Central Nervous System Complications of Infective Endocarditis

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The frequent association between central nervous system symptoms and infective endocarditis (IE) has been recognized for more than a century since it was first described by Sir William Osler. However, important changes in the natural history of infectious endocarditis have occurred in recent decades. The introduction of antimicrobial agents, the increase of age of onset, and a change in frequency of the most common infective agents are among some of the factors responsible for this change. In addition, at the same time that rheumatic heart disease has become less frequent, other underlying cardiac conditions have been recognized as important nidoses of infection, namely, mitral valve prolapse, mitral annulus calcification and calcific aortic valve, and congenital cardiac wall defects. This pattern has been seen in large series of patients with IE and neurologic complications. IE should be suspected in the presence of fever, cardiac murmur, and a neurologic deficit. However, the diagnosis can be particularly difficult because of the similarity with other conditions, the nonspecific character of the symptoms, and sometimes the long latency of valve infection. The diagnosis of IE requires a high index of suspicion supported by echocardiography and blood cultures for confirmation. On the other hand, head CT scan and MRI have improved the recognition of neurologic complications, particularly stroke, occurring in this condition. Despite the introduction of antimicrobial agents and the changing etiologic spectrum, the frequency of neurologic complications in IE has remained unchanged. Three large studies published in the last three decades reported an incidence of neurologic complications between 27% and 39%. A neurologic complication was the presenting symptom of IE in 12–17%. A

Clinical Manifestations

Central nervous system complications occurring in the setting of IE are of three types: 1) cerebrovascular (TIA, stroke, and mycotic aneurysms), 2) infectious (meningitis and abscess), and 3) nonspecific (encephalopathy, seizures, and headaches).

Cerebrovascular Complications

Stroke is the most common neurologic complication occurring during IE. In two pre-CT scan retrospective studies of patients with native valve IE, cerebral embolism occurred in 11.4% to 17%, whereas in two retrospective post-CT scan studies embolism to the brain or eye occurred in 19% and 18% of patients.

Cerebral embolism occurring within 2 weeks of the onset of IE is associated with Staphylococcus aureus, enterococci, or Escherichia coli, tends to be multiple, develops prior to antibiotic treatment, and carries a poor prognosis. Embolism beyond the second week is associated with streptococcal infection and is usually single. Studies comparing the relation between valve involvement and the risk of embolism report different results. One study found an association between mitral valve involvement and the risk of stroke, while another found that the risk was similar regardless of the valve involved. In another series the incidence of embolism among patients with native (17.6%) and prosthetic valve IE (24.1%) was similar. Recurrent ischemic strokes during the acute illness are rare, occurring in 2.7% of patients, at a rate of about 0.3% per day and usually before antibiotic treatment is begun. TIAs prior to the final stroke have been reported in 5.3% and 27.2% of patients.

Intracranial hemorrhage, either intracerebral or subarachnoid, is another type of cerebrovascular complication which occurs in 2.7–7% of patients with IE. Intracranial hemorrhage has traditionally been linked to rupture of a mycotic aneurysm. However, documented cases of mycotic aneurysm by angiography or autopsy are relatively rare among large
clinical series of patients with IE, accounting for only 0.3–1.8% of cerebrovascular complications.\textsuperscript{10,13–15} An analysis of 17 patients with IE and intracranial hemorrhage showed that aneurysm was present in only two. The underlying mechanism in the remaining cases was a hemorrhagic infarct or septic necrosis of the arterial wall.\textsuperscript{16}

Development of mycotic aneurysm was associated with infection with \textit{S. aureus} or streptococci in one study, and 50% had clinical evidence of embolism prior to aneurysmal rupture.\textsuperscript{15} The association of intracerebral hemorrhage and \textit{S. aureus} IE has also been described by other authors.\textsuperscript{16} However, a review of 68 cases with autopsy or angiographically proven aneurysm found that clinical evidence of embolism was present in only 23%. Furthermore, development of mycotic aneurysm was not associated with any single type of microorganism or underlying cardiac condition when compared with 147 patients with IE but no clinical evidence of aneurysm.\textsuperscript{9}

\textbf{Infectious Complications}

Acute meningitis, defined as an elevated white blood cell count in the cerebrospinal fluid (CSF), has been reported in 1.8–16.5% of patients with IE.\textsuperscript{13–15} The wide variation in CSF results depends greatly on the number of lumbar punctures performed. CSF cultures were positive in 15.9%\textsuperscript{15} to 26%,\textsuperscript{13} and the most common microorganism isolated was \textit{S. aureus}. The remaining cases were classified as aseptic meningitis, and the relation to previous antibiotic treatment was unsettled.

Brain abscess is relatively rare, accounting for 1–4% of neurologic complications in patients with IE.\textsuperscript{13–15} Most cases have a rapid course and are associated with \textit{S. aureus} infection. Surgical drainage is rarely indicated since abscesses are often microscopic and multiple in number.\textsuperscript{15}

\textbf{Nonspecific Complications}

Encephalopathy, which has been reported in 1.3–8.5% of patients with IE,\textsuperscript{13–15} has been attributed to microembolism with resultant microinfarcts or microabscesses.\textsuperscript{15}

Seizures, either focal or generalized, occur in 0.5–11% of patients with IE and rarely are the sole neurologic manifestation of IE.\textsuperscript{13–15} Most often, seizures are associated with other neurologic complications, such as stroke, meningitis, and encephalopathy, or occur in patients with a prior history of convulsions and multiple metabolic or iatrogenic factors, such as treatment with high doses of intravenous penicillin.\textsuperscript{14,15}

Headache was the only neurologic complaint in 2.2–3.6% of patients with IE.\textsuperscript{13,14} Isolated headache can occur in brain abscess or with an elevated CSF white blood cell count.\textsuperscript{13} However, in most cases headache has a temporal relation to fever and clears after antibiotic treatment is started.\textsuperscript{14} Severe unremitting headache in the setting of endocarditis should always raise the suspicion of a ruptured mycotic aneurysm and requires investigation with head CT scan or lumbar puncture.

\textbf{Diagnosis}

\textbf{Microbiology}

Comparison of earlier series of IE with those published in recent decades shows an increased number of patients infected with Group D streptococcus whereas \textit{Streptococcus viridans} has become less frequent.\textsuperscript{3,4} Although any single type of microorganism may be responsible for IE, several studies have described an increased risk of neurologic complications in general\textsuperscript{10,13} and stroke and hemorrhage in particular\textsuperscript{16} with \textit{S. aureus} infection.

\textbf{Echocardiography}

Although vegetations detected by echocardiography\textsuperscript{17} and mitral valve involvement\textsuperscript{15} have been linked with the risk of cerebral embolism, one large clinical series failed to confirm this.\textsuperscript{19} In one study comparing the frequency and type of neurologic complications in patients with native and prosthetic valve IE, there was no difference between the two groups.\textsuperscript{13} It is not known if recent diagnostic procedures such as transesophageal echocardiography will provide any additional clinical information.

\textbf{Head CT Scan and Magnetic Resonance Imaging}

Head CT scan with or without intravenous contrast should be performed when any neurologic complications develop. Among 51 patients with central nervous system symptoms in the setting of IE, CT was normal in 26, showed a bland infarct in 18, intracerebral hematoma in 3, and a hemorrhagic infarct and abscess in 2 each.\textsuperscript{13} There is no information regarding the clinical usefulness of MRI in patients with neurologic complications and IE. Since MRI is much more sensitive than CT scan, it is possible that it will detect small infarcts and abscesses not seen with CT scan. The impact of improved demonstration of these lesions on therapy and prognosis requires further study.

\textbf{Prognosis}

Neurologic complications have been associated with a higher mortality in some studies.\textsuperscript{14,15} However, among 175 patients with native and prosthetic valve endocarditis, mortality was not significantly higher in patients with neurologic complications (20.6%) than in those without (13.6%). In this same study the only factor that was related to increased mortality was infection with \textit{S. aureus}.\textsuperscript{13} Several factors may explain this finding: earlier diagnosis, more prompt antibiotic treatment, and an increased number of patients who are surgically treated during the acute phase of the illness, preventing cardiac decompensation. On the other hand, rupture of a mycotic aneurysm carries a grave prognosis and is associated with 80% mortality.\textsuperscript{18}

Neurologic complications are said to occur months to years after an episode of IE.\textsuperscript{19,20} In one study...
recurrent neurologic events after a cured episode of IE occurred in 15 of 140 patients during a follow-up period of 2.2 years, and all patients except one had prosthetic valves. Strokes occurred late (median 22 months) and could be better explained by mechanisms other than the prior episode of endocarditis. The only infarct in a patient with a native valve occurred 56 months after the episode of IE. The patient had a prolapsed mitral valve and was not receiving antplatelet agents. This study indicates that an episode of cured native IE does not increase the risk of stroke associated with valvular disease.13 Likewise, mycotic aneurysm rupture has been reported up to 6 months after a cured episode of IE.15,21 However, among 125 patients discharged after at least 6 weeks of intravenous antibiotic treatment, only one patient, who was on warfarin and had a prolonged prothrombin time, developed an intracerebral hemorrhage during a mean follow-up period of 40 months.9

Management

The keystone of treatment of IE is antimicrobial agents, the choice of which should be based on the isolation of the responsible microorganism on repeated blood cultures. Special attention should also be paid to hemodynamic factors, particularly those that result from sudden cardiac decompensation.

The treatment of cerebrovascular complications is controversial because of the lack of solid guidelines based on large prospective studies. With the low frequency of recurrent strokes and the low risk of cerebral hemorrhage, many authors feel there is no neurologic justification for anticoagulation10 or valve replacement during the acute phase of the illness.10,13

On the basis of experimental studies22,23 and the clinical profile of 68 cases with MA, some authors have advocated that an angiogram be performed 48 hours or more after the development of neurologic complications.9 However, a recent study24 recommended that cerebral angiography be performed without delay because in 2 out of 17 patients with documented mycotic aneurysm, rupture occurred within the first 24 hours after development of neurologic symptoms. These authors24 also suggested that head CT scan and lumbar puncture be performed in all patients with IE although no clear justification for this suggestion was offered.

Most authors recommend surgery for isolated, peripherally located mycotic aneurysm and antibiotic treatment with angiographic monitoring in those cases with multiple, deep aneurysms. Neurosurgical excision or CT guided aspiration is also indicated in the rare instance of large brain abscess associated with progressive neurologic deterioration despite appropriate antibiotic treatment.

References


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