Neurological Manifestations of Infective Endocarditis: A Review

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Abstract:
Neurological Manifestations of Infective Endocarditis: A Review

Neurological complications are seen in patients with bacterial endocarditis and their incidence has not changed with the advent of antibiotics. Patients with abnormal neurological signs have a grave prognosis. Neurological sequelae of bacterial endocarditis are most often due to septic embolization producing ischemia and/or suppuration, resulting in infarction, hemorrhage, meningoencephalitis, or abscess. Clinical findings vary with the portion of the nervous system affected. The diagnosis should be suspected in the febrile patient with neurological signs of acute onset, the young patient with hemiplegia, the older patient with sudden changes in mentation, or the patient of any age with multifocal neurological signs. Diagnostic measures should include a careful history and physical examination, blood cultures and lumbar puncture where not contraindicated. Treatment is based on therapy of the bacterial endocarditis with bactericidal drugs, and therapy of intracerebral lesions with drugs that penetrate the blood-brain barrier. Consideration should be given to surgical intervention in mycotic aneurysms and brain abscesses.

Additional Key Words: infection of central nervous system, mycotic aneurysm, brain abscess, meningoencephalitis, cerebral emboli

"Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties which, in many cases, are practically insurmountable.... The protean character of the malady, the latency of the cardiac symptoms, and the close simulation of other disorders combine to render the detection peculiarly difficult."

Sir William Osler

Particular problems in diagnosing bacterial endocarditis (BE) may arise when the disease presents with symptoms or signs referable to the nervous system, since the clinical syndrome may be so bizarre or so calamitous as to overshadow the endocarditis itself. Because the diagnosis may be so elusive and because the presence of neurological signs often indicates a grave prognosis, we will discuss the frequency of neurological manifestations of BE, their pathology and symptomatology, diagnosis and treatment.

Incidence
In Osler’s series, the incidence of neurological signs was 12.5%; 3% of patients presented with primary neurological problems. Although subsequent studies have placed the incidence as high as 80%, most series (table 1) show that 15% to 30% of the patients will evidence neurological signs at some time during their disease, and that 6% to 15% will present with a neurological chief complaint. The incidence of neurological manifestations in patients with BE has not changed significantly since the introduction of antibiotic therapy.

Bacteriology
Any organism capable of producing bacterial endocarditis may secondarily infect the central nervous system (CNS) via hematogenous spread. Staphylococcus aureus and streptococci, which cause 90% of all cases of BE, are the most common organisms associated with central nervous system complications. Staph. aureus, the most common cause of acute BE, may cause single or multiple brain abscesses, but acute BE caused by Staph. aureus also is frequently associated with purulent meningitis. Streptococcus pneumoniae (the “pneumococcus”), an increasingly rare cause of BE, may cause fulminant meningitis accompanied by evidence of rapid aortic valvular destruction. Streptococci, of the viridans group, and enterococci are usually thought of in connection with subacute BE but, like Streptococcus pyogenes (group A, beta-hemolytic streptococcus), may cause acute BE. Viridans-group streptococci are more commonly...
TABLE 1
Incidence of Neurological Sequelae of Bacterial Endocarditis

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of cases</th>
<th>Presenting with neurological signs</th>
<th>Total no. developing evidence of CNS involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osler</td>
<td>200</td>
<td>11 (5%)</td>
<td>Over 23 (12%)</td>
</tr>
<tr>
<td>Horder</td>
<td>150</td>
<td>8 (5%)</td>
<td>40 (27%)</td>
</tr>
<tr>
<td>Fetterman</td>
<td>42</td>
<td>21 (50%)</td>
<td></td>
</tr>
<tr>
<td>DeJong</td>
<td>68</td>
<td>6 (9%)</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Toone</td>
<td>32</td>
<td>9 (27%)</td>
<td>17 (52%)</td>
</tr>
<tr>
<td>Cates and Christie</td>
<td>442</td>
<td>33 (7.5%)</td>
<td>86 (19%)</td>
</tr>
<tr>
<td>Jones</td>
<td>385</td>
<td>65 (17%)</td>
<td>110 (29%)</td>
</tr>
</tbody>
</table>

associated with CNS manifestations such as sterile, mononuclear cell meningitis, thromboembolism, or mycotic aneurysm but only rarely with brain abscess or purulent meningitis.

**Pathophysiology**

Central nervous system lesions are usually due to embolization, which may be septic at any time during the disease, and either septic or sterile after the disease has been treated. Thus the lesion produced may be that of ischemia or suppuration, or both. The embolic process may involve a single vessel and give focal signs or multiple vessels and produce multifocal signs. The brain, spinal cord, peripheral nerves, or retina may be involved. If ischemia caused by an embolus is reversed before permanent changes occur, the clinical syndrome may resemble a transient ischemic attack. If the embolus produces more lasting obstruction, the result may be infarction or encephalomalacia, with necrosis and softening of the brain. Embolization may occur during antimicrobial treatment or even several months after bacteriological cure.

The effects of suppuration may outweigh those of ischemia, with bacterial proliferation, marked acute inflammatory exudate, and more widespread tissue destruction than would be expected on the basis of infarction alone. If the wall of a vessel or its vasa vasaorum is involved, the result may be a mycotic aneurysm. If the substance of the brain is involved, brain abscess or, less commonly, encephalitis may develop. If the meninges are involved there may be a meningitis. Meningitis also may arise as a superficial reaction to a more deep-seated inflammation within the brain, in which event meningitis may be "aseptic," with sterile fluid, normal CSF sugar, and a mononuclear CSF response.

In addition to the embolic changes described above, proliferative endarteritis of small arteries has been described in the absence of any detectable local bacterial infection or embolization. This process may become so intense as to produce vascular occlusion and distal infarction. Its mechanism is unknown, although similar findings have been reported in a variety of other toxic and infectious processes.

**Clinical Presentation**

**Infarction**

The signs and symptoms vary with the vessel involved and the collateral blood flow available. Most commonly, embolization occurs to the middle cerebral artery, usually resulting in hemiplegia. Hemiplegia occurred in 17 of Horder's 22 patients with CNS involvement, nine of Harrison and Hampton's 24 patients, and 30 of Jones' 110 patients. In a young patient, hemiplegia of sudden onset always should raise the suspicion of endocarditis; in the elderly, the possibility of endocarditis also should be carefully considered. Occlusion of the middle cerebral artery or its branches also may produce parietal lobe signs of sensory loss, neglect, dyspraxia, hemianopia, and, where the dominant hemisphere is involved, aphasia. Embolization to branches of the anterior or posterior cerebral artery may duplicate many of these symptoms, especially involving the lower extremities. Posterior cerebral artery occlusion also may produce homonymous hemianopia. Patients with lesions of the basal ganglia may develop signs of parkinsonism, and chorea may likewise occur, although its presence should suggest the possibility of co-existing active rheumatic fever. Lesions of the median longitudinal fasciculus may produce unilateral inter-nuclear ophthalmoplegia. Brain stem lesions can cause dysphagia, intractable hiccoughs or vomiting. Rarely can myelitis, mononeuritis, polyneuritis, optic neuritis, or unilateral blindness occur with involvement of spinal cord, peripheral nerves, cranial nerves or retina, respectively.

**Mycotic Aneurysm**

This classic neurological complication of subacute BE is unusual, being present in only 5% to 8% of patients with CNS manifestations. The middle cerebral artery is involved four times more often than either the anterior or posterior cerebral artery.
Usually the aneurysm is found in the secondary branches of the artery but may occur so close to the circle of Willis as to mimic a berry aneurysm. They may be single or multiple.

The initiating embolic episode may be silent or may produce transient ischemic symptoms or actual infarction. The arterial wall subjacent to the embolus then may become infected leading to neerosis with weakening of the wall, followed by ballooning outward to form an aneurysmal pouch.

During its evolution, the aneurysm may leak to produce meningeal irritation. Lumbar puncture performed at the time of such a leak may show an initial neutrophilic reaction with a few red cells. Later, the cerebrospinal fluid may show xanthochromia and/or a mononuclear response identical to that seen with a viral meningitis. Most commonly, the initial symptom produced by a mycotic aneurysm is that of rupture with severe hemorrhage. In this event the mortality is in the range of 60% to 90%.

ENCEPHALITIS AND BRAIN ABSCESS
Encephalitis is a common accompaniment of BE, but is more often a pathologic diagnosis than a clinical one (present in 25% of the autopsied cases of Pankey). Brain abscesses are more frequently a feature of acute BE than subacute BE, and in Pankey's series brain abscess was seen in 13 of 54 cases of acute BE versus only two of 167 cases in subacute BE. The abscesses may be single or multiple, and their clinical presentation may be that of a space-occupying lesion, toxic encephalopathy or meningitis. The accompanying meningitis will usually be sterile unless the abscess ruptures into the subarachnoid space. Prognosis in patients with brain abscesses is poor.

Meningitis may occur either as a septic process or as a sterile inflammatory reaction to infection or hemorrhage within the brain. In subacute BE, the CSF cellular reaction is predominantly mononuclear and only rarely will the causative organism be isolated from cultures. In acute BE the CSF cellular reaction is frequently polymorphonuclear neutrophils and the causative organism is frequently isolated. Acute suppurative meningitis is a classic accompaniment of BE due to the *Streptococcus pneumoniae* and was the most common neurological presentation of staphylococcal endocarditis in both the study by Lerner and Weinstein and that by Fisher et al.

CEREBRAL HEMORRHAGE
This may be due to infarction, rupture of a mycotic aneurysm, bleeding into abscessed brain tissue, or generalized vasculitis. The hemorrhage may vary in size from microscopic areas found only at autopsy to massive, rapidly fatal intracerebral bleeding. Of Horder's 150 autopsied patients ten showed meningeal hemorrhage at postmortem examination, and four showed cerebral hemorrhage. In Pankey's series of subacute BE nine of 60 fatal cases showed cerebral hemorrhage as did 11 of Jones' 110 cases.

NONSPECIFIC MANIFESTATIONS
These are legion and may cause the greatest confusion in reaching a diagnosis. Headache was the initially reported symptom in 5% of Cates' and Christie's patients and occurred in 13% of Jones' 110 patients. The mechanisms by which headache is produced are uncertain. It is only rarely accompanied by meningeal or other neurological signs, and by itself has no prognostic import. Convulsions associated with pyrexia or actual brain involvement may occur in any age group and will be found in about 10% of cases.

Psychiatric symptoms may be found in as many as 50% of patients and are especially common among the elderly where change in mental status may be the most prominent feature of the disease. The mental changes may run the gamut from mild confusion (often mistakenly attributed to fever) to paranoia, hallucinations, and a schizophrenia-like picture. Cases exist in which diagnosis of bacterial endocarditis was reached only after the patient had unsuccessfully undergone electroconvulsive therapy.

Diagnosis
Since BE can present with a wide variety of neurological symptoms and signs, BE should be included in the differential diagnosis of most acute neurological illnesses. Particular attention should be paid to hemiparesis in the young, to sudden personality changes in the elderly, and to the patient of any age with multifocal neurological signs.

Among the most useful diagnostic tools are those of careful history and meticulous physical examination. A history of fevers, chills, or night sweats should suggest the diagnosis more strongly. Cardiac murmurs, splinter hemorrhages, petechiae, Osler's nodes, Roth spots, clubbing of the fingers or toes and splenomegaly should be searched for. Laboratory evaluation should include a search for microhemiaturia, anemia, and rheumatoid factor in the serum. It is well to remember Friedberg's axiom that the diagnosis of bacterial endocarditis should be regarded as probable in any patient with an organic cardiac murmur who has, for undetermined cause, a fever of more than one week's duration.

Serial blood cultures remain the most important laboratory study and will often yield the organism even if the spinal fluid proves to be sterile. Lumbar puncture is a valuable diagnostic aid, and patterns of
possible findings have been well summarized by Ziment.\textsuperscript{28} In general, a predominantly polymorphonuclear pleocytosis with elevated protein and depressed glucose suggest meningoencephalitis or abscess, although embolus alone or intracerebral hemorrhage may duplicate this picture. A ruptured mycotic aneurysm classically produces grossly bloody fluid, but if the hemorrhage is intracerebral, blood or xanthochromia may not be present. Slight leakage from a mycotic aneurysm may produce only a minimal cellular reaction without change in sugar or protein and at times without xanthochromia. Occasionally, an underlying abscess or an aneurysm with slight leakage may produce a mononuclear response. The presence of normal spinal fluid in BE does not rule out significant CNS disease.

Cerebral angiography can give precise localization of brain abscesses or mycotic aneurysm and should be readily resorted to where there is a suggestion of a space-occupying lesion or of aneurysm. In some cases, repeated angiography may be required.\textsuperscript{29}

**Treatment**

Antibiotic therapy of CNS complications of BE requires that the antibiotics used must not only be active against the organism involved, but also must be able to achieve effective concentrations in the CSF and brain tissue. For this reason, the usual therapeutic regimens employed in BE sometimes must be altered. Although the antibiotics used for treatment of BE must be bactericidal, a bacteriostatic agent such as chloramphenicol may be required to insure adequate CSF levels of antibiotic. Initial therapy, prior to results of culture, must be empirical, and our recommendations for initial therapy are listed in table 2. It must be emphasized that therapy should be reevaluated when organisms are isolated and antibiotic sensitivity is known. For this reason, it is very important to obtain adequate culture material before empirical therapy is begun.

Where the organism is unknown, preliminary therapy should usually be directed against the enterococcus as this will be adequate also for viridans-group streptococci. Antistaphylococcal coverage also should be used in fulminant infections, in patients who may have a brain abscess, in postsurgical patients, or where there are superficial infections (skin ulcers, furunculosis, etc.) that are a possible primary source of staphylococci. Patients with left-to-right cardiac shunts are at risk of developing anaerobic infection.

**Table 2**

<table>
<thead>
<tr>
<th>Presumed organism</th>
<th>Therapy of choice</th>
<th>Alternate therapy in severely penicillin-allergic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococci of the viridans group</strong></td>
<td>Penicillin, 20 million units IV q.d. plus Streptomycin, 1/2 gm IM b.i.d.</td>
<td>Vancomycin, 500 mg IV q. 6 hrs alone or with Streptomycin, 1/2 gm IM b.i.d. or Cefalothin, 2 gm IV q. 4 hrs plus Chloramphenicol, 1 gm IV q. 6 hrs</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Methicillin or Nafcin 2 gm IV q. 4 hrs</td>
<td>Vancomycin, 500 mg IV q. 6 hrs or *Cefalothin, 2 gm IV q. 4 hrs plus Chloramphenicol, 1 gm IV q. 6 hrs</td>
</tr>
<tr>
<td><strong>Pneumococcus</strong></td>
<td>Penicillin, 20 million units IV q.d.</td>
<td>*Cefalothin, 2 gm IV q. 4 hrs plus Chloramphenicol, 1 gm IV q. 6 hrs</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>*Gentamicin, 80 mg q. 8 hrs plus Carbencillin, 5 gm IV q. 4 hrs (consider intrathecal gentamicin)</td>
<td>*Gentamicin, 80 mg q. 8 hrs plus Chloramphenicol, 1 gm IV q. 6 hrs (consider intrathecal gentamicin)</td>
</tr>
<tr>
<td><strong>Gram-negative organisms including Pseudomonas</strong></td>
<td>Penicillin, 20 million units IV q.d. plus Chloramphenicol, 1 gm IV q. 6 hrs</td>
<td>*Cefalothin, 2 gm IV q. 4 hrs plus Chloramphenicol, 1 gm IV q. 6 hrs</td>
</tr>
</tbody>
</table>

*Poor penetration into CSF. (Average-sized adult with normal renal function.)

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The penicillins, including nafcillin, methicillin, and ampicillin, can achieve adequate CSF concentrations. Experience with carbenicillin in CNS infections is limited. Since gentamicin enters the CSF poorly, consideration should be given to its simultaneous intrathecal use in patients with CNS infections that require this antibiotic. Chloramphenicol CSF penetration is good and this antibiotic is the agent of choice in anaerobic CNS infections. For patients who cannot tolerate penicillin, chloramphenicol is the drug of choice for treatment of pneumococcal, meningococcal or hemophilus meningitis. Clindamycin, although effective against many anaerobic organisms, penetrates CSF poorly and should not be used in the treatment of CNS disease. Once therapy is underway, it may be useful to monitor CSF levels of the antibiotics used, although little is known concerning the penetration of antibiotics into brain tissue itself.

Anticoagulation carries an increased danger of hemorrhage in BE, but should be considered in patients with life-threatening thromboembolic disease. Cerebral edema may require therapy with urea or mannitol and steroids such as dexamethasone. Surgical intervention may be required to drain an abscess, evacuate a hematoma, shunt a developing hydrocephalus, or, occasionally, to provide emergency decompression. Where an unruptured mycotic aneurysm is accessible peripherally, prophylactic ligation should be considered. Where the aneurysm lies centrally and/or has ruptured, the risk of severe bleeding during operation often precludes surgery until the patient has stabilized. In that event, antibiotics, supportive measures, and, where necessary, osmotic agents and dexamethasone should be employed.

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