Infectious Causes of Stroke

Stroke is an often-devastating and not uncommon complication of many central nervous system infections.

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Every year, an estimated 15 million people experience stroke worldwide. The impact and burden of strokes are substantial–one-third of these individuals (5 million) die from stroke, and another one-third are left permanently disabled.[1] Although traditional cardiovascular risk factors account for the majority of strokes, infectious pathogens may add additional risk, and in some cases, have a direct causal role. Systemic infections have been associated with increased risk of strokes, with stimulation of inflammation thought to be the predominant mechanism.[2] A comprehensive review of all systemic infections associated with stroke is outside the scope of this review. Instead, the focus is on direct infections of the central nervous system (CNS) that may cause stroke. Cerebrovascular disease is a complication of many infectious pathogens. The pathogenesis is often similar regardless of the pathogen. In the setting of basilar meningitis, vasculitis and vasospasm are common mechanisms for stroke, as are hypercoagulable states in combination with endothelial dysfunction related to local infection and invasion by pathogens. Vascular complications of CNS infections are often associated with poor neurologic outcomes.

Bacterial Infections

Syphilis

The number of primary and secondary syphilis cases has been increasing in the US and in Europe over the last 20 years. Syphilis is a chronic sexually transmitted infection caused by the spirochete *Treponema pallidum*. CNS involvement is referred to as neurosyphilis and in the modern era is most commonly found in persons with HIV infection. Cerebral infarction occurs in approximately 15% of neurosyphilis cases, typically 5 to 12 years after the initial infection.[3]

Syphilis classically causes an obliterative endarteritis of medium- and large-sized blood vessel walls that is characterized pathologically by intimal fibroblast proliferation, thinning of the media, and inflammation and fibrosis of the adventitia.[2] This meningovascular syphilis causes progressive luminal obliteration, thromboses, and potential for cerebral infarction. In contrast to typical acute ischemic strokes, individuals with strokes caused by neurosyphilis tend to have prodromal symptoms over weeks to months, including headache, malaise, and/or personality and behavioral changes. Neurosyphilis should be considered in any young adult with stroke who lacks traditional cerebrovascular risk factors, particularly if strokes are recurrent and affect the middle cerebral artery (MCA) territory. The treatment for neurosyphilis consists of aqueous crystalline penicillin G given intravenously for 10 to 14 days. Serial serologic and cerebrospinal fluid (CSF) monitoring is often necessary after treatment because neurosyphilis can be difficult to fully eradicate and may recur.

Tuberculosis

Tuberculosis (TB) involving the CNS remains a serious public health problem in much of the developing world. It is the leading cause of death by an infectious agent and 25% of the world's population is infected by *Mycobacterium tuberculosis*.[4] Strokes in TB occur in 15% to 60% of people with tuberculous meningitis.[5] In primary infection or late reactivation of TB, bacillemia facilitates the dissemination and deposition of tubercles in the meninges, brain, or skull. A ruptured tubercle in the subarachnoid space causes a marked inflammatory reaction with exudates, which is most pronounced at the base of the brain. Local arteries and veins may be encased and subsequently develop intimal proliferation and fibrinoid necrosis.[2]

Strokes commonly affect the tubercular zone, which is a region including the head of the caudate nucleus, the anteromedial thalamus, and internal capsule, but may also affect the subcortical white matter and brainstem. Stroke contributes to morbidity and mortality of TB; in a large study including 144 participants with stroke in tuberculous meningitis, the presence of infarction was an independent predictor of functional disability and death.[5]

Guidelines recommend treatment of CNS TB consisting of an initial intensive phase (4 drugs administered for 2 months) followed by a continuation phase (2 drugs for an additional 7-10 months). This regimen can be tailored according to the patient's response and drug sensitivities of isolates.

Bacterial Meningitis

Acute bacterial meningitis is 1 of the 10 most common infectious causes of death worldwide and frequently causes

neurologic sequelae among survivors. Over 80% of community-acquired cases in adults are caused by *Streptococcus pneumoniae* or *Neisseria meningitides*. People more than age 50 or with immunocompromise are also at risk of infection by *Listeria monocytogenes*. Risk factors for acute bacterial meningitis include age more than 65, immunocompromised states (eg, asplenia or hyposplenism), HIV, cancer, diabetes mellitus, alcoholism, and immunosuppressant medications.[6]

Ischemic stroke complicates 15% to 25% of cases and contributes to the substantial neurologic morbidity associated with bacterial meningitis.[2] The stroke rate depends on specific pathogen (eg, the rate of stroke is higher from *Streptococcus pneumoniae* [36%] and lower with *Neisseria meningitides* [9%]).[7] Cerebrovascular complications are associated with worse outcomes. In a 696-participant case-control study from the Netherlands, unfavorable outcome was more probable in those with infarction (OR 3.4; 95% CI, 2.2-5.2). Age and high erythrocyte sedimentation rate (ESR) were independent risk factors for infarction. Bacterial pathogens invoke the formation and release of inflammatory cytokines that damage the endothelium of the blood-brain barrier. Angiographic studies have shown arterial narrowing, focal dilatations, and vessel wall irregularities suggesting that vasculopathy (vasculitis or vasospasm) may be a mechanism for stroke in bacterial meningitis.[6] Meningitis also affects the coagulation cascade; diffuse cerebral intravascular coagulation has also been implicated in the pathophysiology of stroke in these cases.[7] A hypercoagulable state arises from activation of antifibrinolytic, proinflammatory, and procoagulant pathways.[8]

Viral Infections

Varicella Zoster Virus

Varicella-zoster virus (VZV) is a DNA virus that becomes latent within neurons after primary infection. Over 95% of the adult population has latent VZV. Age and immunosuppression are risk factors for VZV reactivation, which most commonly manifests as herpes zoster (shingles), a unilateral painful vesicular rash. Primary infection or reactivation of VZV can cause a small and large vessel vasculopathy/vasculitis, with the potential to cause cerebral infarctions.

A history of a rash, either zoster (shingles) or varicella (chicken pox), is found in about two-thirds of those with VZV vasculopathy. Although the rash and stroke may occur concomitantly, the average time from rash to stroke symptoms is 4 months. Classically, a person may develop herpes zoster ophthalmicus and a contralateral hemiparesis several months later. It is notable that the absence of a rash does not exclude the diagnosis of VZV vasculopathy in the appropriate clinical setting.[9]

Imaging studies will show infarction in most cases of VZV vasculopathy. Commonly, a brain MRI shows lesions in the gray-white matter junction. Vessel imaging typically shows beading with areas of narrowing and poststenotic dilatation (Figure 1). Aneurysm and hemorrhage can also be seen. Pathologically, VZV has been characterized by transmural inflammation with multinucleated giant cells and epithelioid macrophages. There are no large controlled trials to guide the optimal treatment of VZV vasculopathy. Empiric intravenous acyclovir (10 mg/kg every 8 hours) for 14 days has been suggested. Corticosteroids could be considered but are not proven of benefit.

HIV

Infection with HIV has been found to be a risk factor for stroke, which occurs approximately 1.5 times more in people with HIV than in the general population. Poor functional outcomes occur in approximately 25% of people with HIV-related stroke, and are associated with higher CD4 counts on hospital admission.[10] There are several postulated mechanisms of stroke in the context of HIV, including cardiothromboembolism, opportunistic infections, HIV-associated vasculopathy, coagulopathy, concomitant drug use, and metabolic syndrome caused by antiretroviral therapies. Within even 8 days of initial infection, HIV can directly invade the CNS, provoking an inflammatory response in CSF and brain parenchyma. Although studies have been small, aneurysmal dilatation of arteries has been reported and thinning of the arterial media has been found in those with chronic HIV, possibly offering additional mechanisms and insights. In 2016, an expert working group published a consensus statement classifying the various subtypes of stroke etiology in HIV (Table) and suggested appropriate evaluations and a diagnostic algorithm.[11]

Fungal Infections

Invasive fungal infections of the CNS are rare but can be devastating. Yeast, molds that form hyphae, and dimorphic fungi (yeast at body temperature and molds at ambient temperature) are the 3 types of fungi that can cause stroke. In chronic fungal meningitis, which is most often caused by yeasts, several mechanisms can cause stroke including vasculopathy, venous outflow obstruction, and arteritis of small vessels.[2] Yeasts also may form focal abscesses in the brain parenchyma that have a tendency to bleed. Molds, unlike yeasts tend to directly invade blood vessel walls causing arteritis or mycotic aneurysms.

Yeasts

The most common CNS yeast infection is *Cryptococcus spp*, particularly in immunocompromise. In the developed world, approximately 50% of cases are associated with HIV. An immunosuppressed state such as post solid-organ transplant, corticosteroid use, sarcoidosis, and hepatorenal failure also are risk factors, but notably, 13% to 18% of people with *Cryptococcus* infection may be immunocompetent.[12] *Cryptococcus* invades

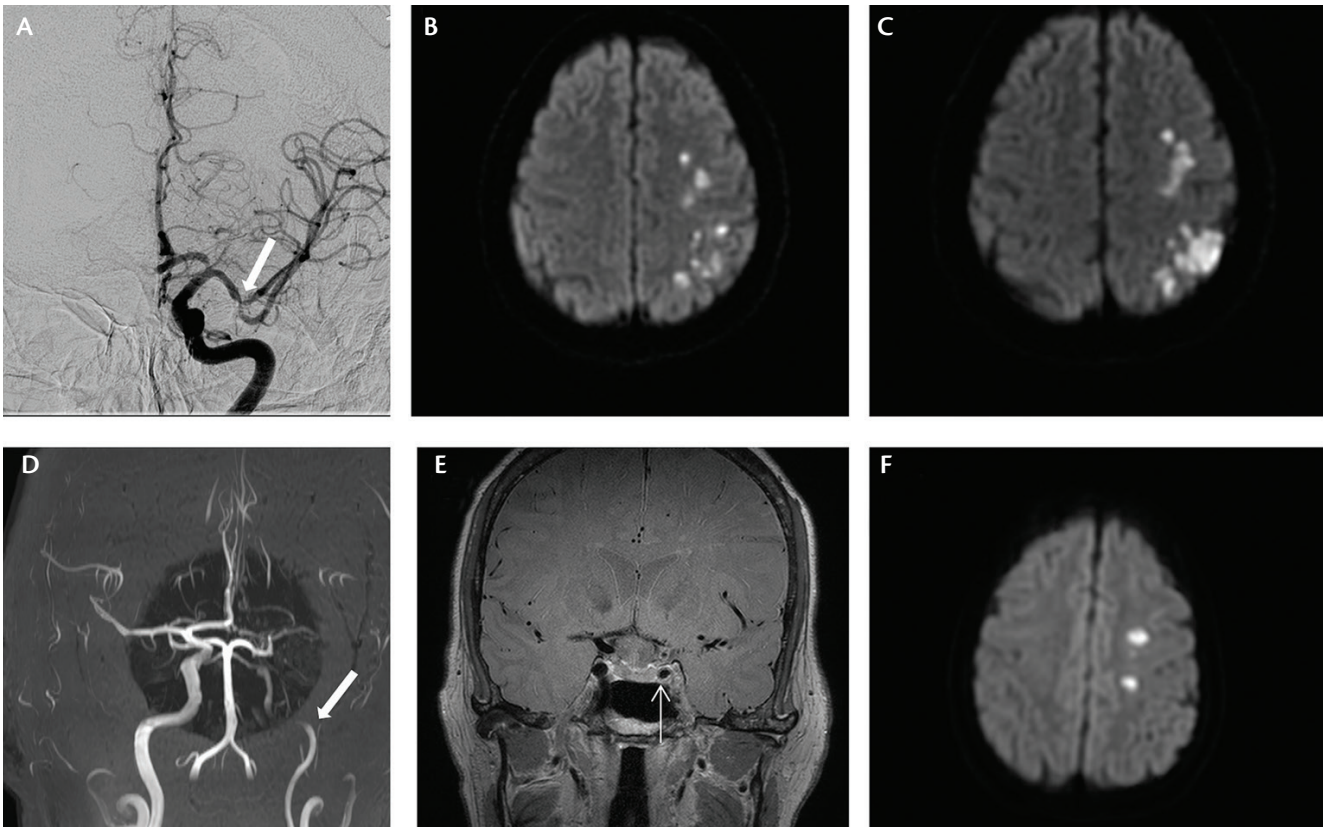

Figure 1. Imaging Findings in Varicella Zoster Virus Vasculopathy. A man, age 50, developed right hemiparesis 5 months after having herpes zoster ophthalmicus in his left eye. Cerebral angiogram shows segmental constriction and dilatation of left hemispheric arteries, particularly at the left middle cerebral artery (A, arrow). Diffusion weighted imaging shows regions of infarction in the left frontal and parietal lobes (B, C). A woman, age 62, presented with transient right arm and leg sensory loss with mild right hand weakness after having herpes zoster ophthalmicus of the left eye. A MR angiogram shows near occlusive stenosis of the left supraclinoid internal carotid artery (D, arrow), and enhancement and thickening of the left terminal carotid artery (E, arrow) on black blood imaging. Diffusion weighted imaging showed two areas of restricted diffusion in the left frontal lobe(F).

the leptomeninges and brain parenchyma, causing meningitis as well as abscesses. In a small series, ischemic stroke complicated cryptococcal meningitis in 8 of 32 (26%) individuals.[13] These strokes were mostly multiple, lacunar, and tended to affect the basal ganglia. Other imaging findings of *Cryptococcus* were often present, including meningeal enhancement in 50% and basal exudates in 13% (Figure 2).[13] Among people with cryptococcal infections, those who had a stroke had a higher rate of disabling neurologic deficits than those who did not. The mechanism by which cryptococcal infection causes stroke is related to vessel compression and inflammation by basal meningeal exudate with resulting stenosis, necrosis, and thrombosis.[8] Infarcts are often found in the basal ganglia, thalamus, and internal capsule because the circle of Willis is often encompassed by heavy inflammatory exudate.[8]

Molds

Aspergillus spp are ubiquitous molds that become invasive, most commonly in immunosuppression. Aspergillosis of the CNS occurs in 10% to 50% of cases and may result from disseminated systemic infection or from direct invasion from sinuses.[8] Most of the strokes reported in the setting of *Aspergillus* infection have been in immunocompromised people. Aspergillosis can take the form of infarction, hemorrhage, or formation and rupture of mycotic aneurysms.[14] Mycotic aneurysms are rare, but uniformly fatal. Infarcts may be territorial, located at the gray-white junction, or involve basal ganglia. Infiltration of blood vessel walls with hyphae extension into the lumen causes thrombosis or embolization of fungal material. Pathologically, tissue and vessel wall necrosis with inflammatory infiltrates and granulomas are found.[8]

Rhinocerebral mucormycosis, caused by *Mucor spp* or *Rhizopus spp*, refers to an invasive infection of craniofacial structures that can lead to stroke. Mucormycosis is rare and generally occurs in immunocompromised states, including diabetes mellitus, especially with ketoacidosis; hematopoietic cell transplantation, solid-organ transplantation, hematologic malignancies, iron overload, deferoxamine treatment infection

TABLE. SUBTYPES OF STROKE ETIOLOGY IN HIV AND SUGGESTED EVALUATIONS

Etiology	Tests
Tuberculosis (TB)	Cerebrospinal fluid (CSF) microscopy for TB; acid fast bacilli (AFB) stain, chest x-ray, CSF and brain histopathology, sputum culture and polymerase chain reaction (PCR) for tuberculosis
Cryptococcus	Blood culture, CSF India ink stain, CSF culture and antigen test, brain histopathology
Syphilis	CSF microscopy, (enzyme linked immunoassay [EIA] and *Treponema pallidum* particle agglutination assay [TPPA]) + (Venereal Disease Research Laborator [VDRL] or rapid plasma reagent [RPR]) blood tests, VDRL/RPR/chemokine ligand 13
Varicella zoster vasculopathy	CSF varicella zoster virus-IgG index, PCR, or brain histopathology
Cardiothrombo-embolism	Holter ECG, transesophageal echocardiogram
Nonatherosclerotic vasculopathy	CT or MR angiography or digital-subtraction angiography (DSA), hemoglobin for sickle cell disease, echocardiography, brain histopathology
Atherosclerotic vasculopathy	CT or MR angiography or DSA, echocardiography, hepatitis C serology, brain histopathology
HIV-associated vasculitis	Hepatitis B and C serology, CT or MR angiography or DSA, histopathology
Small vessel disease	Brain MRI and histopathology
Antiphospho-lipid antibody syndrome	Lupus anticoagulant, anticardiolipin antibody, antiB2-glycoprotein 1 antibody, CT or MR angiography, histopathology
Thrombotic thrombocytopenic purpura	Blood clotting profile, fibrinogen, lactic dehydrogenase (LDH), ADAM metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS13) level, antiADAMTS313 antibody

injection drug use, malnutrition, trauma and burns. Diabetes mellitus has been reported as a predisposing factor for mucormycosis in 36% to 88% of cases.[15]

Inhalation of fungal sporangiospores into the paranasal sinuses causes sporangiospore infection that may spread rapidly into adjacent tissues. Initial symptoms are consistent with sinusitis and often consist of unilateral face pain, fever, and headache. The invasive fungus may spread to involve the palate, sphenoid sinus, or cavernous sinus into the orbits, or cranially into the brain. The fungi have a predilection to invade vasculature, which leads to strokes and mycotic aneurysms. Invasion causes endothelial injury, thrombosis, and inflammatory cascade activation.[8] Cavernous sinus involvement can lead to cranial nerve palsies, thrombosis of the sinus, proptosis, vision loss, and carotid artery invasion.

Dimorphic Fungi

The main dimorphic fungi include *Histoplasma capsulatum*, *Blastomyces dermatiitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, and *Penicillium marneffei*. Involvement of the CNS in dimorphic fungal infection is quite unusual and strokes have been rarely described.

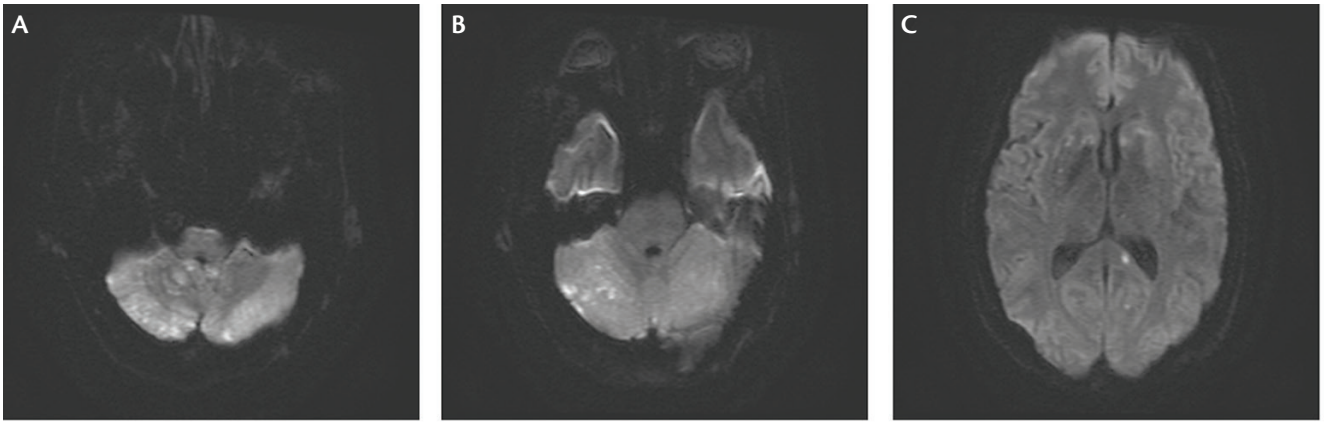

Figure 2. Cryptococcal Meningitis. Axial diffusion weighted imaging sequence shows scattered regions of restricted diffusion in the bilateral cerebellar hemispheres (A and B) and in the left splenium of the corpus callusum (C), consistent with infarctions in the setting of cryptococcal meningitis.

Coccidioides immitis is a soil-based fungus endemic in the southwestern US. Coccidioidomycosis can cause meningitis and vasculitis. In a retrospective study of 62 individuals with coccidioidal meningitis, almost 40% had infarction on brain imaging and nearly all died.[16] An example of stroke in the setting of *Cocidioides* is shown in Figure 3. Neuroimaging and pathologic studies have shown that the basal ganglia, internal capsule, and pons are particularly vulnerable to infection.[8] The mechanism of stroke is similar to other meningitides with perivascular and meningeal inflammation causing a vasculitis with associated intimal proliferation and vessel thrombosis. High dose fluconazole is first-line treatment for *Coccidioes immitis* meningitis.

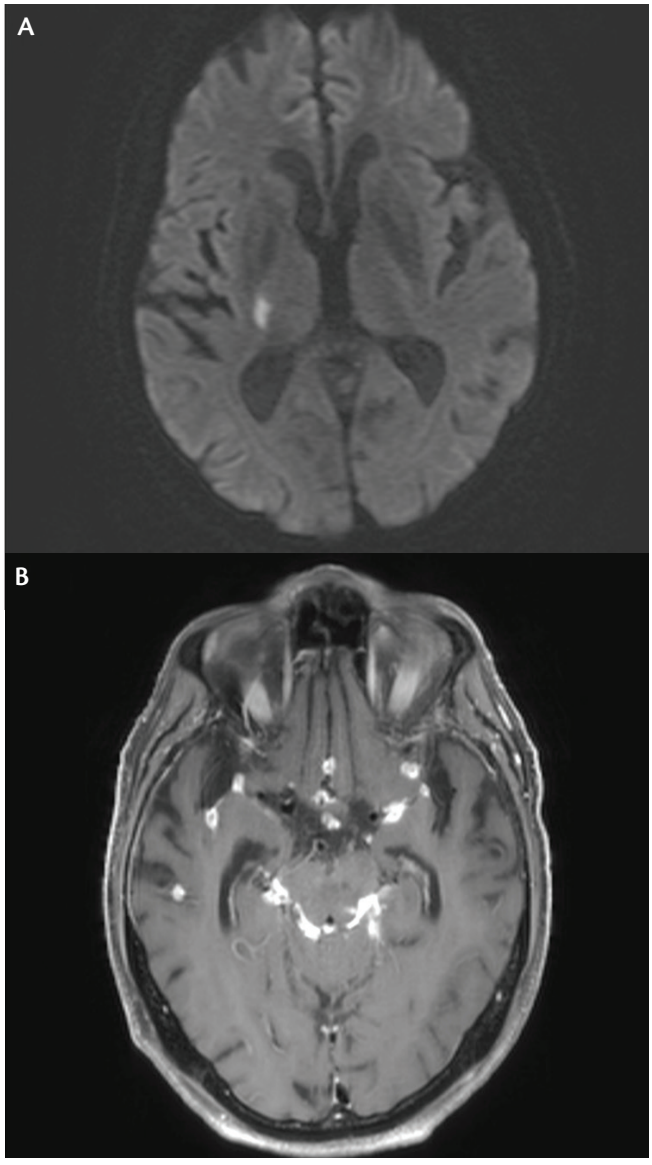

Figure 3. Coccidioides Meningitis. Axial diffusion-weighted imaging sequence of brain magnetic resonance imaging shows acute infarction in the right internal capsule (A). This occurred in the setting of *Coccidioides* meningoencephalitis with other imaging findings such as nodular and plaque-like enhancement of the leptomeninges diffusely, particularly notable in the perimesencephalic cisterns (B).

Conclusion

Stroke is an often-devastating and not uncommon complication of many CNS infections. Strokes are often related to inflammatory basilar meningitis, but in many cases, the exact mechanisms are poorly understood. Although there are often specific treatments available for certain infectious pathogens, cerebrovascular complications themselves may not have specific therapies and often portend a poor prognosis. ■

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Disclosures:
JEF reports no disclosures and has acknowledgements at www.practicalneurology.com