Neurologic Manifestations as Presenting Symptoms of Endocarditis

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ABSTRACT: The features of infective endocarditis include both cardiac and non-cardiac manifestations. Neurologic complications are seen in up to 40% of patients with infective endocarditis and are the presenting symptom in a substantial percentage. We describe in detail the clinical scenarios of three patients admitted to our hospital, compare their characteristics and review the recent literature describing neurologic manifestations of infective endocarditis. Our patients demonstrate that infective endocarditis can develop without comorbidity or a valvular defect. Moreover, our patients were young and lacked the most common symptom of endocarditis: fever. The most common neurologic manifestations were focal neurologic deficits and confusion. We conclude that infective endocarditis should always be considered in patients presenting with new-onset neurologic complaints, especially in those without comorbidities or other risk factors. A prompt diagnosis should be reached and antibiotic treatment initiated as soon as possible.

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KEY WORDS: infective endocarditis, neurologic complications, stroke, fever

Endocarditis is an inflammatory process of the inner layer of the heart, usually involving the heart valves. In most cases, a microorganism is the source of the inflammation. The features of infective endocarditis include both cardiac and non-cardiac manifestations. Cardiac manifestations can include heart murmur, congestive heart failure, cardiac abscess, heart block, and embolic myocardial infarction. The non-cardiac manifestations include bacterial seeding, arterial emboli, subungual hemorrhages, and Janeway lesions [1]. Some of the immunologic phenomena associated with infective endocarditis are Osler's nodes, Roth's spots, and glomerulonephritis [1]. While the latter is often attributed to immune complex deposition in the glomeruli, the commonest type is vasculitic [2]. Neurologic complications are seen in up to 40% of patients with infective endocarditis and are the presenting symptom in a substantial percentage. These include embolic stroke, aseptic or purulent meningitis, micro-abscesses, seizures, encephalopathy, and intracranial hemorrhage due to hemorrhagic infarcts or ruptured mycotic aneurysms [1].

One should always consider infective endocarditis in patients presenting with new-onset neurologic complaints, especially in those without comorbidities or other risk factors. A prompt diagnosis should be reached and antibiotic treatment initiated as soon as possible.

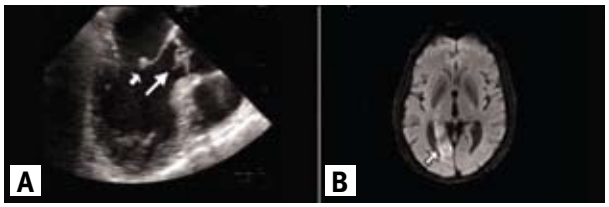
PATIENTS AND METHODS

From March 2008 to May 2009, three patients with infective endocarditis were admitted to our hospital. These patients presented with an array of neurologic manifestations secondary to endocarditis. In the first part of this study, we describe in detail the clinical scenarios and compare the patients' characteristics. For the second part, we performed a Medline search of all English-language review studies published from 1980 to 2009 describing neurologic manifestations of infective endocarditis. Keywords included endocarditis, bacteremia, neurologic manifestations, stroke, and fever. We conclude by comparing our cases to the existing literature.

PATIENT 1

A 69 year old man was admitted with left-sided weakness and difficulty talking. Six weeks before this hospitalization he underwent transurethral resection for benign prostate hyperplasia. This procedure was complicated by a urinary tract infection. On his arrival, his blood pressure was 120/80 mmHg, heart rate was 80 beats/minute, and he had no fever. Physical examination revealed left hemiparesis and dysarthria. The rest of the examination was normal. Blood tests showed elevated C-reactive protein (7.5 mg/dl). Electrocardiogram revealed atrial fibrillation. Brain computed tomography scan was normal. Anticoagulation treatment was initiated while the patient was scheduled for transesophageal echocardiography. By the following day, the patient's weakness and dysarthria had resolved but the echocardiograph demonstrated vegetations on the mitral and aortic valves [Figure 1A], moderate mitral insufficiency and mild aortic insufficiency. The working diagnosis supported endocarditis and treatment

Figure 1. First patient. **[A]** Echocardiography view showing a small vegetation at the free edge of the anterior mitral leaflet (arrow) and two small aortic vegetations (long arrow). **[B]** Brain MRI scan demonstrating a large occipital infarct on the right side (arrow).



with ampicillin and gentamicin was started. Three days later, blood cultures became positive for *Enterococcus faecalis.*

Due to new onset of severe headaches, the patient underwent cerebrospinal fluid examination. Analysis of the fluid revealed 652 white blood cells/ml, of which 70% were segmented. Glucose level was normal and protein level was 69 mg/dl. CSF cultures were sterile. A repeat brain CT scan, this time aided by contrast media, demonstrated mild atrophic changes. A Doppler ultrasound examination of the carotid arteries was normal.

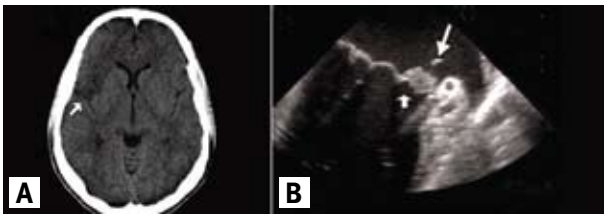
Two weeks into the course of his disease, the patient developed bilateral leg edema. This time, his ECG pattern was consistent with sick sinus syndrome and a follow-up echocardiogran demonstrated severe mitral valve insufficiency. Treatment with diuretics was begun and, soon after, the leg edema resolved. Despite amelioration of the patient's cardiac manifestations and normalization of the CRP levels, he developed a second episode of acute confusion. A brain CT angiogram failed to demonstrate mycotic aneurysms. Due to worsening of his cognitive function, magnetic resonance imaging of the brain was performed. The test demonstrated mild ischemic changes in the white matter and an acute infarct in the right occipital lobe [Figure 1B], findings not previously demonstrated by the CT scan. The rest of his hospitalization was uneventful and the patient's neurologic status remained stable. He was discharged after completing 4 weeks of antibiotic treatment and referred to a rehabilitation center.

PATIENT 2

A healthy 30 year old woman was hospitalized due to prolonged headaches and hypoesthesia of her left arm. On admission her vital signs were normal. Physical examination revealed a systolic murmur at the apex of the heart and weakness of the left leg. Blood tests showed elevated CRP (2.3 mg/dl). Hypodense lesions in the insula and in the right external capsule were seen on a brain CT scan [Figure 2A], and an additional focus in the right parietal lobe consistent with a brain infarct on an MRI scan.

CSF = cerebrospinal fluid
CRP = C-reactive protein

Figure 2. Second patient. **[A]** Brain CT scan demonstrating hypodense lesions in the right insula and external capsule (arrow). **[B]** Echocardiography demonstrating a large, irregular mitral valve vegetation (arrow) with a small mobile part, attached by a thin stalk (long arrow).



Antiphospholipid antibodies, anti-beta-2-glycoprotein, and lupus anticoagulant were negative. Antinuclear and complement levels were normal. A Doppler ultrasound examination of the carotid arteries was normal. Transthoracic echocardiogram demonstrated mitral valve prolapse with moderate regurgitation, but a transesophageal echocardiogram demonstrated a large vegetation [Figure 2B] and perforation of the mitral leaflet. These findings supported the diagnosis of infective endocarditis, and antibiotic treatment with gentamicin, ampicillin and ciprofloxacin was started. The treatment was changed to ceftriaxone based on the sensitivity of the *Streptococcus viridans* grown in blood cultures. With prolonged antibiotic treatment, the patient's symptoms resolved and her CRP levels normalized.

PATIENT 3

An 18 year old healthy male was admitted with a 1 week history of fever accompanied by weakness. His medical history was unremarkable. On arrival, his temperature was 39.2°C, blood pressure was 110/85 mmHg and heart rate 110 beats/minute. Physical examination revealed a systolic murmur and an enlarged spleen. His complete blood count showed $4x10^9$ white blood cells/L, hemoglobin 13.4 g/dl and platelet count $126x10^9$/L. Chemistry panel showed impaired liver function: aspartate aminotransferase 88 U/L, alanine aminotransferase 61 U/L, gamma-glutamyltransferase 105 U/L, lactate dehydrogenase 1279 U/L, bilirubin 3.5 mg/dl. His sodium level was 132 mEq/L and albumin 2.8 g/dl. CRP was 14 mg/dl. The working diagnosis suspected rickettsial infection, and treatment with doxycycline was begun.

Two days into his admission, he became confused and developed right facial nerve palsy. Antibodies to rickettsiae were negative. CSF analysis was normal. A brain CT scan demonstrated two low density lesions [Figure 3A] while MRI scan demonstrated multiple brain infarcts. Abdominal ultrasound demonstrated multiple infarcts in the spleen. In light of these findings, a transthoracic echocardiogram was performed and large vegetations on the mitral valve were detected. The working diagnosis supported infective endocarditis and anti-

biotic treatment with cefazolin and vancomycin was started. *Staphylococcus aureus* was grown in blood cultures. A perforating abscess of the mitral valve was demonstrated by a follow-up transesophageal echocardiogram [Figures 3B and C]. The patient was referred to a tertiary hospital where he underwent successful mitral valve replacement.

PATIENTS' CHARACTERISTICS

The patients' ages ranged from 18 to 67 years old [Table 1]. None had a major comorbidity, including valvular heart disease or history of drug abuse. Two patients had neurologic symptoms as the presenting symptom of infective endocarditis. The third patient developed neurologic symptoms shortly after admission. None of the patients had significant leukocytosis, but all had elevated CRP levels. The mitral valve was involved in all patients. Blood cultures were positive in all three cases, although the causative organisms were different. MRI scans proved superior to CT scans in demonstrating the infarcts.

Figure 3. Third patient. **[A]** Brain CT scan demonstrating low density lesions in the right insula and the frontal operculum (arrow). **[B]** Echocardiography showing a large abscess, attached to the posterior mitral leaflet (long arrow) with a central echoluscent space, penetrating the leaflet (arrow). **[C]** Color-Doppler study demonstrating systolic blood flow into the abscess (long arrow) and through the abscess into the left atrium (arrow).

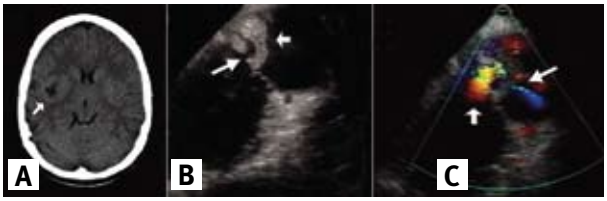


Table 1. Patient characteristics

		Patient 1	Patient 2	Patient 3
Demographic	Age (yrs)	69	30	18
	Gender	Male	Female	Male
Comorbidities		Smoking, enlarged prostate	None	None
Presenting symptoms		Left side weakness, difficulty talking	Headache, left arm hypoesthesia	Fever, weakness
Other neurologic findings		Confusion, headache	Left leg weakness	Right facial nerve palsy, confusion
Lab	White blood cell count	10×10^9/L	9×10^9/L	4×10^9/L
	CRP	7.5 mg/dl	2.3 mg/dl	14 mg/dl
Imaging studies	CT	Mild atrophic changes	Hypodense lesion in the insula and in the right external capsule	Numerous low density lesions in the insula and adjunct to the left frontal operculum
	MRI	Mild ischemic changes in the white matter and an acute infarct in the right occipital lobe	Focus in the right parietal lobe consistent with infarct with luxury perfusion	Infarcts
Bacteria		*Enterococcus faecalis*	*Streptococcus viridans*	*Staphylococcus aureus*
Valve involved		Mitral and aortic	Mitral	Mitral
Treatment		Ampicillin and gentamicin	Ceftriaxone and mitral valve replacement	Cloxacillin

DISCUSSION

William Osler first observed the frequent association between infective endocarditis and central nervous system symptoms in 1885 [3]. Despite the initiation of antimicrobial treatment and profound changes in the epidemiology and diagnosis of infective endocarditis, the incidence of neurologic complications has remained at 20–40% and as a presenting symptom of infective endocarditis in 12–47% [4-6]. There are three types of overt CNS manifestations in infective endocarditis [4]: a) infectious entities such as bacterial meningitis and abscess, b) non-specific manifestations such as encephalopathy, seizures and headache, and c) cerebrovascular entities such as cerebrovascular accidents and mycotic aneurysms. Osler first described mycotic aneurysm formation also in 1885. These are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged [1].

NEUROLOGIC MANIFESTATIONS OF INFECTIVE ENDOCARDITIS

Cerebrovascular complications of infective endocarditis are common and ischemic stroke is the most frequent neurologic manifestation. It is mainly secondary to embolization by unstable vegetations. Infection with *S. aureus* is a risk factor for these complications [4-9]. Studies have also shown an association with other organisms, among them enterococi *and E. coli* [4,10,11] and an inverse correlation with *S. viridans* [7]. The risk for an embolic complication is related to the presence and size of the vegetation, although some authors demonstrated conflicting results [5-7]. It is still controversial whether the type of valve involved is an independent risk factor. Some studies show a higher incidence when either the mitral valve or a prosthetic valve is involved, while others show similar embolic risks regardless of the type of valve involved [4]. Additional factors attributed to embolization are levels of circulating adhesion molecules and antiphospholipid antibodies [7,11]. Fewer than 3% of patients experience recurrent ischemic strokes during the course of the acute illness, and in most cases it occurs prior to initiation of antimicrobial treatment [4,10,12].

Intracerebral or subarachnoid hemorrhages have been reported in 3–7% of patients [4,10,12,13]. Traditionally,

CNS = central nervous system

intracerebral hemorrhage has been attributed to the rupture of a mycotic aneurysm [4,11,12]. However, recent clinical studies of patients with infective endocarditis complicated by cerebral hemorrhages found that only a minority had mycotic aneurysms while the bulk had hemorrhagic transformation of infarcts and septic necrosis of the arterial vessels [4,10-15].

Acute meningitis is the main infectious complication of infective endocarditis. Elevated levels of polymorphonuclear leukocytes in CSF (> $5x10^6$ cells/ml) have been reported in 2–17% of patients with infective endocarditis [4-6,11-13]. CSF cultures are positive in 16–26% of cases [12,13], while the most frequent microorganism is *S. aureus*. Brain abscess is a rare complication, responsible for 1–4% of neurologic complications [11-13]. The main causative organism is *S. aureus*. Most cases do not require surgical intervention since there are usually multiple abscesses, some of which are microscopic [12].

Encephalopathy has been reported in 1–9% of patients with infective endocarditis [4,11-13]. It has been associated with ischemic changes secondary to the spread of multiple emboli [12,15]. A recent study has suggested an association between septic encephalopathy and metabolic disorders. Headache as the sole neurologic complaint has been reported in 2–4% of patients with infective endocarditis. In most cases, it was attributed to fever, thus resolving after initiation of antibiotic treatment. In a minority of cases, it was associated with brain abscesses or an elevated white blood cell count in the CSF [11,13]. It is noteworthy that severe persistent headache can be a symptom of a ruptured mycotic aneurysm and necessitates head imaging or lumbar puncture. Seizures have been reported in 1–11% of patients with infective endocarditis [11-13] and are usually associated with other neurologic complications or occur in patients with preexisting neurologic disorders.

SILENT CEREBRAL COMPLICATIONS OF INFECTIVE ENDOCARDITIS

According to recent studies and postmortem findings, neurologic complications of infective endocarditis may be asymptomatic [6]. The clinical significance of these events is not clear. The main concern is the development of hemorrhagic transformation of asymptomatic brain infarcts. The risk of hemorrhage among patients receiving anticoagulation either for a mechanical heart valve or during valve replacement due to endocarditis is increased. Recently, two studies evaluated the impact of screening patients with infective endocarditis for asymptomatic neurologic involvement. Snygg-Martin et al. [6] screened 60 patients with left-sided infective endocarditis for neurologic complications [6]. These patients underwent brain MRI and neurochemical CSF analysis regardless of neurologic symptoms. The frequencies of symptomatic and asymptomatic neurologic complications were quite similar, 35% and 30% respectively. Despite the high frequency of neurologic complications in this study, routine MRI or CSF analysis for asymptomatic patients with infective endocarditis was not recommended. The other study, by Thuny et al. [16], followed 496 patients of whom 453 underwent brain CT scans. Silent cerebral emboli were found in 4% and symptomatic cerebral emboli in 22%. In this study, regardless of the presence of symptoms, the risk of mortality was similar.

MANAGEMENT AND OUTCOME

Treatment of infective endocarditis consists mainly of antimicrobial agents according to the sensitivity of the causative organism. The occurrence of neurologic complications does not necessitate lengthy treatment with antibiotics. Most studies showed that the majority of neurologic complications occur before initiation of antibiotic treatment [4-7,15], and the incidence dramatically falls after one week of appropriate antibiotic therapy [6]. Moreover, most authorities agree that one episode of embolization is not an indication for valve replacement owing to the low frequency of recurrence under an appropriate antibiotic regimen [5].

It is challenging to provide anticoagulant therapy for patients with hemorrhagic complications of prosthetic valve endocarditis [17]. In one study 28 patients with prosthetic heart valves receiving warfarin were hospitalized for major hemorrhages including intracranial. Anticoagulation was reversed in all patients. None of the patients had thromboembolic complications, suggesting that the thromboembolic risk is low in prosthetic heart valve patients hospitalized with major hemorrhage when their warfarin therapy is reversed or withheld. Despite this study the topic is still controversial, and the risk-benefit ratio of continued anticoagulation needs to be considered.

It is not yet established whether neurologic complications are associated with higher mortality [15]. The type of neurologic complication has a significant impact on prognosis. For instance, one study found that transient ischemic attacks and asymptomatic neurologic complications had no affect on mortality, while stroke was an independent predictor of death. Interestingly, rupture of a mycotic aneurysm is associated with an 80% mortality rate [4]. It is notable that even if neurologic complications do not always influence mortality, they greatly influence morbidity [6].

CONCLUSIONS

Our patients demonstrate that infective endocarditis can develop without comorbidity or a valvular defect. Moreover, two of the patients were very young and two lacked the most common symptom of endocarditis: fever. The most common neurologic manifestations were focal neurologic deficits, confusion and headache either as the presenting symptom or developing during the course of the illness. In one patient, CT scan failed to demonstrate the infarcts, which were seen

on MRI scan, emphasizing the importance of performing advanced imaging when the clinical suspicion is high and the routine investigation is intact. Only one patient eventually needed surgical repair [18].

All three patients in our study had ischemic strokes (proven by imaging), which is the most common complication of infective endocarditis, in addition to headache and/or confusion, which are known, non-specific manifestations of the disease. It is of interest that *Streptococcus viridans,* which was the causative organism in one patient, has an inverse correlation with neurologic complications according to most researchers. The mitral valve was involved in all three patients. A higher incidence of neurologic complications was reported when the mitral valve was involved. As most studies show, our patients experienced neurologic complications before the initiation of antibiotic treatment and only one suffered neurologic deterioration after one week of treatment.

To summarize, neurologic complications are frequent among patients with infective endocarditis, being the presenting symptom in a substantial percent of patients. Infective endocarditis should always be considered in a patient presenting with acute stroke, especially in young patients and when there is a lack of comorbidities or risk factors. Prompt diagnosis should be reached and antibiotic therapy initiated as soon as possible since it is the most effective treatment to prevent deterioration and recurrence of neurologic complications.

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