Chapter 20: Infectious Diseases of the Nervous System

INTRODUCTION

Neurologic infections can be classified by clinical syndrome/localization (e.g., meningitis vs encephalitis vs myelitis vs radiculitis) and by the type of infection (e.g., viral, bacterial, tuberculous, fungal, parasitic). This chapter is organized by clinical syndrome, with each section organized into subsections by the type of infection. At the end of the chapter, the neurologic manifestations of HIV/AIDS are discussed. Table 20–1 provides a summary of the most common types of clinical syndromes caused by each pathogen or group of pathogens.

TABLE 20–1

Neurologic Syndromes Caused By Infections.

	Acute Meningitis	Subacute/Chronic Meningitis	Acute Encephalitis	Vasculitis	Dementia	Focal Brain Lesion(s)	Cranial Nerve Palsies	Spinal Disease	Radiculitis	Neuropathy	Myositis
Bacteria	✓			✓ (with meningitis)		✓ (abscess)		✓ (epidural abscess)			✓
Viruses	✓		✓	VZV HIV	HIV	PML	HIV VZV (Ramsay-Hunt)	✓ (myelitis)	CMV HSV-2	HIV	✓
Fungi		✓		Aspergillus; others in setting of meningitis		✓	✓ (with meningitis)				
Tuberculosis		✓		✓ (with meningitis)		Tuberculoma	✓ (with meningitis)	✓ (Pott's disease, spinal meningitis)			
Syphilis		✓		✓	✓			✓ (Tabes dorsalis)			
Lyme disease	✓		Very rarely				Most commonly CN 7	Very rarely	✓	✓	
Parasites		✓		✓		✓		✓			✓

Abbreviations: CN: cranial nerve; HSV: herpes simplex virus; PML: progressive multifocal leukoencephalopathy; VZV: varicella zoster virus.

MENINGITIS

Meningitis (inflammation of the meninges) can be caused by:

- Infection: most commonly bacterial, viral, fungal, or tuberculous
- Systemic inflammatory disease: e.g., sarcoidosis, inflammatory bowel disease, rheumatoid arthritis, granulomatosis with polyangiitis (formerly called Wegener's

granulomatosis), IgG4-related disease

- Medications (chemical meningitis): nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin (IVIg), trimethoprim-sulfamethoxazole
- Malignancy: leptomeningeal metastases (also called carcinomatous meningitis)

Most infectious meningeal processes predominantly affect the leptomeninges (arachnoid and pia), whereas most inflammatory processes predominantly affect the pachymeninges (dura mater), although there can be simultaneous involvement of both the pachymeninges and leptomeninges in both types of processes (see Figure 2–10 and accompanying discussion "Contrast-enhanced Neuroimaging" in Chapter 2). Carcinomatous meningitis typically refers to leptomeningeal metastases (see "Leptomeningeal Metastases" in Chapter 24). Dural metastases also occur (most commonly with prostate and breast cancer).

Bacterial meningitis and viral meningitis tend to be acute in onset and evolution, whereas fungal meningitis, tuberculous meningitis, inflammatory meningitis, and carcinomatous meningitis are more commonly subacute or chronic in onset and evolution.

Viral meningitis and chemical meningitis are sometimes referred to as **aseptic meningitis**.

Bacterial Meningitis

Bacteria can infect the meninges by spreading from sinus infections or inner ear infections, spreading hematogenously from remote sites of infection, or infecting the meninges directly in the setting of open head trauma or neurosurgery.

The most common causes of bacterial meningitis vary with age and immunocompetence. In infants less than 1 month of age, *Listeria*, *E. coli,* and *Streptococcus agalactiae* (group B) are most common (mnemonic: **less** than 1 month of age: ***L****isteria,* ***E.*** *coli,* ***S****trep. agalactiae*). In children and adults, *Streptococcus pneumoniae* and *Neisseria meningitidis* are most common. *Listeria* should be considered in patients who are older than age 50 or immunocompromised (e.g., HIV, immunosuppressive therapy). In addition to meningitis, *Listeria* may cause involvement of the brainstem (**rhombencephalitis**), producing cranial nerve and cerebellar deficits. *Haemophilus influenzae* should be considered in children, although this is now rare due to widespread vaccination in childhood. In the setting of open head trauma or neurosurgery, *Staphylococcus aureus* and gram-negative bacteria should be considered.

Head trauma does not need to be open to create a passage for entry of bacteria from outside: Basilar skull fracture can create a communication between the meninges and the outside world. A skull defect should be considered as a cause of bacterial meningitis if a patient with prior neurosurgery or head trauma presents with cerebrospinal fluid (CSF) leak (clear fluid from the nose or ears) and/or recurrent meningitis. CSF can be distinguished from nasal secretions by testing fluid for beta-2-transferrin (present in CSF but not mucus) or for glucose (present in CSF but not mucus, although CSF glucose may be extremely low in bacterial meningitis, limiting utility of this test).

Clinical Features of Bacterial Meningitis

Bacterial meningitis can be rapidly fatal, so prompt diagnosis and treatment are crucial. The classic features are fever, neck stiffness, headache, and altered mental status, although a systematic review found that fewer than half of patients have all of these symptoms at presentation (Attia et al., 1999). Additional symptoms can include photophobia and nausea/vomiting. Purpuric rash may be seen with *Neisseria* meningitis.

Meningitis should be considered as a possibility in any patient with fever and headache, although many systemic illnesses that cause fever may also cause some degree of headache. A particularly high index of suspicion for meningitis must be maintained in the elderly, who may have minimal or no fever, and whose neck stiffness may be attributed to osteoarthritis (erroneously or appropriately, but misleadingly in either case if the patient has meningitis). Additionally, careful consideration of meningitis is important in febrile infants, in whom mental status may be difficult to assess.

The classic signs of Kernig and Brudzinski are highly specific when present, but unfortunately quite insensitive (Attia et al., 1999). Both signs demonstrate meningismus by causing traction on the inflamed meninges. The Kernig sign is performed by flexing the hip and then extending the knee with the patient in the supine position. If pain prohibits extension of the knee, this is a positive sign (mnemonic: to look for **K**ernig's sign: extend the **k**nee). The Brudzinski sign is performed by flexing the patient's head: If the patient flexes at the hips and knees, this is a positive sign.

Treatment of Bacterial Meningitis

In most medical texts (including this one), diagnosis of a disease is generally discussed before treatment. In contrast, when discussing bacterial meningitis, *treatment* is discussed first because if bacterial meningitis is being considered, treatment should be rapidly initiated before/while pursuing diagnostic evaluation since delayed initiation of antibiotic treatment—even by hours—leads to poorer outcomes. Therefore, antibiotics should *not* be delayed while awaiting lumbar puncture. CSF cultures remain positive up to hours after initiation of antibiotics, and protein, glucose, and cell count abnormalities persist up to several days following initiation of antibiotics. The theoretical concern that antibiotics should be delayed so as not to alter the CSF results is unfounded, and so antibiotic treatment should be given as soon as possible if bacterial meningitis is in the differential diagnosis. Blood cultures are positive in a large proportion of patients with acute bacterial meningitis and can be drawn at the time of antibiotic administration.

Empiric treatment while awaiting CSF culture for adults with presumed community-acquired bacterial meningitis is ceftriaxone (covers *N. meningitidis* and *Streptococcus*) and vancomycin (to cover potentially resistant strains of *Streptococcus*). Ampicillin should be added to cover for *Listeria* if the patient is younger than 1 month old, older than 50 years old, or immuncompromised. Some practitioners recommend initiating ampicillin in all patients since a patient's immune status may not be known at the time of presentation. If there has been prior neurosurgery or penetrating trauma, or in immunocompromised patients, cefepime or ceftazidime should be used in place of ceftriaxone to expand gram-negative coverage to include *Pseudomonas*. In patients with penicillin/beta-lactam allergy, regimens may include fluoroquinolones, chloramphenicol, and/or trimethoprim-

sulfamethoxazole. Antibiotic treatment can be modified once the culture and sensitivity data from the CSF become available. If there is concern for encephalitis in addition to meningitis based on the clinical picture, acyclovir should be added empirically to treat possible herpes simplex virus (HSV) encephalitis (see "Herpes Simplex Virus Encephalitis" below) while awaiting CSF results and neuroimaging.

Steroids (dexamethasone) are generally also administered in parallel with antibiotics for bacterial meningitis, beginning before or with the first dose of antibiotics (de Gans et al., 2002). This intervention appears to have the most effect on outcomes in patients with meningitis due to *S. pneumoniae*, and some practitioners discontinue steroids if CSF culture reveals an alternative pathogen. In resource-limited/low-income settings with high HIV prevalence, steroids may not necessarily be as beneficial as they are in high-resource/high-income settings (Nguyen et al., 2007; Scarborough et al., 2007). This may be because patients included in studies in low-income settings may not all ultimately have had bacterial meningitis (limited diagnostics), may not have presented early enough in the disease (limited access to health facilities), and may not have had access to adequate resources for supportive care of critical illness.

Lumbar Puncture in Bacterial Meningitis

As discussed above, antibiotics should be administered immediately if there is concern for bacterial meningitis, and lumbar puncture (LP) should not delay initiation of empiric therapy.

Head CT should be considered before LP if the diagnosis of meningitis/encephalitis itself is in question or if the patient is felt clinically to be at risk for a mass lesion (abscess) or diffuse cerebral edema that could raise the risk of herniation with LP. Symptoms/signs that indicate that CT should be considered before LP include focal deficit, seizure, papilledema, depressed mental status, immunocompromise, known intracranial mass lesion, or age greater than 60 (Hasbun et al., 2001).

The classic CSF findings in bacterial meningitis are elevated opening pressure, extremely elevated protein (generally >100 cells/mm^3), extremely elevated white blood cell (WBC) count (>100 cells/mm^3, but often in the 1000s) with neutrophil predominance, and decreased glucose (less than 40% of serum glucose, but often much lower) (Table 20–2). CSF culture is used to diagnose the particular bacterial organism and determine antibiotic sensitivity.

TABLE 20–2

Cerebrospinal Fluid Findings in Central Nervous System Infections.

	Protein (mg/dL)	Glucose (mg/dL)	WBCs (cells/μL)	Other
Bacterial	100s–1000s	< 40% serum glucose (often much lower)	100s–10,000s (Neutrophilic predominance early, lymphocytic later)	Gram stain and culture
Viral	50–100	Normal	100s–1000 (Typically lymphocytic predominance)	Viral PCRs (except for VZV for which IgG is more sensitive, and arboviruses for which IgM is more sensitive) RBCs may be present in HSV
Fungal	100–500	Low	100s–1000 (Typically lymphocytic predominance)	Cryptococcal antigen most sensitive for cryptococcus
Tuberculosis	100–1000	Low	100s–500 (Typically lymphocytic predominance)	Culture, DNA tests

Abbreviations: HSV: herpes simplex virus; PCRs: polymerase chain reactions; RBCs: red blood cells; VZV: varicella zoster virus; WBCs: white blood cells.

Complications of Bacterial Meningitis

The differential diagnosis for an acute neurologic change in a patient with bacterial meningitis includes:

- Seizures, including nonconvulsive seizures, for which continuous EEG may be necessary to make a diagnosis (see "Nonconvulsive status epilepticus" Ch. 18)
- Acute ischemic stroke due to infectious vasculitis (see "Infectious CNS Vasculitis" below)
- Venous sinus thrombosis (see "Cerebral Venous Sinus Thrombosis and Cortical Vein Thrombosis" in Chapter 19)
- Cerebral edema (management of elevated intracranial pressure is discussed in Chapter 25)
- Abscess formation (intracerebral or subdural empyema), which may require surgical drainage (see "Bacterial Focal Brain Lesions" below)

Chronic complications in patients with bacterial meningitis can include:

- Hearing loss
- Epilepsy
- Cognitive impairment
- Hydrocephalus

Isolation of Patients With Bacterial Meningitis and Prophylaxis of Contacts

While awaiting microbiologic diagnosis, patients should be placed on droplet precautions (mask and face protection for providers), but only patients with *N. meningitidis* meningitis require isolation and droplet precautions and prophylaxis of close contacts. If *N. meningitidis* is found to be the etiology, close contacts should receive a single dose of intramuscular ceftriaxone or 2 days of rifampin.

Viral Meningitis

A large number of viruses can cause viral meningitis including herpes simplex viruses (HSV) 1 and 2, enteroviruses, arboviruses, HIV, varicella zoster virus (VZV), and lymphocytic choriomeningitis virus (LCMV). Viral meningitis presents similarly to bacterial meningitis with headache, fever, neck stiffness, and photophobia, but is typically less severe than bacterial meningitis and does not usually cause alterations in consciousness (unless there is an associated encephalitis). Viral meningitis is one type of aseptic meningitis, a term used to describe meningitis with no growth on CSF bacterial culture.

In viral meningitis, CSF protein and WBC count are generally elevated (but not to the degree seen in bacterial meningitis), and glucose is usually normal (see Table 20–2). The CSF WBCs are classically predominantly lymphocytes, although neutrophils may be present early in viral meningitis. Precise diagnosis of the viral pathogen is made by CSF polymerase chain reaction (PCR). Care is supportive with the exception of HSV and VZV encephalitis, which are treated with IV acyclovir.

Aseptic meningitis may occur at the time of HIV seroconversion, so patients with viral meningitis should be screened for HIV risk factors (see "HIV Seroconversion Syndromes Involving the Nervous System" below).

Mollaret's meningitis refers to recurrent viral meningitis, most commonly caused by HSV-2 (the HSV strain that causes genital herpes).

Fungal Meningitis

Fungal meningitis most commonly affects patients who are immunocompromised (e.g., due to HIV infection or immunosuppressive medications), although immunocompetent patients can be affected. The presentation is typically more subacute than with viral or bacterial meningitis, emerging over days to weeks. Headache is almost always present, but the inflammatory aspects of meningitis such as fever and neck stiffness may be minimal or even absent if the patient develops fungal meningitis in the setting of immunocompromise. Therefore, a high index of suspicion for potential fungal meningitis must be maintained in patients who develop headaches while on chronic immunosuppressive therapy or in the setting of diseases causing immunocompromise (e.g., HIV). Cranial nerve palsies and seizures may also be seen, especially in advanced cryptococcal meningitis. Strokes in the basal ganglia may occur due to infectious involvement of penetrating lenticulostriate arteries at the base of the brain.

Cryptococcal Meningitis

Cryptococcal meningitis is the most common fungal meningitis in immunocompromised patients. Due to meningeal inflammation, communicating hydrocephalus can develop, leading to rapid changes in mental status. This often improves with large-volume LP to relieve intracranial pressure. In severe cases, LP may be required daily, and patients may ultimately require ventriculoperitoneal shunting.

CSF in fungal meningitis demonstrates increased protein and WBC count with decreased glucose, but not typically to the extreme values seen in bacterial meningitis (Table 20–2). The most sensitive diagnostic tests for *Cryptococcus* are CSF cryptococcal antigen and CSF cryptococcal culture. Cryptococcal antigen is sensitive and rapid, but not available in many areas of the world most affected by AIDS and accompanying central nervous system (CNS) opportunistic infections. Cryptococcal culture is sensitive and more widely available, but results return much less rapidly. India ink stain is not as sensitive as either test.

Mass lesions of cryptococci (**cryptococcomas**) can occur, appearing as T2/FLAIR hyperintense spherical lesions on MRI, most commonly in the basal ganglia. Treatment of cryptococcal meningitis begins with amphotericin and flucytosine induction therapy, followed by fluconazole until the CD4 count is greater than 200 cells/mm^3 for 6 months.

Other Fungal Causes of Meningitis

Other fungi can also cause meningitis, including *Aspergillus*, *Coccidioides* (Southwest United States), *Histoplasma* (Mississippi and Ohio River regions as well as Latin America), *Blastomyces* (Southeast United States), and *Candida*. These fungi can affect immunocompetent or immunocompromised individuals, except *Aspergillus*, which generally only affects immunocompromised patients. Treatment of fungal meningitis caused by these pathogens is with amphotericin or azoles.

Tuberculous Meningitis

Like fungal meningitis, tuberculous meningitis presents more insidiously than viral and bacterial meningitis, typically over weeks. The clinical presentation can include any of the

classic features of meningitis (headache, fever, meningeal signs, altered mental status), and may also include cranial nerve palsies. As in cryptococcal meningitis, hydrocephalus and subcortical infarcts in the basal ganglia may develop. Many patients who develop tuberculous meningitis have no prior history of pulmonary tuberculosis (clinically or by chest x-ray).

Neuroimaging may demonstrate hydrocephalus, basal ganglia infarcts, and/or meningeal enhancement. CSF profile is similar to that in fungal meningitis with moderate elevations in WBC count (lymphocytic predominance) and protein, and diminished glucose with values less extreme than in bacterial meningitis (Table 20–2). Unfortunately, CSF culture is insensitive, and molecular testing is often not widely available in areas of highest incidence. Therefore, in areas of high incidence and limited diagnostic resources, empiric treatment is often initiated in the following scenarios: patients who present with meningitis and a CSF pattern inconsistent with bacterial meningitis, patients who fail to improve with treatment of bacterial meningitis, or in HIV-infected patients who have a CD4 count greater than 200 cells/mm^3 (making *Cryptococcus* unlikely) or who do not respond to treatment for cryptococcal meningitis.

Treatment generally consists of 2 months of a four-drug regimen (including isoniazid, rifampin, and pyrazinamide with ethambutol or a fluoroquinolone as the fourth agent) followed by an additional prolonged course of isoniazid and rifampin. Corticosteroids are often added during the initial 2 months. In patients with coexisting HIV infection who are not already on antiretroviral therapy, it may be necessary to defer initiation of antiretrovirals until after an initial period of treatment of tuberculous meningitis due to the risk of **immune reconstitution inflammatory syndrome** (IRIS) (see “Immune Reconstitution Inflammatory Syndrome (IRIS)”).

Tuberculosis can also cause focal brain lesions (**tuberculoma**) and disease of the spine (**Pott’s disease**), which are discussed below (see “Tuberculous Focal Brain Lesions” and “Tuberculosis of the Spine”).

Lyme Meningitis

Lyme meningitis may be preceded by the target rash typical of the disease, although many patients do not develop a rash, or may not have noticed it. Diagnosis is confirmed by detecting CSF Lyme antibody, although this is insensitive. Other neurologic manifestations of Lyme disease that can occur early in the illness include seventh nerve palsy (or less commonly other cranial nerve palsies) and radiculits. Meningitis, seventh nerve palsy, and radiculitis can occur together, and may occur in the same time period as systemic features of Lyme disease such as arthritis and carditis. Lyme meningitis is generally treated with IV ceftriaxone. If the only neurologic manifestation of Lyme disease is a seventh nerve palsy (i.e., no meningitis), oral doxycycline is generally used for treatment.

Syphilitic Meningitis

Syphilitic meningitis occurs within the first few years after initial infection with syphilis. In patients in whom positive serum treponemal antibody confirms syphilis, syphilitic meningitis is diagnosed by positive CSF VDRL (Venereal Disease Research Laboratory) test. CSF VDRL is highly specific but relatively insensitive. Treatment is with high-dose IV penicillin G. Meningovascular syphilis can also occur months to years following initial infection, leading to strokes.

Late neurologic manifestations of syphilis include tabes dorsalis (see “Other Infectious Conditions of the Spine” below) and dementia (called general paresis or dementia paralytica). Both are also diagnosed by CSF VDRL (in patients found to have syphilis by positive serum treponemal antibody) and treated with IV penicillin G. Response to treatment is generally followed with CSF VDRL at 6 month intervals until the CSF normalizes.

VIRAL ENCEPHALITIS

Encephalitis (inflammation of the brain) can be caused by:

- Infection: most commonly viral
- Inflammation:
  - Postinfectious: e.g., acute disseminated encephalomyelitis (ADEM; see “Acute Disseminated Encephalomyelitis” in Chapter 21)
  - Paraneoplastic/antibody mediated: e.g., anti-NMDA (*N*-methyl-d-aspartate) receptor encephalitis (see “Paraneoplastic Syndromes of the Nervous System” in Chapter 24)
  - Hashimoto encephalopathy, an immune-mediated encephalitis associated with antithyroid antibodies (See “Hashimoto Encephalopathy” in Chapter 22)

Due to direct brain involvement in encephalitis, altered mental status and seizures may be present early in the course of the illness in addition to headache and fever, while meningeal signs are generally absent (unless there is a combined meningoencephalitis).

A large number of viruses can cause encephalitis including herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus-6 (HHV-6), enteroviruses, and the mosquito borne arboviruses (e.g., West Nile virus, Eastern equine encephalitis virus, St. Louis encephalitis virus, dengue virus). CMV and VZV encephalitis typically occur only in immunocompromised patients.

HSV, VZV, and CMV have specific treatment (IV acyclovir for HSV and VZV; ganciclovir and foscarnet for CMV), whereas care is supportive for other viral encephalitides.

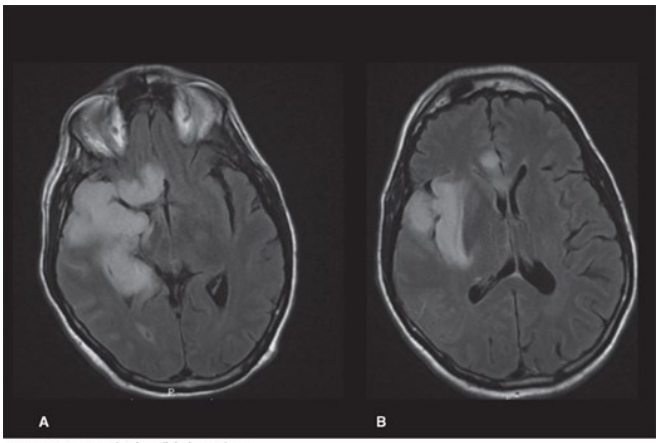
HSV, CMV, HHV-6 and enteroviruses are diagnosed by CSF PCR, VZV is diagnosed most sensitively by CSF IgG, and the arboviruses are most sensitively diagnosed by CSF IgM.

Herpes Simplex Virus (HSV) Encephalitis

HSV encephalitis is the most common viral encephalitis and can be rapidly fatal. Therefore, there must be a low threshold for empiric treatment with IV acyclovir in any patient presenting with a potential infectious encephalitis. HSV encephalitis is most commonly caused by HSV-1 in adults and HSV-2 in infants, though both adults and infants can develop encephalitis from either HSV-1 or HSV-2. HSV encephalitis presents similarly to other viral encephalitides with headache, altered mental status, and/or seizures. MRI demonstrates unilateral or bilateral T2/FLAIR hyperintensities limited to limbic regions (medial/inferior temporal lobe, insula, inferior frontal lobes) (Fig. 20–1). CSF shows a viral pattern (Table 20–2), and CSF red blood cell (RBC) count may be increased due to the hemorrhagic nature of the infection. Temporal lobe periodic lateralized epileptiform discharges (PLEDs) may be present on EEG. Definitive diagnosis is made by CSF HSV PCR. CSF HSV PCR may be negative early in the course of the illness, so a negative test does not exclude the diagnosis, and the test should be repeated if clinical suspicion is high. Treatment is with IV acyclovir.

FIGURE 20–1

HSV encephalitis. Axial FLAIR MRI demonstrating T2/FLAIR hyperintensity in the right medial and anterior temporal lobe (**A**), inferior frontal lobe (**A**), and insula (**B**).



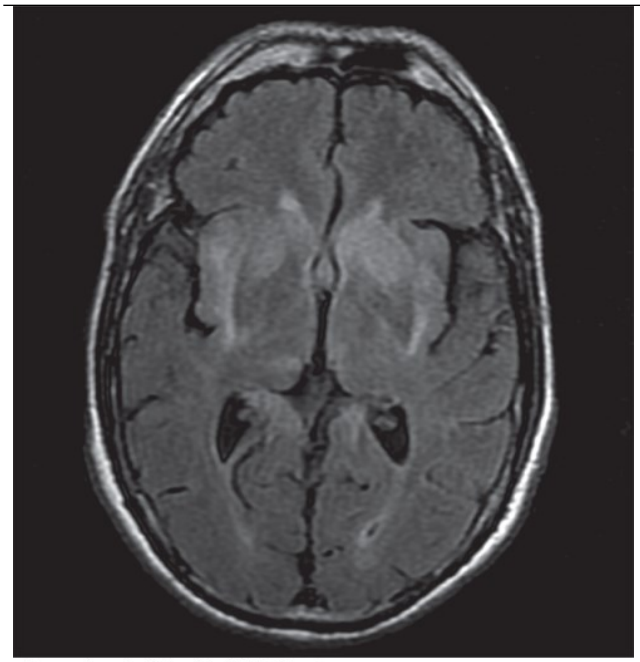
Rarely, HSV encephalitis can relapse. Another course of acyclovir should be administered and the patient should be evaluated for anti-NMDA receptor antibodies, since there is emerging evidence that relapse may be immune-mediated by the mechanism of anti-NMDA receptor antibodies (Armangue et al., 2014) (See “Autoimmune Limbic Encephalitis” in Chapter 24).

Arboviral Encephalitis

Many of the arboviral encephalitides have specific geographic distributions (e.g., Eastern equine encephalitis: east coast of United States; Japanese encephalitis in East/South Asia; dengue in Central/South America, Africa, Asia), although some are now present globally (e.g., West Nile virus). In addition to headache, fever, altered mental status, and seizures, arboviral encephalitides are often accompanied by movement disorders such as tremor and/or parkinsonism. West Nile virus can also cause an acute flaccid paralysis due to involvement of the spinal cord gray matter. MRI of the brain in arboviral encephalitides can reveal symmetric T2/FLAIR hyperintensities in the deep gray matter (basal ganglia and thalamus) (Fig. 20–2). Unlike most other viral CNS infections for which CSF PCR is used for diagnosis, the arboviral encephalitides are diagnosed by CSF IgM, and some patients will have a neutrophilic pleocytosis rather than a lymphocytic pleocytosis in the CSF. Treatment is supportive.

FIGURE 20–2

Eastern equine encephalitis. Axial FLAIR MRI demonstrating T2/FLAIR hyperintensity in the basal ganglia bilaterally.



Source: Aaron L. Berkowitz: Clinical Neurology and Neuroanatomy: A Localization-Based Approach
www.neurology.mhmedical.com

Rabies

Rabies is acquired from contact with an infected animal (dog and bat bites are most common). Encephalitic and paralytic forms (flaccid paralysis) can be seen. Fear of water (hydrophobia) may be seen with the encephalitic form. Once the disease has affected the nervous system, it is fatal, so postexposure prophylaxis is essential in potentially exposed patients, and pre-exposure vaccine should be offered to at-risk individuals.

Cytomegalovirus (CMV), Human Herpes Virus-6 (HHV-6), and Varicella Zoster Virus (VZV) Encephalitides

CMV encephalitis can occur in patients with CD4 <50, and patients often also have other concurrent complications of CMV infection (e.g., retinitis, colitis, radiculitis). HHV-6 encephalitis occurs most commonly in bone marrow transplant patients. On neuroimaging, CMV may cause periventricular white matter changes, whereas HHV-6 typically causes temporal lobe changes. CMV and HHV-6 are diagnosed by CSF PCR and treated with gancilovir and/or foscarnet.

VZV can cause a CNS vasculitis in addition to encephalitis, leading to infarction with focal deficits. VZV is one of the few viruses for which neurologic infection is diagnosed more sensitively by CSF IgG than by CSF PCR. VZV encephalitis is treated with IV acyclovir, and if there is an associated vasculitis, addition of steroids may be considered (See "Infectious CNS Vasculitis" below).

FOCAL INFECTIOUS BRAIN LESIONS

Focal infectious brain lesions should be considered in the differential diagnosis for any patient with acute to subacute onset of focal neurologic symptoms/signs, especially if accompanied by fever or occurring in immunocompromised patients. Headache and seizures are common accompanying features.

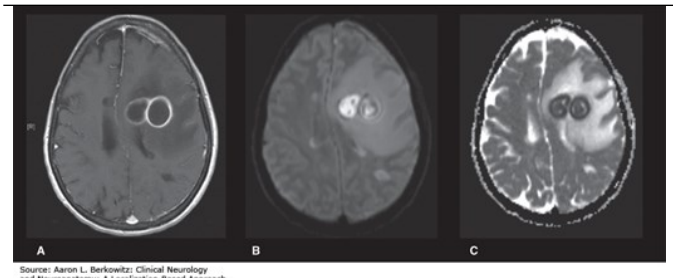
Bacterial Focal Brain Lesions

Cerebral Abscess

Bacterial brain abscesses can arise due to direct spread of bacteria from adjacent compartments (e.g., sinusitis), open skull trauma, neurosurgery, or hematogenous spread from another site of infection (e.g., endocarditis). Neuroimaging reveals a ring-enhancing lesion with surrounding edema, and the center of the abscess often demonstrates diffusion restriction due to high cellularity (Fig. 20–3). If abscess is suspected, blood cultures should be drawn and empiric antibiotics that include anaerobic coverage should be initiated immediately. Surgical aspiration or evacuation is usually necessary. If a clear source of infection is not evident from the patient's history, the patient should be evaluated for endocarditis, cranial infections (e.g., sinus, mastoid), and other potential systemic sources of infection.

FIGURE 20–3

Cerebral abscess. Axial MRI demonstrating ring-enhancing lesions on T1-weighted postcontrast sequence (**A**), and DWI hyperintensity (**B**) with ADC hypointensity (**C**) consistent with diffusion restriction.



Epidural Abscess and Subdural Empyema

Like cerebral abscesses, bacterial infection of the epidural space (**epidural abscess**) or subdural space (**subdural empyema**) can also arise due to trauma, neurosurgery, or local spread of infection from other cranial compartments. Treatment is with antibiotics (including anaerobic coverage as with brain abscess) and surgical drainage.

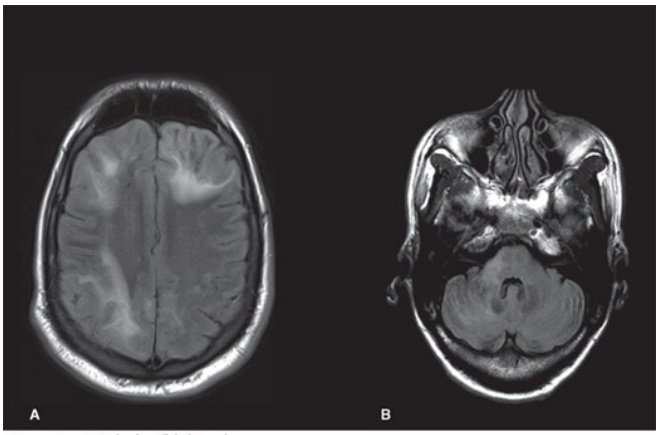
Viral Focal Brain Lesions

Progressive multifocal leukoencephalopathy (**PML**) caused by JC virus infection can be seen in HIV-infected patients (with CD4 <200 cells/mm^3), patients immunosuppressed after organ transplantation, and patients receiving immunomodulatory therapies such as natalizumab (see "Long-term Treatment of Relapsing-Remitting Multiple Sclerosis" in Chapter 21). Focal or multifocal neurologic deficits emerge subacutely, with symptoms/signs depending on the site(s) of lesions.

Neuroimaging in PML reveals juxtacortical T2/FLAIR hyperintensity respecting the boundary between gray and white matter (Fig. 20–4A). The middle cerebellar peduncle is another common site of involvement, leading to presentation with ipsilateral ataxia (Fig. 20–4B). Lesions typically do not cause any mass effect or contrast enhancement, except in the setting of immune reconstitution inflammatory syndrome (IRIS) in which contrast enhancement may be seen (see "Immune Reconstitution Inflammatory Syndrome (IRIS)" below). Diagnosis is made based on clinical features and context, radiologic findings, and PCR confirmation of JC virus infection in the CSF.

FIGURE 20–4

Progressive multifocal leukoencephalopathy. Axial FLAIR MRI demonstrating multifocal juxtacortical T2/FLAIR hyperintensities without mass effect (**A**) and T2/FLAIR hyperinensity in the right middle cerebellar peduncle (**B**).



Unfortunately, there is no proven effective treatment for PML, although some practitioners treat patients with mirtazapine based on case reports suggesting possible clinical benefit (mirtazapine blocks 5-HT2A receptors, which are thought to be the means of JC virus entry into glial cells). In patients who develop PML due to natalizumab therapy, the drug is removed with plasmapheresis, although this raises the risk of development of IRIS (see "Long-term Treatment Of Relapsing-Remitting Multiple Sclerosis" in Chapter 21).

Fungal Focal Brain Lesions

Mucormycosis affects patients who are immunocompromised, diabetic, have elevated serum iron (e.g., hemochromatosis, deferoxamine therapy), or who use IV drugs. **Rhinocerebral mucormycosis** is the term given to extension of infection from the sinuses into the orbit and cavernous sinuses causing ocular motor palsies and other cranial neuropathies. Mucormycosis can also rarely cause a focal brain abscess (most commonly in the basal ganglia). Angioinvasion can cause stroke or hemorrhage. Treatment is with amphotericin and surgical debridement of sinus involvement when present, but prognosis is often poor when there is brain involvement.

Aspergillus can also cause fungal brain abscess in immunocompromised patients, and like mucormycosis, can also lead to angioinvasion causing stroke or hemorrhage. Treatment is with voriconazole.

As described above, cryptococcal lesions known as **cryptococcomas** can occur. These are most common in the setting of cryptococcal meningitis and occur most commonly in the basal ganglia (see "Cryptococcal Meningitis" above).

Tuberculous Focal Brain Lesions

Tuberculomas are focal tuberculous granulomas which may evolve into tubercular abscesses. They appear as ring-enhancing lesions on contrast-enhanced neuroimaging. Treatment is generally with antituberculosis therapy and steroids, with surgery only being necessary in cases with significant mass effect or those complicated by hydrocephalus that does not respond (or does not respond adequately) to anti-tuberculosis treatment.

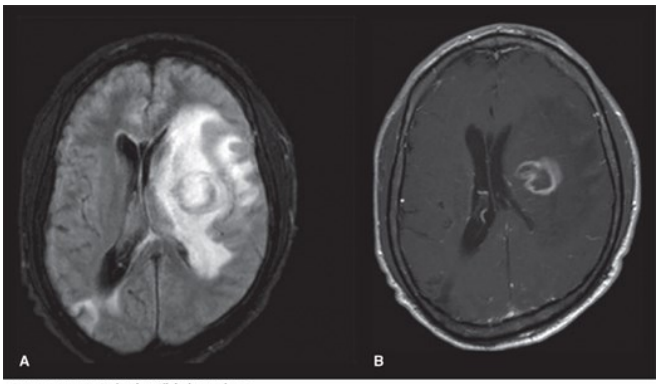
Parasitic Focal Brain Lesions

Toxoplasmosis

Toxoplasmosis can occur in immunosuppressed patients with CD4 <100 cells/mm^3. It causes one or more focal brain lesions with predilection for the basal ganglia and/or deep white matter, leading to subacute development of contralateral hemiparesis, contralateral movement disorder, and/or confusion. Brain imaging reveals one or more ring-enhancing lesions with surrounding edema (Fig. 20–5).

FIGURE 20–5

Toxoplasmosis. A: Axial FLAIR MRI demonstrating left frontal lesion surrounded by extensive edema causing mass effect on the left lateral ventricle. **B:** Axial T1-weighted postcontrast MRI demonstrating that the lesion in **A** is ring enhancing.



In immunocompromised patients, the main differential diagnosis for subcortical ring-enhancing lesions is toxoplasmosis vs primary CNS lymphoma, which can resemble each other clinically (subacute focal/multifocal deficits) and radiologically (subcortical ring-enhancing lesion[s]). If a patient does not have a positive serum toxoplasmosis IgG, this makes the possibility of toxoplasmosis unlikely. However, since the antibody is positive in a significant proportion of the population, IgG positivity does not confirm a diagnosis of CNS toxoplasmosis. Definitive distinction between toxoplasmosis and primary CNS lymphoma can only be made by biopsy, so the usual approach is to treat for toxoplasmosis (sulfadiazine [or clindamycin if sulfa allergy] and pyrimethamine) and follow the patient clinically and radiologically. Steroids should be avoided during this phase if possible, since this can lead to clinical/radiologic improvement of lymphoma as well, obscuring the diagnosis. If there is clinical and radiographic improvement after several weeks of empiric toxoplasmosis therapy, the diagnosis of toxoplasmosis is presumed. If there is no improvement, biopsy should be considered to make a definitive diagnosis.

Neurocysticercosis

Neurocysticercosis (NCC) is one of the most common causes of acquired epilepsy in the world. The *Taenia solium* tapeworm can be acquired from eating undercooked pork. The eggs of the parasite are shed in the stool, and it is the eggs that find their way to the brain to cause neurocysticercosis. The eggs are transmitted by the fecal–oral route by autoinoculation or from one individual to another. This means that a patient does not have to eat pork to acquire neurocysticercosis, a patient only has to shake hands with someone who has the tapeworm and is shedding eggs. The eggs most commonly go to the brain, ventricular system, or subarachnoid space (called **racemose cysts** when in the subarachnoid space), but can also go to the spine or eyes.

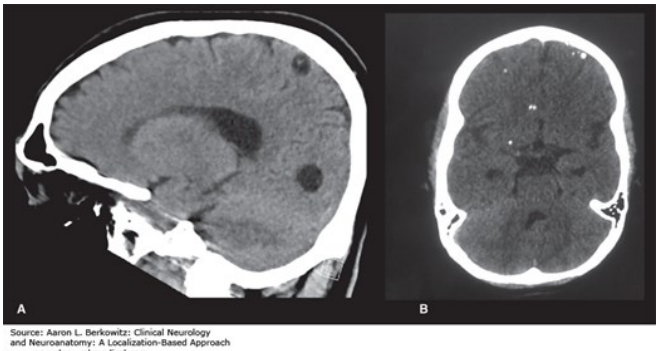
The most common presentation of neurocysticercosis is seizures, although intraventricular or infratentorial subarachnoid cysts can also cause hydrocephalus. Patients may present many years after infection, so NCC should be a consideration in patients from endemic areas, even if they have lived outside of an endemic area for a prolonged period.

In the brain parenchyma, neurocysticercosis passes through several stages with different radiologic manifestations: a vesicular stage (cyst with central hyperdensity, called a **scolex**), colloidal and granular stages (cyst with surrounding enhancement and edema), and finally a calcified stage (Fig. 20–6).

FIGURE 20–6

Neurocysticercosis. A: Vesicular neurocysticercosis. Sagittal noncontrast CT demonstrating cystic hypodensities in the superior parietal lobe and occipital lobe with a central

hyperdensity (scolex) in the parietal lesion. **B:** Calcified neurocysticercosis. Axial noncontrast CT demonstrating multiple punctate hyperdensities in the bilateral frontal lobes consistent with calcified neurocysticercosis.



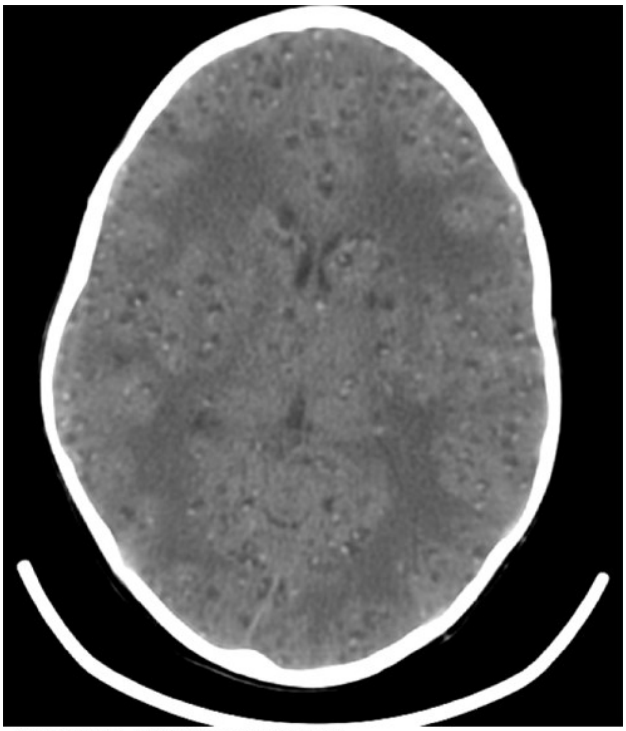
Treatment depends on the stage and location of the cyst(s). At any stage of NCC, if seizures are present, they should be treated with antiepileptics. Antiparasitic treatment (albendazole and/or praziquantel) is used for the stages during which the parasites are active (vesicular, colloidal, and granular, but *not* the calcified stage), and steroids are administered in parallel with antiparasitic treatment to reduce the inflammatory response to cysts dying as a result of antiparasitic treatment. A longer course of antiparasitic treatment may be necessary for racemose cysts, which can be harder to eliminate. Given that patients from endemic regions could also have latent tuberculosis or strongyloides that could worsen with steroids, patients should be screened for tuberculosis (chest x-ray, purified protein derivative [PPD] test) and given empiric strongyloides treatment (ivermectin) prior to initiating steroids.

For intraventricular cysts, surgical removal may be necessary in some cases to treat hydrocephalus.

Rarely, innumerable cysts can be seen, a scenario referred to as **neurocysticercotic encephalitis** (Fig. 20–7). This form of neurocysticercosis is more common in young women. The burden of cysts in neurocysticercotic encephalitis is so high that antiparasitic treatment can provoke a massive inflammatory response leading to cerebral edema. Therefore, antiparasitic treatment should *not* be used for this form of the infection, only steroids (and antiepileptics if seizures occur).

FIGURE 20–7

Cysticercotic encephalitis. Axial noncontrast CT demonstrating innumerable cystic hypodensities with central hyperdensities, consistent with vesicular neurocysticercosis. The extensive burden of lesions represents cysticercotic encephalitis.



Other Parasitic Focal Brain Lesions

A number of other parasitic diseases in endemic areas can cause focal brain lesions including schistosomiasis, echinococcosis, paragonimiasis, and Chagas' disease.

Infectious CNS Vasculitis

Infectious vasculitis leading to stroke can be caused by HIV, VZV, meningovascular syphilis (months to years after initial infection), mucormycosis, *Aspergillus*, and bacterial, tubercular, or fungal meningitis. VZV, *Mucor*, and *Aspergillus* infectious vasculitis occur almost exclusively in immunocompromised patients. Treatment is of the underlying infection. Some practitioners add steroids in patients with VZV vasculitis.

Infectious Cranial Neuropathies

Seventh nerve palsy may be a presenting feature of Lyme disease or HIV seroconversion (see "HIV Seroconversion Syndromes Involving the Nervous System" below), and may occur in isolation or in combination with involvement of cranial nerve 8 in **Ramsay-Hunt syndrome** (VZV reactivation in the geniculate ganglion causing accompanying vesicular rash in the ear and/or on the palate).

The lower cranial nerves are commonly affected in diphtheria leading to palate dysfunction.

Tuberculous meningitis and cryptococcal meningitis can also cause accompanying cranial nerve palsies, as can leprosy (see "Leprosy" below).

Botulism causes multiple cranial neuropathies (see "Infection at the Neuromuscular Junction: Botulism" below).

Infectious optic neuropathies can be caused by *Bartonella* (cat scratch disease; associated with neuroretinitis and a macular star on fundoscopy), syphilis, and rarely by Lyme disease.

INFECTIONS OF THE SPINE

Infections of the spine can occur in various anatomical locations:

- Epidural space (spinal epidural abscess)
- Spinal meninges (spinal meningitis)
- Spinal cord itself (infectious myelitis)
- Anterior horns of the spinal cord (poliomyelitis)
- Spinal interneurons (tetanus)
- Vertebrae (Pott's disease in tuberculosis, osteomyelitis)

Spinal Epidural Abscess

Spinal epidural abscess can occur due to hematogenous spread from a systemic source of infection, IV drug use, local spread from spinal osteomyelitis, exposure of the epidural space due to spinal surgery or trauma, or spontaneously in diabetics, alcoholics, and/or immunocompromised patients. Symptoms include fever, back pain, and rapidly progressive myelopathy. Diagnosis is made by MRI and treatment includes urgent surgical intervention and broad-spectrum antibiotics.

Spinal Meningitis

Spinal meningitis refers to inflammation of the spinal meninges and can occur concurrently with or independent of cerebral meningitis. Two common causes of spinal meningitis are tuberculosis and syphilis.

Infectious Myelitis

Acute Viral Myelitis

Acute transverse myelitis may be infectious, post-infectious, or autoimmune (associated with or independent of demyelinating disease such as multiple sclerosis or neuromyelitis optica; see "Transverse Myelitis" in Chapter 21).

Viral causes of acute transverse myelitis include VZV (which may or may not be associated with the preceding dermatomal rash of shingles), HSV-1 and HSV-2 (the latter more commonly associated with concurrent radiculitis; see "Infection of Nerve Roots" below), CMV, and EBV. CSF analysis in viral myelitis shows elevated protein and lymphocytic pleocytosis. Specific diagnosis is made by CSF viral PCR for all except VZV, for which CSF IgG is more sensitive.

Chronic Viral Myelitis

Causes of subacute to chronic onset viral myelitis include HIV (**vacuolar myelopathy**) and human T-cell lymphocytic virus 1 (HTLV-1) (**tropical spastic paraparesis**). HIV vacuolar myelopathy is a progressive myelopathy (usually thoracic) seen in advanced AIDS. The time of emergence in the disease and time course parallel that of HIV dementia. The dorsal columns and corticospinal tracts are selectively affected, similar to subacute combined degeneration caused by vitamin B12 deficiency. MRI typically shows cord atrophy (see "HIV-associated vacuolar myelopathy" below).

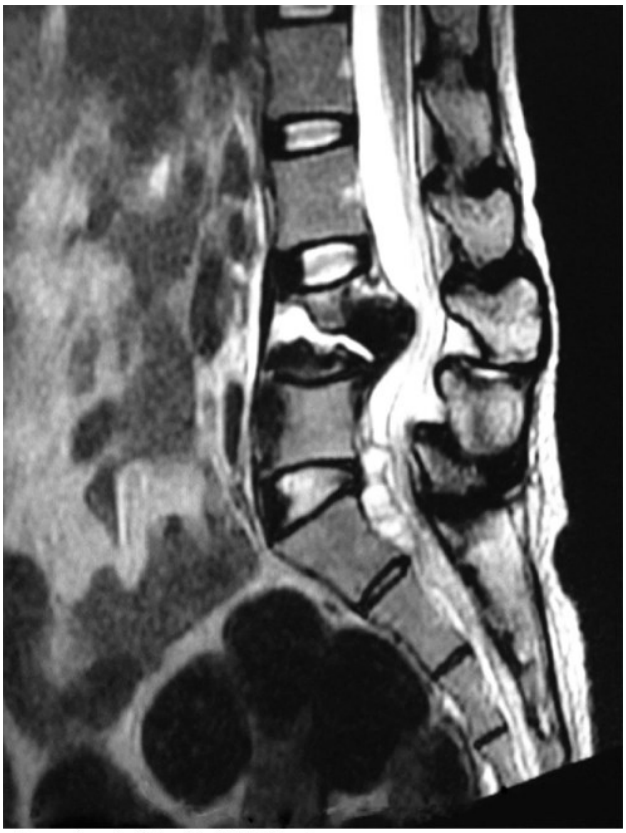
HTLV-1 myelopathy (tropical spastic paraparesis) is seen in a small percentage of the large number of patients infected with the virus, which is endemic throughout the Caribbean, Africa, Central/South America, and Japan. Transmission is by the same modes as for HIV (i.e., blood and sexual fluids). Diagnosis is made by detecting serum or CSF antibodies to HTLV-1. Unfortunately, there are no known effective treatments, although antiretroviral agents are sometimes used empirically.

Tuberculosis of the Spine

Tuberculosis can affect the spine in three ways: involvement of the vertebrae (**Pott's disease**), spinal arachnoiditis/meningitis, or spinal cord tuberculoma. As in tuberculous meningitis, history and/or signs of prior or concurrent pulmonary tuberculosis may be absent. In Pott's disease, tuberculous involvement of the vertebral bodies and discs leads to vertebral destruction, which can ultimately result in vertebral collapse (Fig 20–8). This most commonly occurs in the thoracic or lumbar spine, leading to paraplegia, bowel/bladder dysfunction, and back pain. Irregularity of the spine may be palpated on examination (**gibbus deformity**). Neuroimaging reveals vertebral collapse, which is often apparent on plain film or CT if MRI is unavailable.

FIGURE 20–8

Pott's disease (tuberculosis of the spine). Sagittal T2-weighted MRI of the lumbar spine demonstrating collapse of the L4 vertebra with compression of the roots of the cauda equina.



Source: Aaron L. Berkowitz: Clinical Neurology and Neuroanatomy: A Localization-Based Approach
www.neurology.mhmedical.com

Tuberculous spinal meningitis and spinal tuberculoma can present with either a myelopathy or a polyradiculopathy depending on the site(s) of involvement. Prolonged treatment with a multidrug regimen is used for spinal tuberculosis just as in tuberculous meningitis. Steroids may be considered. Surgery may be indicated in cases of Pott's disease with unstable fracture and/or cord compression, although is unfortunately often unavailable in many regions of the world with high incidence.

Infections of the Spinal Cord Gray Matter: Acute Flaccid Paralysis and Tetanus

Acute Flaccid Paralysis

Arboviruses (e.g., West Nile virus) and enteroviruses (e.g., poliovirus) can selectively affect the anterior horn cells of the spinal gray matter (**poliomyelitis**), causing acute flaccid

paralysis.

Tetanus

Tetanus is caused by exposure to the tetanus toxin by way of wound infection with *Clostridium tetani*. Tetanus is rare where patients are vaccinated, but still occurs in many parts of the world. The tetanus toxin impedes spinal interneuron inhibitory transmission, leading to increased activation of alpha motor neurons. This causes excess muscle contraction leading to spasm and rigidity of the muscles of the jaw (**trismus**) and extremities. Diagnosis is clinical. EMG, if performed, shows evidence of continuous muscle activity. Treatment is with antitoxin, metronidazole, benzodiazepines, and respiratory support (intubation and paralysis are often necessary).

Other Infectious Conditions of the Spine

Mycoplasma can cause an acute infectious or postinfectious myelitis.

The "dorsalis" in tabes dorsalis caused by late-stage syphilis refers to involvement of the dorsal columns and dorsal roots, leading to radicular pain, sensory loss, sensory ataxia, and bladder/bowel dysfunction. By this point in the disease, Argyll-Robertson pupil and/or dementia may be present. Diagnosis is by CSF VDRL and treatment is with penicillin G.

Although neurocysticercosis most commonly affects the brain, it can also affect the spinal cord. In most cases, patients have concurrent racemose (subarachnoid) disease in the brain (see "Neurocysticercosis" above).

Schistosomiasis, acquired by swimming in freshwater in endemic regions (Africa, Central/South America), can cause an acute myelitis. Treatment of schistosomiasis of the spine is with praziquantel and steroids.

INFECTIONS OF NERVE ROOTS

Infectious causes of radiculitis include Lyme disease, CMV (if CD4 <50), HSV-2 (**Elsberg syndrome**), and schistosomiasis. As with any disease process affecting nerve roots (see "Diseases of Nerve Roots" in Chapter 15), infectious radiculitis leads to pain radiating through affected dermatomes, and can also cause weakness, sensory loss, and/or decreased/absent reflexes in the region(s) supplied by the affected root(s). If the roots of the cauda equina are affected, there can also be bowel and bladder dysfunction. Clues to an underlying infectious etiology of radiculopathy may be found in accompanying or preceding systemic and/or neurologic manifestations of the infectious agent, such as rash, fever, cranial nerve 7 palsy, and/or meningitis in Lyme disease; retinitis, colitis, and/or encephalitis in CMV; or genital rash in HSV-2.

INFECTIOUS PERIPHERAL NEUROPATHIES

Peripheral neuropathy is one of the principal features of leprosy, but can also occur in Lyme disease, diphtheria, hepatitis C (associated with cryoglobulinemia), and HIV.

Leprosy

Leprosy is one of the most common causes of neuropathy worldwide, and is endemic in Africa and Asia. The typical presentation is with mononeuropathy multiplex affecting nerves in the coolest regions of the body (i.e., where nerves are closest to the skin): ulnar, peroneal, posterior auricular, and superficial radial. Nerves may be palpably enlarged, especially the great auricular nerve (behind the ear) and the ulnar nerve (at the elbow). Accompanying hypopigmented patches on the skin or other skin changes are seen in most (but not all) patients. Cranial neuropathies (most commonly cranial nerves 5 and 7) may be seen. Treatment is with rifampicin, clofazimine, and dapsone; the combination of medications and the length of treatment depends on the clinical subtype.

INFECTION AT THE NEUROMUSCULAR JUNCTION: BOTULISM

In botulism, the botulinum toxin impedes presynaptic transmission at the neuromuscular junction. The presentation is one of a descending flaccid paralysis beginning with the extraocular muscles and pupils (dilated and poorly reactive), and progressing to involve additional cranial nerves, respiratory muscles, and the extremities. Diagnosis of foodborne botulism may be suspected if onset occurs days following gastrointestinal upset and exposure to home-canned food. Other potential sources of infection include inhalation (in infants) and via wounds.

The main differential diagnosis for botulism is Guillain-Barré syndrome, but botulism is distinct in that symptoms descend (rather than ascend as they most commonly do in Guillain-Barré syndrome), there are no sensory symptoms (pure motor Guillain-Barré syndrome occurs but is not common), pupils are usually involved (does not usually occur in Guillain-Barré syndrome), and CSF is typically normal (albuminocytologic dissociation is usually seen in the CSF in Guillain-Barré syndrome) (see "Guillain-Barré Syndrome" in Chapter 27).

EMG in botulism shows diminished CMAP (compound motor action potential) amplitudes that increase with high-frequency repetitive stimulation as in Lambert-Eaton myasthenic syndrome, another presynaptic neuromuscular junction disorder (see "Repetitive Nerve Stimulation in Lambert-Eaton Myasthenic Syndrome" in Chapter 29). Diagnosis can be made by detecting serum toxin, and treatment is with antitoxin. Although antibiotic treatment is used for wound botulism, antibiotics should not be used for infant botulism or foodborne adult cases of botulism since this may lead to increased toxin burden in the gastrointestinal tract.

INFECTIOUS MYOSITIS

Infections of the muscle can be caused by:

- Bacteria: muscle abscess, pyomyositis, gangrene due to *Clostridium*
- Parasites: trichinosis, cysticercosis (usually asymptomatic infection), toxoplasmosis
- Viruses: myalgias are common with many viral infections, but true myositis may also be seen

Bacterial muscle infection is usually limited to one muscle (e.g., psoas abscess), viral myositis is usually diffuse, and distribution of symptoms in parasitic myositis depends on the pathogen: Trichinosis most commonly affects the muscles of the eyes and face, whereas cysticercosis and toxoplasmosis cause more diffuse muscle involvement. Treatment is directed against the infectious pathogen.

NEUROLOGIC MANIFESTATIONS OF HIV

HIV infection and its sequelae can affect any part of the nervous system from the time of seroconversion to advanced AIDS. The neurologic manifestations of HIV can be caused by (Table 20–3):

- HIV itself
- Opportunistic infections
- Toxicities of antiretroviral therapy, including direct toxicity and immune reconstitution inflammatory syndrome (IRIS) triggered by initiation of antiretroviral therapy

TABLE 20–3

Neurologic Manifestations of HIV.

Direct Effects of HIV	Opportunistic Infections	Treatment Effects
At time of seroconversion • Aseptic meningitis • Cranial nerve 7 palsy • Guillain-Barré syndrome **Chronic HIV infection** • Distal symmetric polyneuropathy • Vacuolar myelopathy • Neurocognitive disorders/dementia	**CNS: Focal deficits** • Toxoplasmosis • Primary CNS lymphoma (EBV) • Progressive multifocal leukoencephalopathy (PML) **CNS: Global dysfunction** • CMV encephalitis **CNS: Meningitis** • Cryptococcal meningitis **PNS** • CMV radiculitis	**CNS toxicity** • Efavirenz (acute neuropsychiatric symptoms) **PNS toxicity** • Neuropathy (didanosine, stavudine, zalcitabine) • HIV-associated neuromuscular weakness syndrome (stavudine) **Immune reconstitution inflammatory syndrome (IRIS)**

Abbreviations: CMV: cytomegalovirus; CNS: central nervous system; EBV: Epstein-Barr virus; IRIS: immune reconstitution inflammatory syndrome; PML: progressive multifocal leukoencephalopathy; PNS: peripheral nervous system.

Direct Effects of HIV on the Nervous System

The nervous system complications directly related to HIV can be divided into those that occur at the time of seroconversion and those that emerge with advanced illness.

HIV Seroconversion Syndromes Involving the Nervous System

Shortly after HIV infection at the time of seroconversion, the patient may experience a flu-like illness. Neurologic manifestations of HIV seroconversion can occur simultaneously with or independently of this flu-like syndrome. The three most common neurologic manifestations of HIV seroconversion are:

- Aseptic meningitis
- Guillain-Barré syndrome
- Unilateral or bilateral cranial nerve 7 palsies

The aseptic meningitis of HIV seroconversion is characterized by headache and neck stiffness, and the CSF shows moderate protein elevation (typically <100 mg/dl) and mild lymphocytic pleocytosis (typically <30 cells/μL) with normal glucose (a typical viral pattern).

The Guillain-Barré syndrome of acute HIV seroconversion clinically resembles classic Guillain-Barré syndrome, but the CSF will demonstrate a lymphocytic pleocytosis (although generally <50 cells/μL), distinguishing it from postinfectious Guillain-Barré syndrome (in which there are generally fewer or no cells).

The diagnosis and differential diagnosis of cranial nerve 7 palsy is discussed in Chapter 13 (see "Lower Motor Neuron Facial Weakness").

It should be noted that since these three syndromes occur at the time of seroconversion, there will not yet be antibodies to HIV, and so the antibody test will be negative. If suspicion is high for HIV seroconversion, viral load should be obtained.

Neurologic Complications of Advanced HIV Infection

Neurologic complications of advanced HIV infection include

- Neuropathy
- Dementia
- Vacuolar myelopathy

HIV-associated distal symmetric neuropathy—HIV can cause various different types of neuropathy. The most common is a symmetric length-dependent distal sensory polyneuropathy. Painful small fiber neuropathy, mononeuritis multiplex, and Guillain-Barré syndrome can also occur. The differential diagnosis for HIV-associated distal symmetric polyneuropathy is primarily an antiretroviral treatment-associated neuropathy (see "Antiretroviral-Associated Neuropathy" below).

HIV dementia and HIV-associated neurocognitive disorders—HIV dementia is the extreme condition in a spectrum of neurocognitive disorders observed in HIV patients referred to as **HIV-associated neurocognitive disorders** (HAND). HIV dementia is characterized by severe cognitive deficits often accompanied by incontinence and symmetric motor deficits, with MRI evidence of atrophy and diffuse white matter abnormalities. The incidence of HIV dementia has decreased with widespread use of antiretroviral therapy, but minor cognitive impairment and asymptomatic/subclinical cognitive impairment (i.e., noted only during neuropsychological testing) are not uncommon. The time course of these cognitive changes is chronic and slowly progressive in comparison to the acuity of cognitive changes seen in CNS opportunistic infections (see "Opportunistic Infections of the Nervous System in HIV/AIDS" below).

HIV-associated vacuolar myelopathy—Just as AIDS may cause progressive cerebral dysfunction, progressive myelopathy may also occur, referred to as **HIV-associated vacuolar myelopathy**. The clinical syndrome is a slowly progressive myelopathy, most commonly thoracic, and typically without back pain. The chronic time course and absence of back pain distinguish vacuolar myelopathy from most infectious myelitides that can present more acutely in HIV patients, with the exception of HTLV-1 (tropical spastic paraparesis), which can present insidiously as does vacuolar myelopathy.

Opportunistic Infections of the Nervous System in HIV/AIDS

Opportunistic infections in patients with HIV can affect any level of the nervous system:

- Meningitis can be caused by *Cryptococcus*
- Encephalitis can be caused by CMV
- Focal brain lesions can be caused by toxoplasmosis, JC virus (PML), and primary CNS lymphoma (an opportunistic malignancy arising from EBV infection in immunocompromised patients)
- Myelitis can be caused by CMV, VZV, HSV, HTLV-1
- Radiculitis can be caused by CMV

The differential diagnosis of altered mental status and/or focal neurologic deficits in HIV-infected patients depends in part on the CD4 count. Cryptococcal meningitis and PML are only seen in patients with CD4 count <200 cells/mm^3, toxoplasmosis and primary CNS lymphoma with CD4 <100 cells/mm^3, and CMV encephalitis and radiculitis are only seen in patients with a CD4 count <50 cells/mm^3. Global encephalopathy in an HIV-positive patient with a low CD4 count could be due to CMV encephalitis, cryptococcal meningitis, or HIV dementia. An encephalopathy may also be seen if there is a high burden of primary CNS lymphoma or toxoplasmosis lesions, although focal signs are generally seen as well. Focal neurologic signs/symptoms are characteristic of toxoplasmosis, primary CNS lymphoma, and PML. Although PML can easily be distinguished from the other two by neuroimaging (see "Viral Focal Brain Lesions" above), toxoplasmosis and primary CNS lymphoma may be difficult to distinguish (see "Toxoplasmosis" above for further discussion).

Antiretroviral Treatment–Related Complications

Antiretroviral treatment complications fall into two broad categories: direct neurotoxicity of the antiretroviral medications themselves and immune reconstitution inflammatory syndrome (IRIS).

Neurotoxicity of Antiretrovirals

Neurologic toxicities of antiretrovirals include:

- Axonal sensory-predominant peripheral neuropathy caused by nucleoside reverse transcriptase inhibitors didanosine, stavudine, and zalcitabine (mnemonic: **DiSt**(z)**al** neuropathy in HIV can be caused by **d**i**d**anosine, **st**avudine, and **zal**citabine)
- HIV-associated neuromuscular weakness syndrome (HANWS) associated with stavudine
- Acute neuropsychiatric symptoms with efavirenz

Antiretroviral-associated neuropathy—Antiretroviral-associated neuropathy emerges within weeks to up to a few months after initiation of antiretroviral treatment with didanosine, stavudine, or zalcitabine. Onset is generally more rapid than in HIV-associated neuropathy, and generally requires a change in antiretroviral regimen to prevent further progression of neuropathy. As with many drug-induced neuropathies, the neuropathy may initially worsen after removal of the offending drug before improving, a phenomenon called "coasting."

HIV-associated neuromuscular weakness syndrome—HIV-associated neuromuscular weakness syndrome (HANWS) is a syndrome of diffuse extremity weakness accompanied by nausea/vomiting, lactic acidosis, and/or hepatomegaly that comes on subacutely within days to weeks after starting (or stopping) stavudine.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is a clinical deterioration that can occur when the immune system is reconstituted (e.g., patient with HIV after initiation of antiretroviral therapy). IRIS can be due to a fulminant response of the immune system against an existing active opportunistic infection, against an undiagnosed subclinical infection, or against HIV itself. The principal risk factors for development of IRIS are the patient's lowest CD4 count (nadir) and the rapidity with which the CD4 count rises after initiation of antiretroviral therapy. IRIS can be prevented if antiretrovirals are initiated before the CD4 count falls too low, but some patients may present initially with a low CD4 count or develop a low CD4 count after a period of nonadherence with treatment. A clinical dilemma occurs when a patient's initial presentation of HIV infection is with an AIDS-defining opportunistic infection, such that initiating antiretrovirals increases the risk of provoking IRIS against the active infection. For many CNS opportunistic infections, it is recommended that the opportunistic infection be treated before initiation of antiretrovirals so as to prevent IRIS. If IRIS occurs, it is generally treated with steroids.

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