INTRODUCTION

Vasculitis or angiitis is defined as inflammation of blood vessels. Vasculitic involvement of large-, medium-, and small-caliber vessels, respectively, leads to arteritis, venulitis, and capillaritis alone or in combination. Central nervous system (CNS) vasculitis typically affects blood vessels within the brain and rarely the spinal cord. It can also lead to a range of complications, including ischemic infarction (stroke), intracerebral or subarachnoid hemorrhage, mycotic aneurysms, venous thrombosis, and transient ischemic attacks (TIA). Three suggestive clinical patterns are shown in Box 1.1 The diagnosis of CNS can be challenging based on the current options for classifying definite case using neuroradiologic and histopathologic studies, which are used to categorize cases of granulomatous angiitis of the brain (GAB) or nervous system,2 the prototypical, albeit least common and most lethal subtype of primary CNS vasculitis (PCNSV).3 Vessel narrowing, beading, multiple dilatations, aneurysms, avascular mass lesions, and normal studies, and granulomatous angiitis with epithelioid cells, giant cells, and vascular necrosis, can be encountered in GAB and angiitis of other...
origins, including diverse infections. However, the management of PCNSV and infectious-mediated vasculitis will differ.

Infection can injure blood vessels in different ways. The pathogen may bind to or actually infect endothelium, or may trigger an adjacent immune or toxic response that indirectly affects vasculature. Blood vessel injury may reflect the sequela of direct infection, compressive inflammatory exudate, septic emboli, or formation of mycotic aneurysms. The infectious agents associated with CNS blood vessel disease are shown in Box 2.

**Box 1**
**Clinical neurologic presentations of central nervous system vasculitis**
- Encephalopathy with headache
- Intracranial mass lesion with headache and other abnormalities
- Atypical relapsing multiple sclerosis picture (with headache, seizures, encephalopathy, and stroke-like features)


**Box 2**
**Infectious agents associated with central nervous system blood vessel disease**

**Bacterial pathogens:**
- Agents of acute bacterial meningitis (*S pneumoniae, N meningitidis*)
- *M tuberculosis*
- Spirochetal infections (*T pallidum, B burgdorferi, and Leptospira*)
- *Mycoplasma pneumoniae*
- *Bartonella*
- *T whippelii*

**Viral pathogens:**
- Herpes pathogens (VZV, CMV, HSV 1 and 2; EBV)
- Retroviruses (HIV, HTLV-1)
- Hepatitis agents (HBV, HCV)
- Parvovirus B19
- West Nile virus

**Fungal pathogens:**
- *Aspergillus*
- *Candida*
- *Coccidioides*
- *Cryptococcus*
- *E rostratum*
- *H capsulatum*
- *Mucormycosis*

**Parasitic pathogens:**
- *T solium*
- *P falciparum*
- *S mansoni*
- *T gondii*

**Rickettsial pathogens:**
- *R rickettsia*
- *Scrub typhus*
Acute septic bacterial meningitis is associated with vascular complications in up to 20% of patients. Vascular complications typically occur early, including days to weeks following initiation of antibiotic therapy. Invasive pneumococcal disease is defined as a proven isolation of *Streptococcus pneumoniae* bacteria from normally sterile sites, such as blood or cerebrospinal fluid (CSF). It remains a major cause of morbidity and mortality worldwide despite the availability of antibiotic therapy and vaccines. Host as well as bacterial factors contribute to its pathogenicity. Ethnicity, extremes of age, comorbidities, and alcoholism are well-known host risk factors associated with increased susceptibility and higher mortality. Pneumococcal meningitis remains a potentially devastating disease with high mortality and neurologic damage among those who survive. Focal neurologic findings may be present during the acute phase of bacterial meningitis, but more often occur after a few days as immunologic complication of meningitis. Case death rates and risk of sequelae following meningitis are higher for *S pneumoniae* than *Neisseria meningitidis* or *Haemophilus influenzae* infection.

The proinflammatory cascade triggered by *S pneumoniae* and self-perpetuated by a dysregulated host inflammatory response triggers mediators with vascular toxicity resulting in seizures, diffuse brain swelling, hydrocephalus, hearing loss, and ischemic or hemorrhagic stroke. Arteries are involved more often than veins and show narrowing on ultrasonography. Ischemic complications result from vasculitis, vasospasm, associated endocarditis, or intra-arterial thrombosis.

Among 87 consecutive adult patients with pneumococcal meningitis, mortality was 24.1%. Cerebrovascular arterial complications were seen in 21.8%, and venous complications were seen in 10.3% of cases. Bacterial meningitis produces a subarachnoid inflammatory exudate that worsens over time, encasing large vessels at the base of the brain. Invasion of blood vessel walls by inflammatory cells leads to edema, focal stenosis and dilation, and intimal thickening. Large and medium vessels are typically involved in the circle of Willis and along the terminal internal carotid artery (ICA), but the process can spread to involve smaller vessels as well. Although vasculitis and vasospasm lead to cerebral ischemia and infarction however, disseminated intravascular coagulation may also supervene in the setting of septic meningitis and hypercoagulability, with activation of antifibrinolytic, proinflammatory, and procoagulant pathways. Pneumococcal meningitis was associated with cerebral venous thrombosis and carotid and vertebral artery dissection in one reported patient. There are reports of late stroke with pneumococcal meningitis involving small penetrating arterioles.

There can be delayed or chronic vasculopathy and progressive arterial stenosis consistent with late immune-mediated mechanisms, the hypercoagulable state, or rebound inflammatory effects. Such patients are exceptional but may respond to corticosteroid therapy.

Infection of the endocardial inner lining of the heart can involve heart valves, mural endocardium, and septal defects; valvular heart disease is a predisposing factor for infective endocarditis. The commonest site of valvular infection is the mitral followed by the aortic valve; the pulmonic valve is the least frequently involved. Mitral valve carries the highest risk for CNS emboli, as noted in Box 2. Both sterile and infected emboli may occur because of endocarditis.

Endocarditis is generally due to bacterial infection, although fungi, *Rickettsiae*, and viruses are occasional agents. The microorganisms most commonly implicated are *Staphylococcus aureus*, followed by *Streptococcus viridans*, coagulase-negative
Staphylococci, other streptococci, and gram-negative rod organisms; S aureus in particular infects endothelial cells. Streptococcus bovis is a rare cause of infective endocarditis in association with occult gastrointestinal tumors in up to 56% of cases. Bacteremia associated with gingivitis due to HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella) organism with pneumonia or pyelonephritis can infect sterile fibrin-platelet vegetation. Infection occurs with trivial everyday activities, such as brushing of teeth, bowel movements, and invasive procedures, such as dental extraction, prostate removal, endoscopy or colonoscopy, barium enema, and transesophageal echocardiography. Intravenous (IV) drug use is a risk factor for infectious-related endocarditis. Indwelling lines can be a source of bacteremia. Internal jugular lines are more likely to become infected than subclavian lines. Not only is subacute endocarditis associated with embolism but also it promotes the formation circulating immune complexes, cryoglobulins, and agglutinating and complement-fixing bactericidal antibodies.

CNS complications occur in 20% to 40% of patients with infective endocarditis, the commonest of which is stroke due to septic embolism. Clinically diagnosed intracranial mycotic aneurysms complicate 2% to 3% of infective endocarditis cases, although the postmortem rate is in the range of 5% to 10%. About 2% to 6% of all intracranial aneurysms are due to infection, tending to affect distal portions of secondary and tertiary branches of the middle cerebral artery (MCA).

The clinical features of neurologic involvement in endocarditis may initially be very subtle with nonspecific fever; headache, fatigue, and malaise are common. Abnormalities on physical examination suggestive of embolism include Janeway lesions, splinter hemorrhages, and Roth spots; multiple ischemic strokes may also be present. Rupture of resultant mycotic aneurysm can lead to acute catastrophic hemorrhage, the symptoms of which depend on the location. Multiple microscopic emboli can lead to nonfocal encephalopathy.

A recent analysis of neurologically asymptomatic patients with infective endocarditis found that 71.5% of cases manifested occult brain MRI abnormalities consisting mainly of multiple small infarcts in a watershed distribution, and cerebral microscopic hemorrhages within cortical regions.

Most affected patients demonstrate leukocytosis, elevated acute phase reactants, and positive blood cultures. Diffusion-weighted and gradient-echo MRI sequences are recommended to image the commonest findings in affected patients that include ischemia and hemorrhage. Although brain computed tomographic angiography (CTA) and MR angiography (MRA) detect mycotic aneurysms measuring 3 mm to 4 mm or larger in size, digital subtraction angiography (DSA) remains the gold standard, but can be associated with serious complications.

The differentiation of infective endocarditis and primary cerebral vasculitis is extremely important. Therapy for infective endocarditis includes both supportive care and medical interventions, whereas cerebral vasculitis requires immunosuppression. Failure to accurately distinguish the 2 can result in treatment failures and heightened morbidity and mortality. A comparison of the findings of 6 patients with biopsy-proven CNS vasculitis with the data of 6 patients with infective endocarditis showed that the former was generally younger (27–62 years) and presented with multiple strokes (n = 4), intracerebral hemorrhage (n = 1), epileptic seizures (n = 2), or encephalopathy (n = 1). All had pathologic CSF findings, including pleocytosis (n = 5), protein elevation (n = 4), and angiography that revealed multilocular stenosis in 2 cases, whereas DSA was normal in 4. Those with infective endocarditis were generally older (32–77 years) and presented with multiple (n = 3) or single ischemic strokes (n = 2) or encephalopathy and headache (n = 2). Although all patients showed
inflammatory serum findings (C-reactive protein, n = 6; leukocytosis, n = 4), CSF-pleocytosis was present in 2 cases only. Angiography revealed a vasculitic pattern in 2 patients. The diagnosis of bacterial endocarditis was established based on transesophageal echocardiography and blood cultures. Leptomeningeal and brain biopsies performed in 2 cases were normal. Patients with either cerebral vasculitis or infective endocarditis may present with multiple strokes and encephalopathy. The frequency of a vasculitic pattern in angiography is similar in both conditions. Although inflammatory serum findings are the rule in infective endocarditis, pathologic CSF findings were present in all of those with cerebral vasculitis. Transesophageal echocardiography and blood cultures should be performed in order to diagnose or exclude infective endocarditis in those at higher risk. Notwithstanding, immunosuppressive therapy may be dangerous in suspected cases of cerebral vasculitis without confirmatory brain and leptomeningeal biopsy.

Mycobacteria

*Mycobacterium tuberculosis* (TB) meningitis was the first type of meningitis to be described clinically as *dropsy* of the brain in 1768 and subsequently shown to be inflammatory when meningeal tubercles and visceral tubercles were found to be identical in 1830. The tuberculoma, once the commonest intracranial tumor, is now exceptionally rare. The chief neurologic signs and symptoms of tuberculous meningitis reflecting meningeal irritation are neck stiffness and positive Kernig sign, and raised intracranial pressure notably headache and vomiting with mental changes, seizures, and focal neurologic signs. Arteritis is the rule in the vicinity of tuberculous lesions, wherein vessel walls are invaded by mononuclear cells, with the adventitia more heavily involved than the media.\(^\text{16}\) The subintimal and intimal regions form a layer of homogenous fibrinoid material that later involves the media, and the vessel lumen is reduced by inflammatory cell exudation beneath the fibrinoid material, the end results of which are reduction or complete obliteration of the lumen, proliferative endarteritis, and cerebral infarction. The vessels most heavily involved are those at the base of the brain and others in the Sylvian fissure. CNS involvement, which occurs in only 1% of TB infections, has the greatest mortality of any organ involvement, with fatality or severe residual mortality noted in up to one-half of cases of resultant TB meningitis.\(^\text{17}\) Children and human immunodeficiency virus (HIV)-infected individuals are at special risk for developing CNS involvement. Polymorphisms in genes involved in the innate immune response, such as the toll-like receptor 2 gene, may influence dissemination and development of TB meningitis.\(^\text{17}\) The pathogenesis of infection is usually due to rupture of a previously seeded meningeal, subpial, or subependymal focus. Chronic meningitis produces a thick, gelatinous inflammatory exudate that results in intimal thickening with obliterative vasculitis involving vessels at the base of the brain. Stroke occurs in 15% to 60% of affected patients and may be more common in HIV-infected individuals.\(^\text{4,18,19}\) Cerebral infarction can be clinically silent, overshadowed by the meningeal features, or insidious in development. TB-related strokes show a prediction for the anterior rather than posterior circulation. A basal exudate produces inflammatory vascular changes within the circle of Willis. Distal ICA, proximal MCA, and its perforating branches are particularly affected.\(^\text{17}\) More severe meningitis carries a greater risk for vascular involvement. Vasospasm affects strokes in the early period, whereas proliferative intimal disease is a factor in later outcome. The immune reconstitution inflammatory syndrome (IRIS) can supervene during treatment of extraneural TB, unmasking latent TB meningitis and presenting with neurologic features, including stroke. Hydrocephalus is a common sequela with often-associated meningeal enhancement, particularly along basal brain regions. Contrast-enhanced MRA is
more sensitive in the detection of small-vessel involvement. Pathologically proven TB-associated CNS vasculitis has been described in 5 heterogeneous patients to date.16

The diagnosis is confirmed by detection of TB bacilli in CSF using a Ziehl-Neelsen stain and culture as well as a positive polymerase chain reaction (PCR). A positive yield is increased with large sample volumes, and ventricular CSF demonstrating an even higher yield than lumbar CSF. Interferon (IFN)-γ releasing assays and TB antigen analysis can be studied in CSF.20 Neuroimaging features of basilar exudate and hydrocephalus are suggestive.

Treatment involves induction therapy for 2 months with isoniazid, rifampin, pyrazinamide, and a fourth drug, either streptomycin or ethambutol, followed by maintenance therapy with 2 drugs for an additional 7 to 10 months, typically isoniazid and rifampin. Fluoroquinolones are used in multidrug-resistant cases. Adjunctive corticosteroids may be warranted in the first 6 to 8 weeks. Aspirin is potentially useful in reducing stroke and mortality.20

**Spirochetes**

**Syphilis**

Syphilis is a spirochetal infection due to *Treponema pallidum*. Infection is acquired or congenital, with an estimated worldwide annual incidence of 12 million new adult cases.21 About 4% to 10% of untreated patients develop CNS involvement. Symptomatic neurosyphilis presents with meningitis and meningovascular syndromes. Meningitis occurs in the first year of infection, producing basilar meningitis often culminating in stroke and vasculitis.

Meningovascular syphilis comprises 39% to 61% of all symptomatic cases of neurosyphilis. It is characterized by obliterative endarteritis that affects blood vessels of the brain, spinal cord, and leptomeninges, precipitating substantial ischemic injury. Often referred to as Heubner arteritis, it involves medium-sized to large arteries with lymphoplasmacytic intimal inflammation and fibrosis; however, there is a variant form termed Nissl-Alzheimer arteritis that characteristically affects small vessels and produces both adventitial and intimal thickening. Both types can lead to vascular thrombotic occlusions and cerebral infarction, with preferential involvement of the MCA.

Meningovascular syphilis occurs months to years later and is associated with perivascular inflammatory endarteritis that leads to luminal narrowing and rarely dilatation. It typically involves large and medium-sized intracranial vessels, in particular the MCA, as many small intracranial vessels, altogether comprising 15% to 23% of cases.4 Patients may experience prodromal symptoms of headache, vertigo, insomnia, and behavioral changes. Stroke symptoms developed in a subacute progressive pattern in one-quarter of patients. A recent Australian series21 noted a prevalence of 4% for stroke or TIA among those with seropositive meningovascular syphilis.

The affected supraclinoid ICA and proximal vessels of the circle of Willis show smooth or beaded segmental narrowing on neuroimaging, without common or cavernous ICA involvement atypical for atherosclerotic disease. Amorphous proteinaceous firm masses with a necrotic center surrounded by inflammatory tissue termed gumma are noted in the brain of patients with tertiary syphilis and meningovascular disease.

The fluorescent Treponemal antibody, which detects specific *T pallidum* antibodies later in the course of the disease, can be used to confirm the results of plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests, which register reactivity to cardiolipin-lecithin-cholesterol antigen elaborated early in the course of syphilis exposure. The CSF in affected patients with neurosyphilis demonstrates pleocytosis, reactive VDRL, and increased intrathecal *T pallidum* antibody index. All
patients should be checked for HIV infection. Treatment of neurosyphilis is IV penicillin for 10 to 14 days with CSF monitoring in HIV-positive individuals to document normalization. Aspirin 81 mg daily can be added for stroke prophylaxis.

The search for the cause of stroke in young adults should include meningovascular syphilis as a potential cause. Sudden acute severe headache heralded onset of occlusion of bilateral vertebral and proximal basilar artery documented by MRA and was noted in an African man who responded to thrombectomy with restoration of blood flow but succumbed to fatal pontine and subarachnoid hemorrhages. Postmortem examination revealed RPR and a positive VDRL test in CSF with CNS vasculitis characterized by mural thrombi along the vertebrobasilar arteries with well-defined lines of Zahn of alternating layers of fibrin, platelet, and red blood cell aggregates, and inflammatory cell infiltration of the arterial walls particularly in the adventitia. Another patient with abrupt onset of confusion, aphasia, and hemiparesis had carotid angiography that documented normal named cerebral vessels except for smaller than average caliber, with an abnormal complement fixation test of the blood and CSF, positive colloidal gold curve test, and leptomeningeal biopsy that showed lymphocytic infiltration, focal fibrosis, and chronic perivasculitis consistent with meningovascular syphilis.

**Lyme neuroborreliosis**

Veenendaal-Hilbers and colleagues introduced the term Lyme neuroborreliosis in 1988 to emphasize CNS involvement due to Lyme disease. *Borrelia burgdorferi sensu lato* is the spirochete responsible for Lyme disease. *B burgdorferi sensu stricto*, hereafter referred to as *B burgdorferi*, is the species agent that causes Lyme disease and its neurologic complications in North America; *Borrelia garinii* and *Borrelia afzelii* species predominate outside of North America. Virtually all cases result from an infected *Ixodes* tick bite. Lyme disease is a systemic infection with most patients manifesting the prototypical expanding skin lesion at the bite site termed erythema migrans. Both the CNS and the peripheral nervous system (PNS) are targeted body organs. CNS vasculitis, although exceedingly uncommon, probably accounted for less than 1% of all Lyme disease cases in endemic areas. Patients with Lyme neuroborreliosis may present with cerebral infarction, intracerebral or subarachnoid hemorrhage, and TIA.

Only 3 patients reported in the literature with neurovascular clinical syndromes ascribed to CNS vasculitis in which detailed information was available, including documentation of positive CSF Lyme serology, were ultimately found to have verified vasculitis. Two patients, who presented with headache, were ultimately noted to have histopathologically confirmed vasculitis on brain biopsy. Patient 3 of Oksi and colleagues was an 11-year-old boy with headache and hyperactivity syndrome who developed gait difficulty concomitantly with a stroke visualized on brain MRI. Subsequent craniotomy and biopsy of the area of enhancement disclosed lymphocytic vasculitis of small vessels without fibrinoid necrosis, and CSF *B burgdorferi* serology was positive. Headache and the MRI improved with IV antimicrobial therapy. Patient 2 of Topakian and coworkers presented with headache, fatigue, malaise, nausea, and vomiting first considered migrainous and then psychosomatic until subsequent MRI disclosed ischemic brain infarctions. MRA was compatible with diffuse vasculitis, and CSF showed lymphocytic pleocytosis with positive oligoclonal bands, and diagnostic CSF and serum *B burgdorferi* serology. Brain biopsy showed vasculitis involving leptomeningeal arteries comprising lymphoplasmacytic vessel wall infiltration with focal necrosis. Epithelioid cells were beaded in multiple granuloma-like formations in the leptomeninges. There was symptomatic improvement after a course of IV antimicrobial therapy. The third patient reported by Miklossy and colleagues, a 50-year-old
man with leg spasticity and CSF pleocytosis for 15 months who progressed to hemi-
paresis and ventilatory support, was later found to have diagnostic B burgdorferi
serology in serum and CSF. Postmortem examination showed perivascular lympho-
cytic inflammation of leptomeningeal vessels, some of which displayed infiltration of
the vessel walls, duplication of the elastic lamina, narrowing of lumina, and complete
obstruction of some leptomeningeal vessels by organized thrombi.

There are rare instances of cerebral venous sinus thrombosis. B burgdorferi infec-
tion in the CNS may be associated with lymphocytic cerebral vasculitis preceding
clues of which include headache, arthralgia, myalgia, peripheral facial nerve palsy,
and flulike illness during the summer months. Laboratory evaluation may demonstra-
mento enhancement on brain MRI, although there appears to be a propensity of
vasculitis to involve the posterior circulation. Lumbar CSF analysis typically reveals
pleocytosis, increased protein, and intrathecal Lyme antibody production. CNS
vasculitis due to Lyme neuroborreliosis should be treated with IV ceftriaxone 2 g daily
for 4 weeks via midline or PIC (permanent intravenous catheter) line with daily aci-
dophilus to lower risk of Clostridium difficile colitis.

**Leptospira**

Leptospirosis is a worldwide zoonotic infection due to a spirochete from the genus
Leptospira. It is transmitted by the urine of infected animals to people exposed to
the pathogenic organism through contact with contaminated water, blood, or soil.
Infection is biphasic, with flulike symptoms, followed by a second immune phase
that can involve meningitis, jaundice with liver injury, and renal failure. Infection can
be asymptomatic. About 90% of symptomatic infections manifest a benign biphasic
febrile illness with 10% involving icteric Weil disease, and a fatality rate of 10%. Spi-
rochetes are found in blood and CSF early in the course of the illness, and in the urine
later in the disease. Leptospirosis more commonly causes meningitis or meningoen-
cephalitis. Clinically apparent CNS vascular involvement is unusual but can result in
stroke, hemorrhage, and venous sinus thrombosis. Diagnostic tests include
screening serology via enzyme-linked immunosorbent assay, microscopic agglutina-
tion test, and PCR. Vasculitis is a recognized feature of this infection involving capil-
laries, with consequent edema, necrosis, and lymphocytic infiltration. Therapy
involves primarily doxycycline; however, other effective antibiotics include cefotax-
ime, penicillin, ampicillin, and amoxicillin.

**Relapsing fever**

Relapsing fever is spread by tick or lice bites. Louse-borne relapsing fever is due to
Borrelia recurrentis. Tick-borne relapsing fever is due to at least 15 different Borrelia
species. Clinical illness is characterized by febrile episodes accompanied by promi-
nent headache and myalgia. Neurologic involvement is characterized by meningitis,
facial palsy, myelitis, radiculitis, and focal or diffuse CNS dysfunction. Neuropatho-
logic changes involve edema, subarachnoid, and parenchymal hemorrhage, with peri-
vascular mononuclear infiltrates. Spirochetes can be found in the cerebral
microvasculature and interstitial spaces. Diagnosis is based on culture and stain.
Treatment includes administration of doxycycline, oxytetracycline, or cephalosporin.

**Other Bacteria**

**Mycoplasma**

Mycoplasmas are very small bacteria that have a plasma membrane boundary, but
lack a cell wall. The nervous system is a major extrapulmonary target, and neurologic
disease can occur after primary atypical pneumonia or de novo. Mycoplasma en-
cephalitis reflects direct brain invasion or an immune-mediated syndrome. There is
evidence for vascular injury and microthrombi, with endothelial cell infection. Stroke occurs in both children and adults. Diagnosis is based on serology and PCR when positive. Therapy involves a course of macrolide antibiotics, although neurologic involvement may be postinfectious and immune mediated. Anticoagulation can be considered for thrombotic disease.

Rosales and colleagues described isolation of *Mycoplasma gallisepticum* and *Mycoplasma synoviae* from the brains of poultry showing meningeal vasculitis and encephalitis, postulating a role for invasive mycoplasma species in human across the blood-brain barrier.

**Bartonella**

*Bartonella* are facultative gram-negative intracellular bacteria that cause human and zoonotic disease. *Bartonella henselae* causes cat scratch disease. Several *Bartonella* species are associated with neuroretinitis, a retinal vasculitis. Immunocompromised hosts are vulnerable to more severe infections. *Bartonella* species can produce cutaneous and systemic vasoproliferative lesions. *B henselae* is known to invade and colonize vascular endothelial cells, among others. Among a broad neurologic spectrum, there are rare cases of ischemic stroke and cerebral arteritis. Diagnosis is based on serology and PCR. Therapy involves doxycycline or azithromycin.

Balakrishnan and colleagues described isolation of *B henselae* DNA by PCR from a 12-year-old with headaches, visual and auditory hallucinations, anxiety, vision loss, bouts of paralysis, facial palsy, chronic insomnia, seizures, dizziness, cognitive dysfunction, and memory loss, resulting in cerebral infarction. However, frank vasculitis lesions were not observed.

**Whipple disease**

*Tropheryma whippelii*, a member of gram-positive Actinobacteria family, is the etiologic agent of Whipple disease, which is the soil-borne gram-positive bacillus. CNS involvement, which occurs in up to 43% of cases, may be the initial presentation of infection in 5% of cases. CNS involvement occurs in the setting of active Whipple disease as well as in those relapsing previously treated disease and isolated CNS involvement. Stroke presentation, although very rare, has been described and should be in the differential diagnosis of CNS vasculitis. Stroke also occurs with leptomeningeal arterial fibrosis and thrombosis, or associated with endocarditis. Clues to diagnosis are extraneural disease, including weight loss, fever, polyarthritis, diarrhea, and uveitis. Oculomasticatory myorhythmia and supranuclear gaze palsy are characteristic neurologic features. The diagnosis can be confirmed with PCR and tissue biopsy that reveal macrophages that stain positive for glycogen with the periodic acid Schiff assay, or the identification of the causative organism by immunoreactive antigen. Effective treatment includes administration of third-generation cephalosporins followed by long-term, on average 2 years of ,trimethoprim-sulfamethoxazole and doxycycline.

Famularo and colleagues identified arterial and arteriolar fibrosis, thrombosis, and thickening associated with inflammation of adjacent brain parenchyma and leptomeninges and cerebral vasculitis in a patient with cerebral Whipple disease and stroke syndrome of without gastrointestinal involvement due to hematogenous spread of *T whippelii*.

**VIRUSES**

**Herpesviruses**

Herpesviruses are a large family of enveloped DNA viruses. Several distinct agents affect humans, and all result in lifelong latent infection. Varicella zoster virus (VZV) is the cause
of childhood chickenpox, and most children manifest only mild neurologic sequelae, and an important infectious agent of associated blood vessel disease. After the infection resolves, the virus becomes latent in neurons of cranial and spinal ganglia of nearly all individuals and has the propensity to reactivate in elderly adults and immunocompromised individuals to produce shingles. An uncommon but serious complication of virus reactivation is ischemic and hemorrhagic stroke. VZV vasculopathy affects both immunocompetent and immunocompromised individuals, typically presenting with headache and mental status changes with or without focal neurologic deficits and a spectrum of vascular damage from vasculopathy to vasculitis with stroke. Both large and small vessels can be involved, and MRI shows multifocal ischemic lesions, commonly at gray-white matter junctions. The diagnosis of VZV can be missed when symptoms and signs occur months after zoster, or in the absence of a typical zoster rash.

It is the only virus documented to replicate in human arteries and is a recognized risk factor for ischemic stroke in children, and stroke and TIA in adults under age 40.\textsuperscript{44,45} It is latent in cranial nerve, dorsal root, and autonomic nervous system ganglia. VZV, when reactivated, spreads to arteries of the brain and spinal cord to produce a large- and small-vessel vasculopathy. Cerebral blood vessels show multinucleated giant cells, Cowdry type A inclusion bodies with viral particles, and detectable VZV antigens and DNA, consistent with direct infection. In one series of 30 patients,\textsuperscript{7} 50% had both large- and small-vessel involvement; 37% showed small artery involvement, and 13% manifested large-artery invasion.\textsuperscript{46} Clinical sequelae include infarction, aneurysm, hemorrhage, and ICA dissection.\textsuperscript{47} Recently, VZV vasculopathy was recognized as an etiologic agent in patients presenting with giant cell arteritis despite noninformative temporal artery biopsy. Vascular involvement can be unifocal or multifocal. Both immunocompetent and immunocompromised hosts are affected, although more commonly it is the immunocompromised patient. Infarctions can be superficial or deep. Gray-white matter junction lesions are suggestive. With regard to primary infection, there are unusual cases of cerebral infarction or hemorrhage in children. With regard to reactivated infection, vasculopathy can occur up to 6 months after a zoster outbreak. Herpes zoster ophthalmicus (HZO) can be followed weeks later by delayed contralateral hemiparesis, with segmental carotid siphon arteritis, typically in immunocompetent individuals.

Small-vessel involvement may lead to central retinal or posterior ciliary artery involvement, with monoclonar vision loss. Neuroimaging in these VZV cases is typically abnormal. CSF is often abnormal with an increase in white and red blood cells, raised CSF protein content, and present oligoclonal bands. The CSF VZV immunoglobulin G (IgG) antibody should be measured along with a sample for PCR analysis; however, the former is more likely to be informative in true cases. CNS VZV vasculopathy often presents with headache and progressive neurologic deficits without a history of zoster rash; rarely is VZV associated with spinal cord infarction. Treatment involves antiviral therapy with IV acyclovir; however, oral valacyclovir can be used to extend the length of treatment in more profoundly affected or refractory cases due to concomitant HIV infection.

Thirteen patients with VZV-related vasculopathy with detailed clinicopathologic data including histologic findings of vasculitis have been described in the literature. VZV DNA and VZV-specific antigen were found in 3 of 5 cerebral arteries examined with histologically confirmed CNS vasculitis involving the circle of Willis. Patient 1 of Eidelberg and colleagues\textsuperscript{48} who presented with headache and HZO rash was deemed to have CNS vasculitis based on complete occlusion of the MCA and so treated; however, postmortem examination showed no evidence of vasculitis. One patient with contralateral hemiplegia 1 month after HZO was found at postmortem examination to have endarteritis of unilateral anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA)\textsuperscript{49} with VZV DNA from the involved vessels.
Cytomegalovirus (CMV) replicates in leukocytes and vascular endothelial cells during primary infection with single patient reports of CMV associated with vasculitis. Venous involvement can be found in addition to occlusive arteritis. Affected individuals are usually HIV-positive or an immunocompromised host. Diagnosis involves serologic studies, PCR, culture, and histopathologic tissue analysis for the causative organism. Therapy includes IV ganciclovir, foscamet, or a combination of both. One recently described elderly woman with CMV encephalitis later developed a postinfectious PCNSV. Koeppen and coworkers described rapidly progressive CNS and PNS deterioration 2 years after chemotherapy for small cell undifferentiated lymphoma in whom postmortem examination demonstrated occlusive arteritis in gray and white matter with involvement of veins indicative of vasculitis, in addition to Cowdry A inclusions and chorioretinitis.

Herpes simplex virus (HSV), types 1 and 2, and Epstein-Barr virus (EBV) have been associated with CNS vasculitis; however, vessel wall contrast enhancement may be a clue in suspected patients, and a positive findings in CSF PCR is adequate to justify antiviral therapy. However, in contrast to VZV, where reactivation is the mechanism of causation, CNS vasculitis may be problematic due to latency of infection. Kano and colleagues described EBV-associated CNS vasculitis in brain biopsy tissue of a patient with rapid CNS deterioration and positive EBV DNA in CSF.

Retroviruses

**Human Immunodeficiency Virus**

Approximately 1% to 5% of individuals infected with HIV are at risk of developing a stroke due to opportunistic infections, coagulopathy, cardioembolism, HIV-associated vasculopathy, and frank vasculitis. Moreover, HIV-associated arterial vasculitis is thought to account for 13% to 28% of ischemic strokes. CNS vasculitis, which is estimated to occur in less than 1% of cases of HIV infection, is a diagnosis of exclusion. Typically, patients are in an advanced stage of the infection. HIV can be associated with a granulomatous inflammation involving small arteries and veins within the brain and leptomeninges. HIV patients with vasculitis should be assessed for cryoglobulins and accompanying infection, especially TB, syphilis, CMV, VZV, hepatitis B and C virus (HBV and HCV), or a drug-induced vasculitis. Therapy typically involves highly active antiretroviral therapy (HAART), with corticosteroids reserved for refractory cases due to vasculitis.

Early in the HIV and the AIDS epidemic, it was clear that a significant proportion of infected persons were IV drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles, thereby increasing the risk of spread of HIV and other blood-borne infections. The 2 postulated periods in the neurobiology of HIV when autoimmune disease manifestations and cerebral vasculitis can occur are shortly after seroconversion and before the spread of productive infection, and after initiation of HAART in association with the IRIS. The timing of early HIV infection has been difficult to ascertain based on the presence of one or more well-recognized clinicopathologic HIV/AIDS syndromes, including HIV encephalitis, HIV-associated dementia, and AIDS-dementia complex, all of which are indicative of symptomatic infection. Six presymptomatic HIV-seropositive drug abusers by Gray and colleagues had nonnecrotizing cerebral vasculitis at postmortem examination.

**Human T-cell lymphotropic virus-type 1**

Human T-cell lymphotropic virus-type 1 (HTLV-1) was the first described human retrovirus. It causes adult T-cell leukemia and lymphoma as well as a progressive
myelopathy referred to as tropical spastic paraparesis–HTLV-1–associated myelopathy in less than 1% of infections. Neurologic syndromes associated with HTLV-1 infection appear to be due to active and selective expansion of retrovirus-infected T cells that harbor provirus that selectively expresses HTLV-1 proteins, such as Tax. In particular, activated cytotoxic CD8\(^+\) T cells are increased. Perivascular inflammation is a frequent histopathologic feature. The laboratory diagnosis of HTLV-1 infection is based on serologic and PCR studies. There is no proven antiviral therapy. Ma and co-workers\(^56\) reported vasculitis in brain biopsy tissue of a patient with HTLV-1 infection.

### Hepatitis Virus Agents

Hepatitis C is estimated to affect 170 million people worldwide with extrahepatic involvement that occurs in 38% to 74% of cases. Hepatitis C is associated with cryoglobulinemia, arthritis, and palpable purpura. There is an immune response to the Fc portion of immunoglobulin, characterized by the Wa idiotype. The resulting immune complex, which contains virus, idiotypic antibody, and antibody, precipitates in the cold and produces a small-vessel vasculitis. HCV can cause CNS vasculitis independent of cryoglobulinemia, and CNS vasculitis may be the first clinical manifestation of hepatitis C infection.

Affected patients present with progressive headache, multiple strokes, and typical angiographic patterns. Therapy includes the antiviral agent interferon (IFN), ribavirin, sofosbuvir, protease inhibitors, and corticosteroids. Both HBV and HCV have been associated with polyarteritis nodosa\(^59\) that typically involves the PNS, but unusual cases may involve the CNS. In such cases, antiviral therapy is added to corticosteroids, and cyclophosphamide, in more severe cases. The resultant choice of therapy might involve the virostatic agent lamivudine or IFN-\(\alpha\) for HBV and ribavirin for HCV.\(^60\) Plasma exchange and rituximab can be added in specific cases as needed.

### Parvovirus B19

Parvovirus B19 is a small nonenveloped DNA virus that only infects humans. It causes erythema infectiosum, also known as fifth disease, a benign childhood condition characterized by a classic slapped-cheek appearance. It can cause anemia with preexisting disease as well as arthritis. The cellular receptor for parvovirus B19 is an antigen of the P blood group present on endothelial cells and erythroid progenitor cells. Rare patients with CNS vasculitis have been reported in association with parvovirus B19 infection.\(^61\) The diagnosis is based on serologic studies and PCR testing. There is no specific antiviral therapy for parvovirus B19 infection; however, both intravenous immune globulin (IVIG) and corticosteroids have been used therapeutically.

### West Nile Virus

West Nile virus is a flavivirus typically transmitted by the bite of infected culex mosquitoes. Less than 1% of patients develop invasive neurologic disease that includes meningitis, encephalitis, and resultant flaccid paralysis, with rarely reported cases of ischemic infarction and CNS vasculitis\(^62\)–\(^64\) and occlusive retinal artery vasculitis. Patients with a history of diabetes and alcohol abuse, and older individuals are at increased risk for ischemic complications. Diagnosis is based on IgM antibody and viral RNA detection as well as virus isolation. There is no antiviral therapy, but IVIG has been beneficial in individual patients.

### Zika Virus

Zika virus is an arbovirus belonging to the Flaviviridae family. Younger\(^55\) has reviewed the epidemiology of Zika virus. Originally isolated in Uganda, Zika virus is known to
cause mild clinical symptoms similar to those of dengue and chikungunya. Zika is transmitted by different species of *Aedes* mosquitoes. Nonhuman primates and possibly rodents play a role as reservoir. Direct interhuman transmission has been reported to occur perinatal, through blood transfusion, and sexually. The first human cases were reported in Africa, but recent outbreaks have been seen in several regions of the world, including Brazil, highlighted the needs of the scientific and public health community to consider it an emerging global threat.

Its clinical profile is that of a dengue-like febrile illness, but recently, associated Guillain-Barré syndrome and microcephaly have appeared. There is neither a vaccine nor prophylactic medications available to prevent Zika virus infection, so current public health recommendation advises pregnant women to postpone travel to areas where Zika viral infection is epidemic, and if not, to follow steps to avoid mosquito bites to avert fetal brain injury associated with intrauterine infection. Viral RNA indicating Zika virus, Chikungunya virus, and Dengue infection can be pathogenically isolated from the CSF of adults with neurologic symptoms with meningitis or encephalitis, Guillain-Barré syndrome, and CNS vasculitis.

**Fungi**

*Aspergillus*

Aspergillosis is the most common invasive mold infection worldwide. It typically causes disease in immunocompromised hosts, although CNS vasculitis and stroke occur in immunocompetent patients. The major human pathogens are from the *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus* species. Patients with hematologic malignancies and a history of bone marrow transplantation can have fulminant CNS courses with mortalities of 85% to 99%. The *Aspergillus* organisms invade blood vessels with resultant production of proteases that weaken the vessel wall leading to aneurysm formation. The course can be more chronic and insidious in those with lesser degrees of immune compromise, such as due to diabetes mellitus. Spread to the CNS occurs via hematogenous routes from the lung or by direct extension through the paranasal sinuses and orbits. CNS involvement, which occurs in 10% to 50% of systemic infections, includes meningoencephalitis and intracerebral hemorrhage as well as vasculopathy, and mycotic aneurysm formation leading, respectively, to stroke and potentially fatal subarachnoid hemorrhage with greater involvement of penetrating than larger named vessels.

*Aspergillus* infection should be considered in immunocompromised hosts with pulmonary disease and either ischemic or hemorrhagic stroke. The diagnosis can be difficult because CSF cultures are positive in less than 50% of cases, and PCR is investigational. Two antigen assays, each for biomarkers including galactomannan and beta-D-glucan, have not been standardized in the CSF. Tissue biopsy can be confirmatory. Brain neuroimaging may demonstrate ring-enhancing lesions, meningeal enhancement, and ischemic or hemorrhagic stroke. Therapy involves oral voriconazole and surgical resection of focal cerebral and extraneural sites of involvement.

*Candida*

*Candida* species are part of normal human flora and thus typically are not pathogenic unless there is mitigating systemic immune compromise. Neutropenia is a major risk factor for invasive disease. *Candida* is considered a yeast infection with *Candida albicans* the most common agent in humans. It invades small blood vessels and can be associated with thrombosis and infarction. Neurologic involvement most often takes the form of meningitis that may predispose to basilar artery thrombosis. One
affected patient with HIV/AIDS and subacute meningitis who was treated empirically for tuberculosis and initiated on HAART therapy developed fatal worsening due to postmortem-proven basilar Candida meningitis and cerebral vasculitis characterized by CD8+ T-cell infiltration and microinfarcts, consistent with IRIS. The diagnosis of Candida infection is based on a positive culture and informative PCR, and suggestive findings on antigen assays to mannan and beta-D-glucan are not routinely performed. Effective treatment depends on the age and severity of infection with lipid formulations of amphotericin, fluconazole, or echinocandin.

Lipton and colleagues described CNS vasculitis at postmortem examination in 48% of 29 patients with systemic candidiasis, only 21% of whom had suspected antemortem involvement, noting that immunosuppression represents a risk factor for both systemic and cerebral mycoses.

Coccidioides immitis

Coccidioides immitis is a soil-based fungus endemic to the arid southwest and Latin America. Infection may be asymptomatic or the cause of mild pulmonary issues, such as occurs in valley fever. About one-half of disseminating cases involve the CNS, resulting in basilar meningitis with a local vasculitis of small and medium arteries, and occasionally, larger ones that are more likely to occur in immunocompromised hosts. Cerebral infarction complicates about 40% of patients with coccidioides meningitis, leading to alteration of mental status and emergency of focal deficits. Stroke can occur years later following the initial infection. In general, acute infectious-related injury can predispose to vasculitic changes that include transmural inflammation with thrombosis and fibrinoid necrosis, whereas chronic injury leads to intimal thickening, proliferation, and narrowing of the lumen with little or no inflammation.

CSF culture is positive in 33% of cases, often in association with eosinophilic pleocytosis. Complement fixation is positive in about 40% of serum and CSF specimens, but seroconversion can take up to 12 weeks. Treatment involves high-dose fluconazole followed by maintenance therapy. Voriconazole is a second-line agent. A self-limited course of corticosteroids can be given in the setting of cerebral infarction to reduce inflammation.

Eron and colleagues described vasculitis and encephalitis as complications of C immitis infection of the CNS in 6 cases of apparent and 4 cases of histologically proven vasculitis, including one with vasculitis and encephalitis associated with coccidoidal meningitis. Vasculitic complications include mental status changes, aphasia, hemianopsia, and hemiparesis.

Cryptococcus neoformans

The yeast form, Cryptococcus neoformans, is the commonest cause of fungal meningitis. Vessels of the circle of Willis are most affected by the resultant basilar exudate. Vascular involvement occurs early or late in 4% to 32% of cases. Diagnosis is made by the presence of CSF cryptococcal antigen, India ink stain, and culture. Treatment involves induction therapy with IV amphotericin and flucytosine for 2 weeks followed by consolidation with fluconazole once CSF cultures are negative. Corticosteroids may offer a benefit in the setting of stroke.

Exserohilum rostratum

Exserohilum rostratum is a dematiaceous fungus and black mold that does not typically cause human disease. It is a major contaminant in iatrogenic infections due to mold contamination of methylprednisolone acetate. There was one fatal case of...
meningitis and CNS vasculitis in an immunocompetent host who received a cervical epidural steroid injection for chronic neck pain. The diagnosis is based on culture and PCR of CSF. Recommended therapy is liposomal amphotericin B and voriconazole, with monitoring of drug levels.

Lyons and colleagues described angioinvasive septate fungal hyphae associated with diffuse vasculitis at postmortem examination in the brainstem of a patient with fatal Exserohilum meningitis following cervical epidural methylprednisolone injection for new occipital headaches.

**Histoplasma capsulatum**

*Histoplasma capsulatum* is a dimorphic fungus that is endemic in the Ohio and Mississippi River Valley as well as parts of Latin America, Asia, and Africa. Although infection in immunocompetent hosts may remain asymptomatic or lead to mild lower respiratory tract illness, others can experience disseminated infection with CNS involvement in up to 20% of cases. The latter most commonly manifests meningitis; however, strokes may accompany associated infective histoplasma endocarditis or associated meningovascular disease with ensuing mortality of 11% to 100%. Antihistoplasma antibodies can support CSF culture and antigen studies, which show evidence of CNS infection. Treatment includes liposomal amphotericin followed by itraconazole or fluconazole for at least 1 year.

**Mucormycosis**

Mucormycosis is due to infection by filamentous fungi of the order Mucorales and class Zygomycetes. They are ubiquitous organisms in bread mold, soil, manure, and decaying vegetation, and the second commonest invasive mold infection. *Rhizopus*, *Mucor*, and *Lichtheimia* are the most common genera to cause mucormycosis. Immunocompromised hosts are at particular risk. Underlying conditions include diabetes mellitus, hematologic malignancy, trauma, solid cancers, and solid organ transplants.

Sites of infection include lung, skin, gastrointestinal tract, and the rhino-orbito-cerebral region. Iron is an important component in this infection. These fungi contain spore coat homolog proteins that are unique and required for angioinvasion. The result of this blood vessel invasion is vessel thrombosis and tissue necrosis. The rhino-orbito-cerebral form may produce suggestive necrotic nasal or sinus eschars. Patients may experience carotid or basilar artery thrombosis, cavernous sinus thrombosis, or intracerebral hemorrhage.

Diagnosis is based on clinical suspicion confirmed by biopsy, scraping, or culture. PCR is being evaluated. Treatment involves a combination of surgery and systemic therapy. Liposomal amphotericin B is favored therapy; however, thiazoles and posaconazole antibiotics have been used in selected individuals.

**PARASITES**

**Taenia solium**

Cysticercosis due to infection with the larval stage of the pork cestode tapeworm *Taenia solium* is the commonest CNS parasite, accounting for 10% of stroke cases in endemic areas, and a major cause of headache and seizures. Lenticulostriate lacunar infarcts are more common than large artery stroke; however, TIA and intracranial hemorrhages also occur. Among 28 patients with subarachnoid cysticercosis, 15 (53%) had angiographic evidence of cerebral arteritis, 12 (80%) of whom had a stroke syndrome (*P* = .02). Eight of the 15 patients (53%) with cerebral arteritis...
had evidence of cerebral infarction on MRI, whereas only one patient without cerebral arteritis had cerebral infarction (P = .05). The most commonly involved vessels were the MCA and PCA. Small vessels are preferentially affected, with superficial cortical vessel thrombosis, occlusive endarteritis, and focal arteritis. Larger circle of Willis vessels are involved when severe arachnoiditis is present. Diagnosis involves antibody testing and suggestive findings on neuroimaging; however, antigen testing is not routinely used. Antihelminthic therapies include the benzimidazole drug albendazole and the antihelminthic drug praziquantel with corticosteroids.

**Plasmodium falciparum**

*Plasmodium falciparum* is a unicellular parasitic protozoan that infects humans, causing more severe forms of malaria. The disease is typically transmitted by the bite of an infected female *Anopheles* mosquito. Inoculated sporozoites infect and multiply in liver cells and then differentiate into merozoites that are released and invade red blood cells. Infection leads to expression of adhesive surface proteins that cause the red cells to stick to the walls of small blood vessels. Intercellular adhesion molecule-1 is a major host binding site.

Falciparum malaria is a leading cause of morbidity and mortality in tropical countries. Cerebral malaria is the most severe neurologic manifestation. It is defined by coma that is not due to seizures, hypoglycemia, or any other identifiable cause, and that is associated with a positive blood smear for parasitized red blood cells.

Pathophysiology is thought to be due to parasitic sequestration in cerebral microvessels. As infected red cells adhere to the endothelium, they cause further erythrocyte agglutination along with platelet clumping. There is endothelial activation, and direct cytotoxic injury. Perfusion is abnormal, and tissue oxygenation is compromised. There may also be injury mediated by soluble factors, including various chemokines, cytokines, nitric oxide, and quinolinic acid. Diagnosis is based on blood smear and antigen-based rapid diagnostic tests. Patients diagnosed with uncomplicated malaria can be effectively treated with the oral antimalarial drug chloroquine phosphate (Aralen) or hydroxychloroquine (Plaquenil). Patients who are considered to have severe disease should be treated aggressively with parenteral antimalarial therapy. Treatment of severe malaria involves parenteral quinidine gluconate given by continuous infusion for at least 24 hours in an intensive care setting plus one of the following: doxycycline, tetracycline, or clindamycin orally or IV followed by oral administration for a full course of 7 days.

There is an investigational new drug protocol that can be obtained by contacting the Centers for Disease Control and Prevention that uses artesunate followed by one of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine (Lariam).

**Schistosoma mansoni**

This Trematode infection, which involves a flatworm, is endemic to sub-Saharan Africa and South America. There is percutaneous penetration of cercariae in the invasive stage followed by mating worms that inhabit the inferior mesenteric veins where they excrete eggs in the adult stage. Neurologic involvement occurs in later stages of infection wherein adult worms can be found in spinal meningeal veins and the intracranial venous system. Ectopic eggs migrate to the brain provoking granuloma formation. Cerebrovascular lesions are found in 20% of patients from postmortem series.

CNS vasculitis occurs in both early and later stages of *Schistosoma* infection associated with multiple infarctions, marked eosinophilia, and a corticosteroid response reflective of eosinophil-mediated injury. Presumptive diagnosis is suggested...
by a known travel history and compatible clinical presentation combined with serologic testing and documentation of eggs in the stool. Treatment involves praziquantel.

Toxoplasma gondii

*Toxoplasma gondii* is an obligate intracellular protozoan that causes toxoplasmosis. During the initial acute phase of the infection, rapidly dividing tachyzoites spread throughout the host. The development of an effective cellular immune response suppresses the replication of tachyzoites and eradicates most of them, ending the acute phase of the infection. In the brain, the parasites undergo conversion to bradyzoites, which remain viable in the form of cysts because of the low levels of class I major histocompatibility complex and, in addition, the parasites within the cyst are surrounded by the parasitophorous vacuole that is enclosed by a cyst wall; thus, a small amount of antigen escapes into the cytoplasm of the cyst-containing host cell. The organisms reproduce slowly throughout the life of the host and can remain viable within intact nerve cells. Cyst rupture occurs rarely and, in immunocompetent individuals, a rapid immune response leading eventually to microglial nodule formation limits the damage to small inflammatory foci. However, in immunocompromised hosts, cyst rupture may reactivate the infection, leading to the conversion of bradyzoites to the active and rapidly replicating tachyzoites and development of severe tissue injury. Therefore, the CNS may be affected in congenital toxoplasmosis, as a primary infection in immunocompetent individuals or as an opportunistic infection in immunosuppressed individuals. Thus, most CNS infections represent reactivation of old lesions and hematogenous spread from prior infections instead of primary infection.

The resulting disease is widely distributed worldwide among domestic animals and humans. The oocyst form is excreted in cat feces and can be the source of infection. Eating infected raw or undercooked meat is another source of infection. Most infections are asymptomatic; however, immunocompromised hosts are particularly vulnerable to clinical disease. Toxoplasmosis is the leading cause of focal CNS disease in patients with HIV/AIDS and low CD4\(^+\) T-cell counts.

Congenital toxoplasmosis causes the characteristic eye lesion termed chorioretinitis, cerebral calcifications, hydrocephalus, and CSF pleocytosis. The pathologic features include periventricular microglial nodules surrounded by lymphocytic vasculitis and necrotic foci. Toxoplasma encephalitis shows well-circumscribed areas of hemorrhage and necrosis, with vascular thrombosis and present tachyzoites. The resulting clinical presentation is usually headache with constitutional symptoms that progress to encephalopathy and focal neurologic deficits.

Pittella\(^{85}\) has reviewed toxoplasmosis as an opportunistic infection in immunosuppressed individuals. In HIV-infected patients, the disorder presents as a mass lesion, usually multiple, with the basal ganglia, thalamus, and the cerebral gray and white matter junctions being the preferred sites. The lesions consist of well-defined areas of coagulative necrosis, with or without hemorrhage, containing karyorrhectic debris. Blood vessel changes are common, characterized by necrosis, vasculitis, and thrombosis. Mononuclear inflammatory cells and reactive astrocytes in variable numbers are seen surrounding the necrosis. Bradyzoites and tachyzoites are present in large numbers, the former at the periphery of the lesion and the latter within the necrosis. The immunohistochemical identification of tachyzoites is especially useful when bradyzoites are not seen. In more chronic lesions, macrophages may surround the necrosis associated or not with calcification, and parasites are reduced in number. In treated patients, the lesions undergo cystic change and are surrounded by macrophages, scanty inflammatory infiltrate, and astrocytosis.
Serologic testing is generally positive, but may not be so in immunocompromised patients. Parasites can sometimes be observed in biopsy-stained tissues and CSF; however, a positive CSF PCR is helpful. Culture is typically too time-consuming to perform. Compatible features of the disorder on brain MRI include single or multiple lesions in the basal ganglia and white matter, with mass effect and homogeneous or ring-enhancing lesions. However, brain neuroimaging may also be normal when there is diffuse CNS involvement.

Treatment includes pyrimethamine, sulfadiazine, and folinic acid administered for 6 weeks and treatment of any underlying immunocompromised condition. Alternative therapy includes trimethoprim-sulfamethoxazole and clindamycin for patients allergic to sulfa medication.

Rickettsial Pathogens

*Rickettsiae* are obligate intracellular gram-negative coccobacillary agents that multiply in eukaryotic cells. Phylogenetically, they fall between bacteria and viruses. Both mammals and arthropods are natural hosts. Within the genus *rickettsia*, there are 3 biogroups that cause illness: the spotted fever group, the typhus group, and the scrub typhus biogroup. *Rickettsiae* adhere to and invade endothelium with increased vascular permeability, leakage, edema, and hypotension. They are capable of eliciting a generalized vasculitic response in the CNS.

*Rickettsia rickettsia*

*Rickettsia* causes Rocky Mountain spotted fever. More than 90% of infections in the United States occur from April through September via tick bite. The tick vectors are larger soft ticks, including *Dermacentor andersoni* and *Dermacentor variabilis* and *Amblyomma americanum*. Within the CNS, the vasculitis provokes a damaging immune response that is predominantly cell mediated. The overall associated mortality is about 4%.

Symptomatic infection involves severe headache, abdominal pain, persistent fever, peripheral macular centripetal rash, confusion, and myalgia. The classic triad is fever, headache, and rash. Conjunctivitis may also be noted. Neurologic involvement includes meningoencephalitis, focal deficits, and coma. Suggestive laboratory abnormalities are thrombocytopenia, hyponatremia, and elevated liver enzymes. A deficiency of glucose-6-phosphate dehydrogenase enzyme is associated with more severe infection.

Diagnosis is made on clinical grounds, confirmed by positive serology. Therapy involves doxycycline for 7 to 14 days. Kumar and Pramod described a young male Indian with high fever and severe acute headache followed by mental change who developed facial weakness, hyperreflexia, and right posterior cerebral and bilateral thalamopeducular infarcts on computerized tomography of the brain, with filling defects in the origin in the P1 segment of the right PCA on CTA. CSF showed lymphocytic pleocytosis and a positive Weil-Felix test for the proteus antigen OX19. The patient was diagnosed with cerebral vasculitis; however, confirmatory histopathology was not obtained.

*Scrub typhus*

Scrub typhus (Tsutsugamushi disease) involves infection with different species of *Orientalia tsutsugamushi*. Most cases occur in the southwest Pacific and Southeast Asia. Infection occurs with the bite of the larval form of trombiculid mites or chiggers, resulting in small-vessel perivasculitis. The ensuing illness is typically mild and self-limited, but can progress to life-threatening neurologic illness including meningoencephalitis.
Suggestive features of the disorder include necrotic eschar at the site of the mite bite so
noted in 50% of case; generalized lymphadenopathy, and mild truncal rash. CSF shows
a pattern of aseptic meningitis. Serologic testing is available, and therapy involves doxy-
cycline or another tetracycline.

SUMMARY

Underlying infections are important to consider in patients with CNS vasculitis, and
when seriously suspected, warrant prompt and thorough investigation. Selected anti-
microbial therapy combined with supportive care can be lifesaving; however, a self-
limited course of corticosteroids can lead to prompt reduction in associated inflamma-
tion and preservation of neurologic integrity.

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