicated in every patient with IE presenting with intracranial hemorrhage, to rule out a ruptured MA. Conventional cerebral angiography is thought to be much more sensitive than non-invasive neuroimaging (CT or MRI), particularly for detection of small MA (< 3 mm) [47] (Fig. 1e, f). Nevertheless, in recent studies, the absence of hemorrhage on non-invasive imaging provides a strong negative predictive value for the presence of MA. [48]. The sensitivity of multislice CT angiography has been reported to be 100% for large MA (> 13 mm) and 90.6% for medium-size MA (5–12 mm) [49]. However, as small aneurysms may not be identified with non-invasive imaging, conventional angiography remains the gold standard for the detection of MA. Considering these data and risks of the procedure, conventional angiography might be reserved for patients with evidence of hemorrhage on non-invasive imaging.

Given the lack of evidence-based data due to the rarity of MA, there are no current recommendations to guide clinicians in management. Ruptured MA should be immediately secured by surgical or endovascular approach. In such cases, cardiac surgery is often delayed. For unruptured MA, the literature supports a medical approach. In fact, MA may be resolved with antibiotic therapy. Surgical or endovascular treatment should be considered in case of persistent MA despite directed antibiotics, or if cardiac surgery is indicated [1]. Some authors suggest an endovascular approach prior to cardiac surgery, which should not be delayed. The decision-making process should take into account the risk of rupture, based on symptoms, size, location, growth rate, and anatomic characteristics of MA. Smaller MA may be monitored by clinical and imaging follow-up, wherever possible since MA are dynamic lesions [47]. Assessing medical practices is difficult, due to the heterogeneity of the studies. In a meta-analysis, surgical management was performed in 45% versus an endovascular approach in only 17% of patients. Overall, 5% of patients died prior to surgical or endovascular intervention, 12% died following intervention, 20% had neurological decline, and 62% had favorable outcome after intervention [46]. Progress is needed in MA detection and management to improve outcome.

Antibiotic Therapy and Neurologic Complications

Early appropriate antibiotic therapy is the cornerstone of IE management. Of note, the incidence of neurologic events appears to be dramatically reduced 2 weeks after antibiotic initiation [8, 50]. Significant neurotoxicity may occur in patients treated with high-dose beta-lactams, especially in older patients with renal failure [51]. A recent study monitored therapeutic drug concentrations in patients treated with oxacillin 12 g/day for severe staphylococcal infections, and revealed overdosed plasma concentrations in more than 80% of cases. Oxacillin overdose contributed to significant neurological deterioration during antibiotic therapy, in the form of delirium or coma [52]. In this regard, monitoring plasma concentrations of beta-lactams during IE treatment may be necessary in case of unexplained neurologic symptoms (i.e., deterioration of mental status or non-convulsive seizures). The presence of neurologic complications does not modify the recommended antibiotic regimens except in patients who develop *S. aureus* brain abscess requiring the use of molecule with high cerebral diffusion (rifampin, fluoroquinolones).

Uncertainties about Anti-thrombotic Therapies

There is scant data regarding the management of anti-coagulation in IE patients with mechanical valve and neurologic complications. Decisions must consider the need for embolism prevention, versus the risk of brain hemorrhage progressing or hemorrhagic transformation of ischemic lesions. European guidelines suggest that unfractionated or low molecular weight heparin should replace oral anti-coagulation for 1 to 2 weeks in patients with ischemic stroke, or with high risk of neurologic lesion. Interruption of anti-coagulation is recommended in case of brain hemorrhage, and should be reinitiated as soon as possible [4••]. In case of indicated cardiac surgery in patients with brain lesions, some authors prefer bioprosthetic to mechanic valves to not extend the duration of anti-coagulation [53].

Thrombolysis is not recommended in IE patients presenting with acute ischemic stroke, because data on efficacy and safety are few, contradictory, and based on case reports [54]. Thrombectomy could be an alternative in selected patients [55], but no data are currently available in IE patients.

Decisions on anti-thrombotic therapies may be discussed on a case-by-case basis with a multidisciplinary experienced team for IE patients presenting with brain lesions.

Conclusions

Neurologic complications of left-sided IE, mainly consisting of ischemic or hemorrhagic events, are frequent and associated with poor outcomes. Pathophysiology may involve synergistic mechanisms leading to neurologic events, including thromboembolism form vegetations, sepsis, meningitis, and cerebral vasculitis. Asymptomatic neurologic lesions may be identified in the majority of patients through radiographic screening, and may impact prognosis and therapeutic plans. Systematic brain MRI on all patients with IE should be considered, especially before cardiac surgery. Recent studies suggest that early cardiac surgery, when indicated, can be performed safely in patients with cerebral ischemic events. Many other important points remain debated in IE patients presenting with neurologic complications, including optimal anti-infectious therapy, use of anti-thrombotic therapy, and the management of intracranial mycotic aneurysms. Management of such patients requires a multidisciplinary experienced team for decisions made on a case-by-case basis.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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