

Neurologic Complications of Infective Endocarditis

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Infective endocarditis has few pathognomonic clinical or laboratory features; typically, the diagnosis is made relatively late compared to the onset of valvular infection.¹ This delay may be associated with end-organ septic embolization before antimicrobial treatment can be instituted. Complications of infective endocarditis are documented in up to 60% of patients and are thought to result from a delay in diagnosis.² Although cardiac abnormalities such as valvular dysfunction, arrhythmia, and congestive heart failure are the most frequently encountered sequelae of endocarditis, neurologic complications occur in approximately 20% to 40% of this population.³ Generally, neurologic manifestations such as ischemic or hemorrhagic stroke, meningitis, encephalopathy, or microabscesses⁴ are accepted indicators of poor prognosis in patients with infective endocarditis, and mortality rates as high as 58% have been reported.⁵

We present a patient with infective endocarditis whose course was complicated by the development of a spontaneous subdural hematoma secondary to a ruptured mycotic aneurysm. This unusual but significant result of septic embolization occurs in 4% to 10% of patients with infective endocarditis and challenges the clinician with decisions beyond the selection and duration of antibiotic therapy.^{6,7}

CASE PRESENTATION

History

A 63-year-old man presented in the emergency department with complaints of new onset generalized weakness that gradually worsened over the previous 48 hours. Five days before presentation, the patient had been discharged from the hospital after evaluation for intermittent hematuria, which was attributed to bladder stones. During that admission, a transthoracic echocardiogram was performed to define the significance of a newly detected systolic heart murmur. It was

noted that the mitral valve leaflets were thickened, but no vegetations were observed. The patient did not have any diagnostic procedures that warranted endocarditis prophylaxis while he was hospitalized.

Previously, the patient had been diagnosed with coronary artery disease and hypertension. His family and social history was unremarkable. His routine medications included aspirin, metoprolol, furosemide, and lorazepam.

Physical Examination

On examination, the patient was pale and anxious, and he appeared his stated age. He was agitated and was oriented only to person and place. His oral temperature was 37.5°C (99.5°F). Supine blood pressure was 120/80 mm Hg with a heart rate of 76 bpm, which changed to 90/78 mm Hg with a heart rate of 108 bpm when he was placed in an upright position. The patient had a regular heart rate and rhythm. A grade 3/6 holosystolic murmur was noted at the right fifth intercostal space and radiated across the precordium. His motor strength and sensory perception were intact. Cranial nerves functioned normally and no focal neurologic deficit could be defined. The remainder of the physical examination revealed no further abnormalities.

The patient's hemoglobin concentration and hematocrit were measured at 7.5 g/dL and 23.4%, respectively. His hemoglobin level 5 days earlier (during his previous hospitalization) was 9.7 g/dL. An electrocardiogram

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showed no significant changes since the patient sustained an inferior myocardial infarction 6 years earlier. The chest radiograph was free of active disease. To further evaluate his continued agitation and change in mental status, a computed tomographic (CT) scan of his brain was obtained but no abnormalities were identified.

Clinical Course

The patient was given the provisional diagnoses of worsening anemia and sepsis, and he was admitted to the hospital. Cultures of urine, blood, and cerebrospinal fluid (CSF) were acquired. Broad spectrum antibiotics were instituted. On the third day of his hospitalization, blood cultures grew *Streptococcus intermedius* that was sensitive to penicillin G. A transthoracic echocardiogram was performed and compared with his earlier study. Vegetations approximating 0.9 cm in diameter were now evident on both leaflets of the mitral valve. With the diagnosis of infective endocarditis confirmed, the antibiotic coverage was modified to include penicillin and an aminoglycoside.

Despite appropriate antibiotic coverage, the patient's cardiac function deteriorated with the development of pulmonary edema and hypoxemia. Endotracheal intubation and mechanical ventilatory support were necessary. On the tenth day of hospitalization, an abrupt deterioration in his mental status was observed. CT scan of his brain was repeated and a new subdural hematoma was identified in the right frontotemporal area. Neurosurgical consultation established a working diagnosis of acute subdural hematoma secondary to a ruptured mycotic aneurysm. The patient was transferred to another facility for cerebral and cardiac angiography in anticipation of cardiac surgery and neurosurgery. The patient, however, died prior to the planned surgical intervention.

DISCUSSION

Embolization from endocardial vegetation explains most of the neurologic complications of infective endocarditis. In all major studies, the mortality rates in infective endocarditis complicated by a central nervous system event are significantly higher than in infective endocarditis patients without neurologic involvement.⁷ Interestingly, most neurologic complications are already evident on admission to the hospital or develop early in the hospital stay.⁸ In recent reports, 27.6% to 47% of patients with infective endocarditis presented with neurologic manifestations as the first clinical indication of endocarditis.^{7,9} The decrease in neurologic complications following the correct diagnosis of endocarditis is likely due to stabilization of the vegetations

during the healing process.¹⁰ Only 24% of all neurologic complications occurred after the start of antibiotic therapy.⁷ By the same token, recurrent neurologic complications following treatment are distinctly uncommon.⁸ The exception is rupture of a mycotic aneurysm, which can occur months or years after the treatment of endocarditis.

Risk Factors

The risk factors for major embolic events and neurologic complications have traditionally centered on the presence and size of vegetations, the site of involvement, and the infecting organism. Before the use of transesophageal echocardiography, it was proposed that patients with visible vegetations on transthoracic echocardiogram had a higher likelihood of cerebral embolization than patients without visible vegetations.¹¹ With the better visualization of the valves provided by transesophageal echocardiography, there is now some suggestion that the size of the vegetation may be of importance. Although there is no consensus, some investigators believe that patients who have vegetations larger than 10 mm in diameter experience more frequent embolic events than those patients with vegetations smaller than 10 mm.^{11,12}

The impact of the infected valve site on the frequency and prognosis of cerebral embolization and neurologic complication is contested. In one study, a combined infection of both mitral and aortic valves had a higher frequency of embolization than did either valve site alone.⁷ Earlier studies suggested that the risk of developing neurologic complications was greatest for mitral valve endocarditis,¹³ whereas others found aortic valve endocarditis to be more troublesome.¹⁴ Not surprisingly, other investigators could not determine a difference in the incidence of neurologic complications between the two left-sided valves.³ This issue remains to be settled.

There is, however, little controversy regarding the importance of the infecting organism. *Staphylococcus aureus* endocarditis is more likely to lead to cerebral embolism and neurologic complications than other pathogens. It follows then that in most studies, *Staphylococcus aureus* is the pathogen for endocarditis that is most strongly associated with patient mortality.^{5,8,15}

Neurologic Complications

The most common neurologic occurrence is an ischemic or hemorrhagic stroke resulting from mechanical occlusion of cerebral arteries by the septic embolus. As might be expected, such emboli usually involve the middle cerebral artery tree, leading to cortical lesions.

In addition to being the most common neurologic complication, cerebral embolism also has the poorest prognosis. In an early study, 37 of 84 patients (44%) with infective endocarditis and neurologic complications sustained an embolic stroke and 30 of the 37 (81%) subsequently died in the hospital.¹³ This high mortality remains unchanged today, and most cerebral artery septic embolism with ischemic stroke is fatal.^{16,17}

Less common neurologic sequelae of infective endocarditis are multiple small embolic lesions that typically lodge in the supratentorial gray-white junction. These lesions present less dramatically than cerebral embolism with ischemic stroke and may be clinically silent. The majority of these microdeposits lead to meningitis or brain abscesses that are characterized by slowly progressive focal neurologic deficits.

Subarachnoid hemorrhage is the most dramatic neurologic complication of infective endocarditis. Fortunately, it is rare, as is subdural hematoma. Subarachnoid hemorrhage is associated with the rupture of a mycotic aneurysm³ and usually is seen during the early phase of infective endocarditis.¹³ Nevertheless, rupture of the mycotic aneurysm has been reported months to years after the valvular infection has been cured.

Diagnosis

Suspicion of a neurologic complication of endocarditis should be raised when headache, change in mental status, or neurologic defect develops in a septic patient. By the same token, a careful cardiac examination in a patient with new onset neurologic findings is imperative because neurologic findings may be the first clinical sign of endocarditis. After the history and physical examination are complete, additional support for the diagnosis of a septic embolism may be found in CSF analysis and neuroimaging. When examined, the CSF analysis is likely to reveal evidence of inflammation with an elevated protein and a low glucose level.¹⁸ A CSF polymorphonuclear cell content indicates endocarditis caused by virulent organisms such as *Staphylococcus aureus*. Less virulent organisms, such as viridans streptococci, usually are accompanied by an aseptic or normal CSF cellular profile.¹³

The standard initial modality for neuroimaging is CT. Cortical lesions are typically categorized into 4 patterns: infarct, parenchymal hemorrhage, nodular or ring enhancing lesions, and nonenhancing lesions.¹⁹ The identification of isolated, ring enhancing lesions in the white matter is thought to be a valuable indication of septic embolization. The presence of intracerebral hemorrhage suggests that the patient should undergo additional investigation for mycotic intracranial aneurysm in the form of cerebral angiography. The role of magnetic

resonance imaging in suspected neurologic complications of infective endocarditis is still emerging.²⁰

Treatment

With the exception of a ruptured mycotic aneurysm, treatment for the neurologic complications of infective endocarditis consists of antimicrobial therapy and general supportive measures as dictated by the individual's clinical presentation. Management of angiographically demonstrated mycotic aneurysms is dependent upon the presence or absence of hemorrhage, the anatomic location of the aneurysm, and the clinical course of the patient.¹³ Healing and resolution of mycotic aneurysms have been documented during the course of effective intravenous antibiotic therapy in up to 80% of patients, so neurosurgical intervention is not necessary in all such patients.^{21,22}

Patients with valvular disease may require anticoagulation for atrial fibrillation. Anticoagulation should be discontinued at the first indication of neurologic complication because this therapy is strongly associated with death caused by neurologic damage.^{7,23} Most investigators believe that anticoagulation can be safely restarted after the septic phase of the disease is resolved.

Issues regarding the necessity and timing of elective surgery in the patient with neurologic complications and infective endocarditis are still being resolved.⁷ It is not clear that early valve surgery prevents neurologic complications in patients with vegetations visualized by echocardiography.^{7,11,12} Once the neurologic complication has occurred, most investigators agree that recurrent cerebral embolization is uncommon with controlled infection and would not move to early valve replacement.^{8,24}

Emergent cardiac surgery is dictated by valvular competency, and neurosurgery by the consequences of intracranial hemorrhage.²⁴ Because all patients who undergo valve surgery during acute endocarditis will require anticoagulation, these patients should be radiographically imaged to exclude the possibility of a mycotic aneurysm.⁷

CONCLUSION

In summary, mortality is significantly increased in infective endocarditis patients with neurologic complications. Delay in the diagnosis of infective endocarditis contributes to the development of neurologic complications. Although some delay in diagnosis seems inevitable as nearly half of neurologic complications present prior to the diagnosis of infective endocarditis, a high index of suspicion with appropriate diagnosis and

treatment with antibiotics is critical in reducing the frequency and impact of central nervous system septic embolization.

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