Infectious Myelopathies

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ABSTRACT

Purpose of Review: Infections and secondary inflammatory changes play an important role in spine pathology leading to myelopathy or myelitis. To achieve optimal clinical outcomes and accurate prognosis, physicians must promptly recognize these disorders. This review provides a contemporary overview of the major pathogens known to cause myelopathic symptoms and focuses on unique clinical syndromes and signs to aid the differential diagnosis and further workup. This article will help neurologists to consider infectious etiologies during the initial evaluation of patients with myelopathic symptoms.

Recent Findings: The spectrum of neurologic infectious diseases is ever evolving because of immigration and travel, aggressive antibiotic use, vaccinations, and effective antiretroviral therapies. One example of this is illustrated by the enteroviruses. Poliovirus is an enterovirus that causes an acute flaccid paralysis but can be prevented by vaccination. A different enterovirus, enterovirus 71, is increasingly reported as the etiologic agent of acute flaccid paralysis similar in presentation to poliomyelitis. This review recognizes the shifting spectrum of infections in immunocompromised hosts, including patients with HIV in the era of effective antiretroviral therapy. It outlines unique features of primary HIV complications as well as closely associated infections, such as tuberculosis, syphilis, and varicella-zoster virus. Finally, each section of this article outlines molecular and immunologic tools that are becoming paramount for effective and rapid diagnosis of the pathogens.

Summary: This article offers a basic review and definitions pertinent to myelopathic processes. Parainfectious, viral, bacterial, parasitic, and fungal infections are discussed. Each section offers clinical descriptions, pathophysiologic mechanisms, diagnostic strategies, and an approach to treatment and prognosis. Clinical vignettes describe clinical presentations and imaging findings of prototype disorders leading to myelopathy.

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INTRODUCTION

Infections are an important cause of spinal cord dysfunction. In addition to direct neuronal invasion, many infections have a predilection for stimulating an inappropriate immune attack on the spinal cord. The clinical signs and symptoms of spinal cord dysfunction are caused by perturbation of afferent sensory nerves and efferent motor or autonomic pathways. Spinal cord dysfunction of any etiology—whether focal or diffuse, because of intrinsic or extrinsic pathologies—is referred to as myelopathy. *Myelitis* denotes the presence of inflammation, and *acute transverse myelitis* is a more specific term referring to an acute inflammatory process causing a functional transection of the cord with motor and sensory dysfunction below the level of the lesion. Some infections preferentially involve anterior horn cells or motor roots, leading to a syndrome of *acute flaccid paralysis*.

History and physical examination of the patient with myelopathy are used to localize the lesion to the root or specific level of the cord, which can guide imaging. The tempo of the illness, exposure history, and host immune status help to

KEY POINT

■ Myelopathy refers to spinal cord dysfunction, and myelitis refers to inflammatory spinal cord dysfunction.

TABLE 6-1 Geographic Distribution of Select Infectious Myelopathy Pathogens

Pathogen	Endemic Region
Viruses	
Human T-cell lymphotropic virus	Japan, sub-Saharan Africa, Middle East, Caribbean islands, and Central and South America
Poliovirus	Sub-Saharan Africa, Middle East, and Indian subcontinent
Japanese encephalitis virus	China, and South and Southeast Asia
Tick-borne encephalitis	Europe, Russia, and China
Bacteria	
Borrelia burgdorferi Bannwarth meningoradiculitis	Northern hemisphere: central Europe, United States (New England, Atlantic coast, northern Midwest, and Pacific Northwest)
Parasites	
Gnathostoma spinigerum	Southeast Asia (Cambodia, Laos, Myanmar, Indonesia, Philippines, and Malaysia)
Echinococcus granulosum (Hydatid)	Middle East, South America, New Zealand, and the Mediterranean coast
Taenia solium	Central and South America, sub-Saharan Africa, and South and Southeast Asia
Schistosoma mansoni	Central and South America
S. mansoni and *haematobium*	Sub-Saharan Africa
Fungi	
Blastomyces dermatitidis	Southern, Midwestern, and Eastern United States
Coccidioides immitis	Southwestern United States, Mexico, and Central and South America

narrow the differential diagnosis. Patient demographic information is crucial for evaluating the risks for endemic infections (**Table 6-1**). CSF is useful to differentiate among viral, bacterial, parasitic, fungal, or autoimmune etiologies of the disease (**Table 6-2**). Timely recognition and diagnosis of infectious spinal cord disorders is critical for specific treatment and prognosis. This review provides a general overview of the infectious agents that cause prominent myelopathic symptoms and includes epidemiologic and clinical characteristics unique to each infectious agent.

PARAINFECTIOUS CAUSES

Acute transverse myelitis is an inflammatory process resulting in demyelination and neuronal injury with functional transection of the spinal cord. The general diagnostic approach to acute transverse myelitis is reviewed elsewhere.[1] As many as 30% to 60% of cases of acute transverse myelitis are preceded by a systemic infectious process or vaccination

TABLE 6-2 Typical CSF Patterns in Infectious Myelopathy

	Protein (mg/dL)	Glucose (mg/dL)	Nucleated Cells (cells/μL) [cell predominance]
Normal	15–45	45–85	<5
Pyogenic abscess[a]	Increased	Decreased	Increased [neutrophilic]
Tuberculosis	Increased	Decreased	Increased [lymphocytic]
Viral	Increased	Normal	Increased [lymphocytic][b]
Fungal	Increased	Decreased	Increased [lymphocytic][c]
Parasitic	Increased	Normal	Increased [eosinophilic]
Parainfectious	Increased	Normal	<500 [lymphocytic]

[a] Lumbar puncture is not recommended in patients with epidural abscess as it has low yield and significant risks of introducing bacteria into CSF.
[b] West Nile virus and cytomegalovirus may cause neutrophilic pleocytosis.
[c] *Blastomyces* and *Aspergillus* may cause neutrophilic pleocytosis.

KEY POINT

- Acute transverse myelitis is a focal functional transection of the cord usually caused by parainfectious demyelination.

and are referred to as parainfectious acute transverse myelitis. The mechanism of parainfectious demyelination is likely due to activation of specific arms of the immune system through molecular mimicry, leading to generation of antibodies against pathogen proteins that cross-react with host antigens present within the spinal cord. Countless systemic infections have been implicated in causing acute transverse myelitis. Myelopathy usually develops 2 to 4 weeks after systemic infection or vaccination. The CSF profile in these disorders is variable but usually reveals an elevation in protein concentration and pleocytosis with lymphocytic predominance. Oligoclonal bands may be present, and IgG index may be elevated. Diagnosis is usually confirmed by the presence of pathogen-specific serology or antigens in CSF or serum (**Case 6-1**). Corticosteroids are the mainstay of treatment. Refractory cases can be treated with IV immunoglobulin (IVIg), cyclophosphamide, or rituximab, but no controlled trials have been done.

VIRAL CAUSES

Viral infection may cause a parainfectious neurologic injury or invade the CNS and cause myelitis (**Table 6-3**). A few viruses—varicella-zoster virus (VZV), herpes simplex virus (HSV), rabies, and polio—are capable of productive infection of neurons. Retroviruses (HIV and human T-cell lymphotropic virus) tend to cause subacute to chronic myelitis. Herpes family viruses (HSV, VZV, cytomegalovirus [CMV], Epstein-Barr virus [EBV]) and coxsackieviruses tend to cause white matter inflammation (transverse myelitis), while other enteroviruses (poliovirus, enterovirus 71 [EV71]) and flaviviruses (West Nile virus, Japanese encephalitis virus, and tick-borne encephalitis virus) target anterior horn cells (acute flaccid paralysis) (**Table 6-4**).

Retroviruses

HIV affects more than 34 million people worldwide and 1.2 million people in the United States. The virus gains access to the CNS early during the illness by infecting lymphocytes and microglia, which migrate across the blood-brain barrier. HIV has not been found in neurons, but rather causes neuronal insult through the toxicity of viral proteins and the chronic proinflammatory state induced by local viral replication.[2]

Case 6-1

A 19-year-old female college student developed 5 days of fevers, headache, nausea, and vomiting. She was brought to the emergency department after two episodes of syncope with postural changes. She was found to have nuchal rigidity. CT of the brain was unremarkable, and CSF demonstrated normal glucose concentration, elevated protein concentration (137 mg/dL), and pleocytosis (327 cells/μL) with lymphocytic predominance. Viral meningitis was suspected, and supportive care was provided. Ten days after the onset of symptoms the patient developed urinary retention; multidirectional nystagmus was noted, followed shortly by right-sided numbness and diffuse weakness culminating in profound encephalopathy. Neurologic examination within hours was significant for ocular bobbing and severe flaccid quadriparesis. Mental status and weakness continued to worsen, and mechanical ventilation was required. MRI of the brain and spinal cord revealed diffuse expansion and intrinsic T2 signal hyperintensity of the spinal cord from the cervicomedullary junction to the conus (**Figure 6-1**). Serum studies were significant for IgM and IgG antibodies against mycoplasma. CSF studies for infectious organisms, including mycoplasma antibodies and PCR, were negative. The patient was treated with azithromycin, levofloxacin, and high-dose corticosteroids and ultimately received a course of IVIg. Later testing revealed an increase in mycoplasma IgG antibodies in convalescent serum. Despite initial lack of improvement, after intense rehabilitation she recovered well enough to walk independently and return to school.

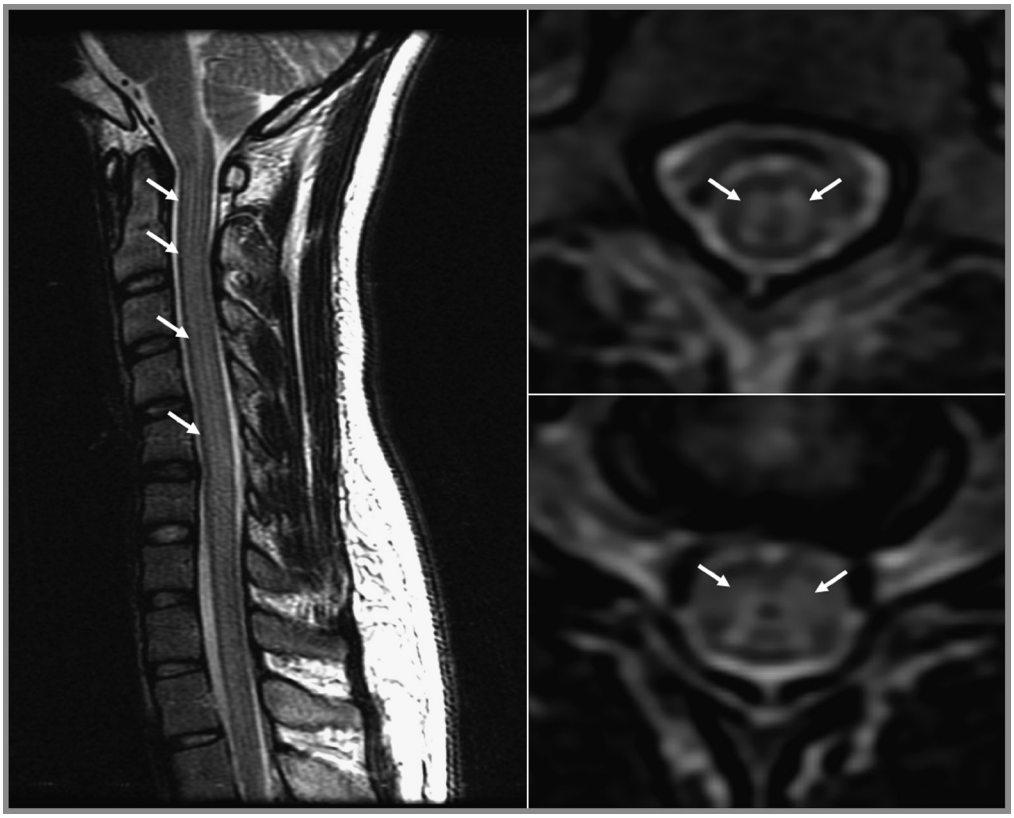

FIGURE 6-1 Mycoplasma-associated encephalomyelitis. Sagittal and axial T2-weighted MRI of cervical and upper thoracic spinal cord demonstrate diffuse T2 signal changes (*arrows*) throughout the length of the cord focused predominantly around the central and ventral portions of the spinal cord. Diffuse cord edema is also seen.

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Comment. This case outlines some key features of parainfectious acute transverse myelitis. The syndrome begins with nonspecific infectious symptoms, including fever. Before the onset of myelopathic symptoms, the patient had an aseptic meningitis. The combination of autonomic dysfunction, sensory dysfunction, and bilateral weakness suggests a functional transverse spinal cord lesion. The eye movement abnormalities and encephalopathy further suggest brain involvement, which is not unusual in parainfectious myelitis (technically, this would be considered acute disseminated encephalomyelitis). The lack of positive CSF microbiology studies is common. When available, specific antimicrobial treatments directed at identified infections should be instituted, along with corticosteroids, to reduce the duration of symptoms.

Early HIV infection has been associated with immune-mediated syndromes through immune dysregulation even before the development of immunodeficiency. Like other viruses, it may cause an acute transverse myelitis

TABLE 6-3 Classification and Features of Viral Causes of Myelopathy

Virus	Genus/Family	Features	Target Cells	Toxicity
HIV	*Lentivirus*/ Retroviridae	Enveloped, single-stranded (ss) RNA(+)	Lymphocytes, microglia, astrocytes	Parainflammatory, envelope glycoprotein gp120, tat protein
Human T-cell lymphotropic virus	*Deltaretrovirus*/ Retroviridae	Enveloped, ssRNA(+)	Lymphocytes	Parainflammatory, tax protein, heterogeneous nuclear ribonucleoprotein A1
Polio Coxsackieviruses Echoviruses Enterovirus 71	*Enterovirus*/ Picornaviridae	Nonenveloped, ssRNA(+)	Neurons, astrocytes, glia	Translational inhibition
West Nile virus Dengue Yellow fever Tick-borne encephalitis	*Flavivirus*/ Flaviviridae	Enveloped, ssRNA(+)	Neurons, astrocytes	Parainflammatory, translational inhibition
Rabies	*Lyssavirus*/ Rhabdoviridae	Enveloped, ssRNA(-)	Neurons	Translational toxicity, immune stimulating
Herpesvirus types 1 and 2	*Simplexvirus*/ Herpesviridae	Enveloped, double-stranded (ds) DNA	Neurons	Parainflammatory
Varicella-zoster virus (Human herpesvirus [HHV] 3)	*Varicellovirus*/ Herpesviridae	Enveloped, dsDNA	Neurons	Vasculitis
Epstein-Barr virus (HHV-4)	*Lymphocryptovirus*/ Herpesviridae	Enveloped, dsDNA	Lymphocytes	Parainflammatory
Cytomegalovirus (HHV-5)	*Cytomegalovirus*/ Herpesviridae	Enveloped, dsDNA	Monocytes, lymphocytes	Parainflammatory

KEY POINTS

- Acute HIV may cause acute transverse myelitis.
- Chronic HIV causes vacuolar myelopathy.
- HIV vacuolar myelopathy must be distinguished from opportunistic infection, neoplasm, and cobalamin deficiency.

TABLE 6-4 Viral Pathogens and Characteristic Myelopathy Syndromes

- ▶ **Acute Flaccid Paralysis**
  - Picornaviruses
    - Poliovirus
    - Coxsackievirus A and B
    - Echoviruses
    - Enterovirus 71
  - Flaviviruses
    - West Nile virus
    - Japanese encephalitis virus
    - Tick-borne encephalitis virus
  - Rhabdovirus
    - Rabiesvirus
- ▶ **Chronic Spastic Paralysis**
  - Retroviruses
    - HIV
    - Human T-cell lymphotropic virus
- ▶ **Mixed Transverse Myelitis +/– Radiculitis**
  - Herpesviruses
    - Herpes simplex virus
    - Varicella-zoster virus
    - Cytomegalovirus
    - Epstein-Barr virus

responsive to steroids and combination antiretroviral therapy during this stage of infection.[3] As cellular immunity wanes below 200 CD4 cells/μL, patients may develop HIV-associated vacuolar myelopathy. Vacuolar myelopathy is pathologically present in 20% to 50% of patients with AIDS, but only 10% to 20% have clinical symptoms.

Patients with vacuolar myelopathy present with a slowly progressive and typically painless myelopathy, with lower-extremity weakness, gait difficulties, spasticity, mild paresthesia, and erectile dysfunction. Urinary urgency and incontinence are common later in the course. Examination reveals decreased vibration sense and proprioception, hyperreflexia, and increased muscle tone. The lower-extremities are disproportionately affected. Vacuolar myelopathy frequently co-occurs with HIV-related encephalopathy and polyneuropathy, the latter of which may mitigate hyperreflexia. Vacuolar myelopathy is a diagnosis of exclusion in patients who are HIV-positive and should be questioned if the presentation is acute, a spinal level or prominent pain is present, the upper extremities are prominently involved, or CSF is significantly inflammatory (white blood cell count greater than 20 cells/μL). Vacuolar myelopathy must be distinguished from opportunistic infection, neoplasm, and cobalamin deficiency.

Imaging is frequently normal, but spinal cord atrophy and findings similar to subacute combined degeneration have been reported. The pathologic changes also resemble subacute combined degeneration, with predominant involvement of the lateral and posterior thoracic cord. Microscopic findings include spongy vacuolation of myelin with lipid-laden macrophages.[4] The pathogenesis is unknown, and despite its similar pathologic features, vacuolar myelopathy does not respond to B_{12} supplementations or to combination antiretroviral therapy, IVIg, or corticosteroids. However, the incidence of vacuolar myelopathy has decreased significantly since the introduction of effective antiretroviral therapy.

Human T-cell lymphotropic virus (HTLV), another retrovirus, is the pathologic agent of adult T-cell leukemia and HTLV-I associated myelopathy (HAM), also known as tropical spastic paraparesis (TSP).[5] Approximately 20 million people are infected with HTLV-I, but only 4% will develop HAM/TSP. The virus is transmitted through exposure to body fluids.[6] HTLV-I has a strong female predominance, likely due to a higher transmission in male to female sexual encounters. The virus is endemic to Japan, sub-Saharan Africa, the Middle East, the Caribbean islands, and Central and South America.[6]

The pathophysiology of HAM/TSP is poorly understood. Some evidence suggests virus-induced CD8+ T-cell mediated neurotoxicity or inappropriate CNS immune attack through molecular mimicry.[7] HAM/TSP has also been described as a two-phase disease consisting of an acute inflammatory phase and a chronic neurodegenerative phase. Pathologic examination reveals chronic inflammation, perivascular infiltration with macrophages, gliosis, and long tract degeneration.[8]

Most patients who develop HAM/TSP become symptomatic within 2 years of the infection, with an insidious onset and slow progression of spastic lower-extremity weakness, prominent bladder dysfunction (frequency and urgency, as well as retention), and constipation. Patients also report back pain and limb paresthesia. On physical examination, patients are typically spastic in the lower extremities but have hyperactive reflexes throughout, despite lack of significant weakness in the upper extremities.

Diagnosis is based on the appropriate demographic and clinical scenario, with supportive serologic studies. Peripheral atypical lymphocytes are characteristic. CSF usually demonstrates a mild lymphocytic pleocytosis with slightly elevated protein concentration and presence of oligoclonal bands. An ELISA is used for screening, with confirmation by Western blot. In addition, PCR in peripheral blood mononuclear cells allows for distinction between HTLV-I and -II, as well as quantification of proviral load for prognostic purposes. Early in the disease course, imaging demonstrates focal T2 prolongation predominantly in the lower cervical cord, occasionally with contrast enhancement, similar to lesions seen in multiple sclerosis. The most common MRI finding is cervical and thoracic cord atrophy. More than 50% of patients also have small intracranial white matter T2 changes; in contrast to multiple sclerosis, however, periventricular and juxtacortical regions are usually spared.[9]

HAM/TSP responds poorly to treatment, with no effective clinical trials to date. Based on the presumed pathophysiology and some similarities to multiple sclerosis, most patients receive steroids. Limited evidence suggests that interferon alpha, cyclosporine, or azathioprine may be effective, particularly in the early phase of the disease. Some patients have received antiretroviral therapy, with incomplete and temporary effectiveness. In the United States, information on clinical trials for HAM/TSP may be found at *http://clinicaltrials.gov/*.

Enteroviruses

Enteroviruses are ubiquitous RNA viruses in the Picornaviridae family. They are easily transmitted by direct contact because they reproduce in the upper respiratory and gastrointestinal tracts. Most infections are asymptomatic, but they can cause herpangina, pericarditis, myocarditis, conjunctivitis, and hand, foot, and mouth disease. Enteroviruses are the most common cause of viral meningitis but occasionally affect the brain or spinal cord parenchyma, characteristically as an acute flaccid paralysis.

Poliovirus is an enterovirus that causes acute flaccid paralysis through infection of anterior horn cells. While largely eradicated in developed countries through vaccine campaigns, poliovirus is still present in parts of sub-Saharan Africa, the Middle East, and the Indian subcontinent. Patients present with high fevers, meningismus, and muscle spasms followed by asymmetric, proximal more than distal, flaccid paralysis evolving over 48 hours. The lower extremities tend to be involved more often, but a bulbar form of the disease has also been described. Older patients are more likely to develop paralysis.

Postpolio syndrome has been described in patients with a remote history

KEY POINTS

- Human T-cell lymphotropic virus causes insidious spastic lower limb paresis.
- Enteroviruses characteristically manifest in the spinal cord as acute flaccid paralysis.

KEY POINTS

- Enterovirus 71 and West Nile virus may cause a poliomyelitislike syndrome.
- West Nile virus may present with generalized maculopapular rash and may cause incontinence.

of poliomyelitis who present with a slowly progressive recrudescence of prior polio symptoms. The pathophysiology of this syndrome is highly debated and poorly understood, with theories ranging from degeneration of large motor units to orthopedic alterations over time. The most consistent risk factor is severity of initial disease. It remains unclear whether postpolio syndrome is a unique entity or a consequence of aging in a neurologically and orthopedically impaired individual.[10]

Nonpolio enteroviruses have surpassed poliovirus as causes of infectious flaccid paralysis throughout the world in the postvaccine era. A recent review from India implicated group B coxsackie viruses and echovirus 11 and 12 as the most frequent strains isolated from children with flaccid paralysis. A surge of these infections occurs in late summer and early fall, predominantly affecting children.[11]

Enterovirus 71 (EV71) is an emerging pathogen in this family. It is associated with hand, foot, and mouth disease, but it may also cause a severe brainstem encephalitis and flaccid paralysis similar in presentation to poliomyelitis. Epidemics have been reported throughout the world, with the largest outbreaks in the Asia-Pacific region.[12] It is a highly contagious disease more common in children and presenting with a characteristic mucocutaneous rash and fever. Neurologic symptoms usually develop rapidly 3 to 5 days after the onset of systemic disease. MRI characteristically reveals T2 hyperintense signal in the lower brainstem and deep cerebellar nuclei. Examples of unilateral T2 changes over the anterior cord as well as ventral root enhancement have been published.[13] CSF usually demonstrates a mild lymphocytic pleocytosis (10 cells/μL to 100 cells/μL). Fever exceeding 38.5°C (101.3°F) or lasting more than 3 days is a risk factor for development of neurologic symptoms. No effective specific treatment has been established for enteroviral myelitis, but IVIg has been used with variable results. The antiviral medication pleconaril, which has in vitro activity against several enteroviruses, has shown only modest effect against EV71 and is not available for clinical use.[14]

Flaviviruses

Flavivirus is a genus of RNA viruses that includes West Nile virus (WNV), dengue virus, yellow fever virus, Japanese encephalitis virus, tick-borne encephalitis virus, and others.[15] Most of these viruses can cause encephalitis, but WNV in particular is associated with a flaccid poliomyelitislike syndrome and is widely distributed in the United States. Transmitted by a mosquito vector, WNV has been reported in over 20,000 cases since the first documented case in the United States in 1999. Symptoms of encephalitis are present in few (less than 1%) patients, and among these fewer than 10% present with flaccid paralysis. However, WNV acute flaccid paralysis carries a mortality in the range of 50%.[16] Patients present with fever and a nonpruritic generalized maculopapular rash (19% to 50%). Myelitis develops over a period of 2 to 8 days and may be unaccompanied by fever. Flaccid paralysis is usually asymmetric and frequently impairs respiratory and bladder function. Examination may be complicated by encephalopathy but usually demonstrates hyporeflexia. The clinical syndrome and pathology are similar to poliomyelitis.[17] Immunosuppression and age older than 50 years are associated with an increased risk for neurologic symptoms in WNV-infected individuals, although WNV myelitis tends to occur at younger ages than encephalitis. In addition to stimulation of an inflammatory process, WNV directly infects neurons in the anterior horn, which

undergo necrosis and/or apoptosis. In addition to neuronal loss, pathologic examination demonstrates glial nodules and perivascular cuffing with mononuclear cells. Patients frequently present with peripheral leukocytosis, thrombocytopenia, and mild elevations of liver enzymes and lipase. WNV is one of the few viruses that may provoke a polymorphonuclear or mononuclear pleocytosis (mean 200 cells/μL), as well as elevated protein and normal glucose concentrations. Viral levels are low in CSF, so diagnosis is usually made by serologic testing. CSF IgM, the most sensitive and specific test, may persist for 6 months. Spinal cord imaging is typically normal. Surprisingly, the severity of initial illness does not correlate well with outcome, suggesting that edema or reversible inflammation may play a role in the symptoms. Treatment is supportive. Despite evidence from in vitro and animal models for the effectiveness of ribavirin, interferon alpha, and IVIg (containing high titers of WNV antibody), these therapies have not been shown to be beneficial in human studies. Anecdotal reports of their use, along with corticosteroids, are available with varying results.[16]

Japanese encephalitis virus, a closely related flavivirus to WNV, is an important cause of epidemic viral encephalitis in Asia (China, and South and Southeast Asia). It predominantly affects children in endemic areas, but rare cases have been reported in travelers of all ages. Myelitis may occur but rarely in isolation from encephalitis. The clinical syndrome is similar to WNV with acute flaccid paralysis. Diagnosis is made with CSF IgM but should be tested only in patients from or travelers to endemic areas. Treatment is supportive. A vaccine is available but has been anecdotally associated with transverse myelitis and other adverse side effects, so it is recommended only for travelers to endemic areas with particularly high risk.[18]

Tick-borne encephalitis virus is another flavivirus that causes encephalitis and less commonly myelitis in Central Europe, Russia, and China. Only five cases were identified in the United States from 2000 to 2009, all with recent travel to endemic areas and four of the five patients recalling tick bites. Patients with myelitis most commonly present with acute flaccid paralysis. CSF IgM is the diagnostic test of choice (available through the Centers for Disease Control and Prevention). No specific treatment is used, and a vaccine is available in Europe and Canada but not the United States.

Rabies

Rabies virus is an RNA lyssavirus carried in bats and other small animals in developed countries, while dogs remain the largest reservoir worldwide. Over 55,000 people die every year from rabies, mostly in developing countries, with a few cases reported each year in the United States.[19] Although presentations are variable, two forms of the disease are classic. About two-thirds of patients experience ''furious'' or encephalitic rabies. A prodrome of focal paresthesia around the site of inoculation is followed by focal weakness and pain; psychosis, hydrophobia, and aerophobia; and finally coma, autonomic instability, and death. In about one-third of cases, ''paralytic'' rabies occurs with a clinical presentation of acute flaccid paralysis (resembling Guillain-Barré syndrome or poliomyelitis) but proceeds to encephalopathy and death. The exact pathophysiologic mechanisms of neuronal compromise remain unclear. Rabies should be considered in patients with a history of dog or animal bites in developing countries or bat exposures in developed countries. PCR for virus in a skin biopsy from the nape of the neck is the most sensitive and specific

KEY POINTS

- The initial severity of West Nile virus infection does not predict clinical outcome.
- Rabies should be considered in patients with exposures to animals, including bats.

KEY POINTS

- Elsberg syndrome is a form of radiculomyelitis caused by reactivation of herpes simplex virus type 2.
- Shingles may be followed by varicella-zoster virus–related myeloradiculitis.

diagnostic test, but a combination of serologic screening and virus amplification in skin, saliva, and CSF is most reliable. Although no effective treatment is available, diagnosis is important for adequate prophylaxis of family and health care workers as well as for a clear understanding of prognosis.[20]

Herpesviruses

The herpesviruses are a family of ubiquitous DNA viruses, including herpes simplex virus types 1 (HSV1) and 2 (HSV2), VZV, EBV, and CMV. These viruses share an ability to remain dormant in the peripheral nervous system, in sensory ganglia neurons or lymphocytes and endothelial cells, for years after primary infection. When associated with spinal cord involvement, they tend to cause transverse myelitis.

HSV1 and HSV2 are closely related viruses, and both can cause myelitis. HSV1 primarily enters the host through oral mucosa and is a less common cause of myelitis, occurring typically in children. HSV2 is transmitted through genital mucosa; it is responsible for most HSV-related myelitis and occurs in adults.[21] Primary HSV2 infection is usually asymptomatic, but the virus enters peripheral sensory nerves and is transported to the dorsal root ganglia, where it incorporates into the cell genome and may remain latent for years. During reactivation, the viral particles are transported back to the sensory dermatome and may cause asymptomatic shedding of viral particles and a vesicular rash. Rarely the reactivation leads to inflammation in the dorsal roots and the neighboring spinal cord, causing radiculomyelitis (Elsberg syndrome).[22] Patients usually present with subacute lower extremity weakness, which may ascend as the virus spreads rostrally. Other common clinical features include numbness or tingling in lumbosacral dermatomes and urinary retention. Patients often report lower back pain. A more severe form of HSV myelitis, acute necrotizing myelopathy, occurs in immunocompromised patients.[23] Neurologic examination reveals flaccid paraplegia with absent reflexes. Frequently no evidence of a systemic inflammatory response is present. CSF examination usually demonstrates a mild lymphocytic pleocytosis (10 cells/μL to 200 cells/μL) with elevated protein concentration, although acute necrotizing myelitis may show a significant polymorphonuclear pleocytosis.[24] CSF PCR amplification of DNA is the mainstay of diagnosis. Imaging typically demonstrates enlargement of the spinal cord, T2 hyperintense signal, and contrast enhancement of radicular roots and cord.[25] Most patients are treated with 14 days of IV acyclovir followed by oral acyclovir or valacyclovir until symptoms resolve or stabilize. The role of corticosteroids is uncertain, but they should not be given without concurrent antiviral therapy.[26] Outcomes are variable, but complete recovery is possible. In up to 20% of cases, the myelitis may recur.[24]

Primary VZV infection causes chickenpox and then becomes latent in the sensory root ganglia. When it occurs, reactivation of the virus usually involves a single dermatome and happens only once during the lifetime of a host. Rarely, patients may develop myeloradiculitis during reactivation, usually in immunosuppressed individuals. Pathologic studies suggest that the virus causes a necrotizing vasculitis with local demyelination and neuronal inclusions.[27] While zoster usually precedes myelitis, cases have been reported without rash. Patients most often present over days to weeks with progressive asymmetric paraparesis and sensory loss (pain and temperature more often than vibration and position). CSF typically demonstrates a mononuclear pleocytosis and elevated protein concentration, although this pattern is also quite

Case 6-2

A 55-year-old man with a history of advanced HIV and recurrent Burkitt lymphoma status postsystemic and intrathecal chemotherapy presented with 2 weeks of progressive but painless left and then right lower-extremity weakness. He had not been adherent to antiretroviral therapy for the past 6 months. On examination he was afebrile with profound distal more than proximal weakness in the left lower extremity and mild weakness in the right lower extremity, normal sensation, and absent reflexes. Laboratory testing revealed a CD4 lymphocyte count cell count of 169 cells/μL (8.6%) and an HIV viral load of 56 copies/mL. MRI demonstrated intramedullary T2 hyperintense foci in the lower thoracic spinal cord and conus medullaris with patchy contrast enhancement (**Figure 6-2**). CSF revealed normal glucose and protein, and a mild pleocytosis (68 cells/μL) with lymphocytic predominance.

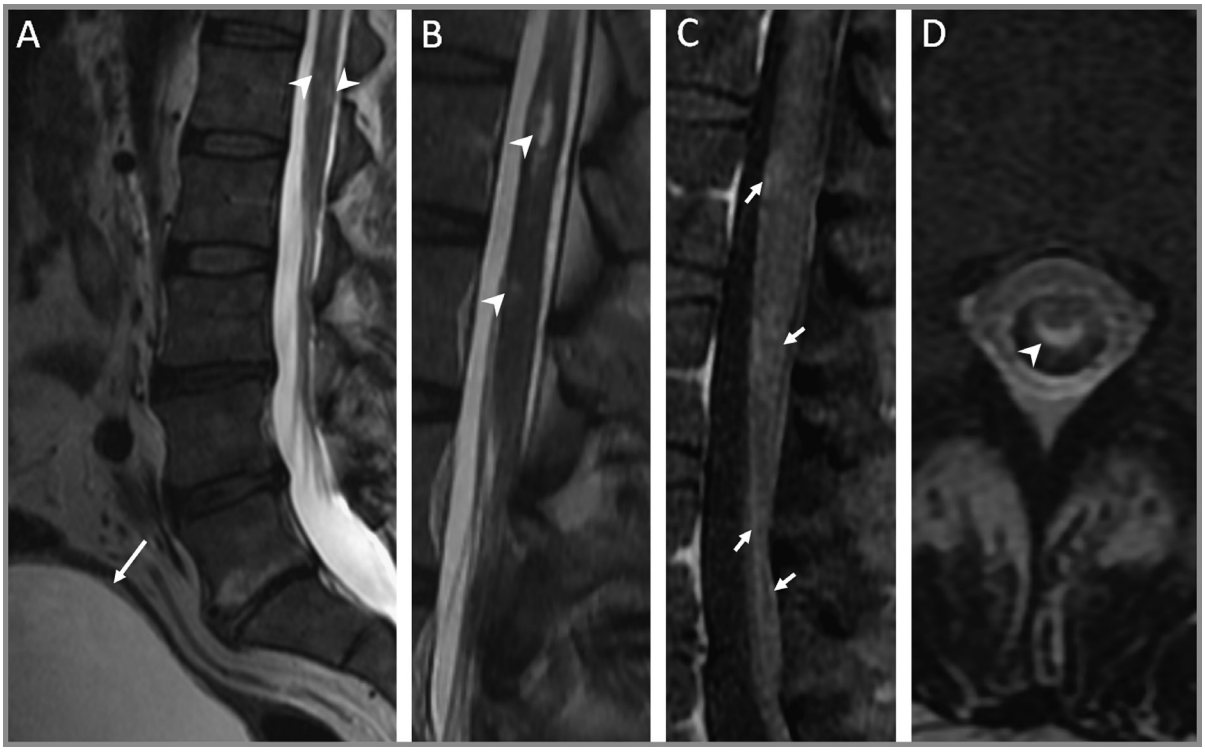

FIGURE 6-2 Varicella-zoster virus myeloradiculitis. *A*, *B*, *D*, Sagittal and axial T2-weighted and T1-weighted MRI with contrast of the lumbar spine demonstrates T2 changes intrinsic to the lower spinal cord (*arrowheads*). *C*, Patchy enhancement of these intramedullary lesions as well as diffuse root enhancement are evident (*arrows*). Of note, evidence of severely distended bladder consistent with urinary retention is shown (*arrow in panel A*).

CSF cytology was negative. CSF PCR was positive for VZV DNA, although CSF VZV IgG was negative. Despite treatment with IV acyclovir and corticosteroids, his examination worsened over the subsequent 2 weeks, with left lower-extremity paralysis, profound right lower-extremity weakness, and development of urinary retention. He required intensive rehabilitation but had a significant improvement, such that at 3-month follow-up he could ambulate with a walker, although he had ongoing urinary retention.

Comment. This is a challenging case that demonstrates the variability in clinical presentation of infections in immunocompromised hosts. The patient did not have shingles preceding his weakness, which is reported in a significant minority of patients with CNS VZV involvement. An asymmetric weakness progressing over weeks, as seen in this case, is typical for VZV. This case also demonstrates the importance of a high index of suspicion for VZV and CSF evaluation by PCR as well as serology.

KEY POINTS

- CSF anti–varicella-zoster virus IgM serology is more sensitive than PCR in varicella-zoster virus–related CNS disease.
- *Treponema pallidum* enters the CNS early in the course of syphilis.

common in uncomplicated zoster.[27,28] Anti-VZV IgM antibody assays in CSF are more sensitive than PCR, although both should be tested, since PCR results are more rapidly available.[29] Imaging usually shows asymmetric T2 hyperintense lesions in the spinal cord corresponding to the dermatome involved. Treatment based on case reports and expert opinion includes prolonged IV acyclovir and corticosteroids (**Case 6-2**).[26]

CMV is a ubiquitous virus capable of infecting neuronal and glial cells but rarely causes symptoms in normal hosts. In profoundly immunocompromised patients, particularly in HIV patients with CD4 counts below 100 cells/μL, CMV may cause a lumbosacral polyradiculomyelitis characterized by superficial meningitis extending into nerve roots and the spinal cord, with focal necrosis of the myelin.[30] Less frequently, necrotizing myelitis may occur without radiculitis. Imaging typically demonstrates cord swelling and peripheral contrast enhancement as well as spinal nerve root swelling, meningeal thickening, and adherence of spinal roots to the thecal sac. CSF examination reveals polymorphonuclear pleocytosis, and the protein concentration is elevated, occasionally with a low glucose concentration. Experts recommend treatment with a combination of ganciclovir and foscarnet, but prognosis is poor.

EBV is the causative agent of infectious mononucleosis. Neurologic involvement usually occurs in children and young adults at the time of primary infection, and less frequently in immunocompromised hosts, such as transplant patients, through reactivation. Neurologic syndromes associated with EBV infection include aseptic meningitis, meningoencephalitis (especially cerebellitis), cranial and peripheral neuritis, Guillain-Barré syndrome, and myelitis.[31] EBV does not infect neurons, and the few pathologic studies available suggest an immune-mediated mechanism of injury rather than direct viral invasion.[32] Patients with myelitis usually present 2 to 3 weeks after primary infection with flaccid weakness, a sensory level, and often radiculopathy and urinary retention.[26] CSF usually demonstrates a mononuclear pleocytosis with elevated protein and normal glucose concentrations. Acute and convalescent serologic testing can confirm acute EBV infection, and detection of EBV DNA in CSF through PCR is strong supportive evidence for a pathogenic role in myelitis associated with primary infection. Imaging may demonstrate T2 hyperintense cord signal abnormalities, contrast enhancement, and thickened nerve roots frequently coalesced in the posterior thecal sac. Although acyclovir inhibits viral replication, it has little impact on the clinical course of EBV infectious symptomatology. Most patients are treated with steroids, with relatively good outcomes.[33]

BACTERIAL CAUSES

Syphilis

Syphilis is caused by *Treponema pallidum*, a fragile, corkscrew-shaped spirochete. While antibiotics have dramatically altered the incidence and course of syphilis, it continues to be a significant pathogen around the world, particularly in patients with HIV coinfection. Neurosyphilis has traditionally been divided into distinct syndromes with characteristic onset in the course of infection: asymptomatic, meningitic, meningovascular, general paresis, and tabes dorsalis. *T. pallidum* enters the CNS in a significant proportion of patients (some have argued all) during the primary and especially secondary stages, and may cause a relatively mild and often asymptomatic meningitis.[34] As not all of these patients go on to symptomatic stages, this is the most common form of neurosyphilis in modern times. The other syndromes are

often grouped into meningovascular (meningitic and meningovascular) and parenchymatous (general paresis and tabes dorsalis) forms. While spinal cord involvement in the form of tabes dorsalis was historically the most common manifestation of neurosyphilis, in the postantibiotic era its incidence has decreased dramatically, with a relative rise in the incidence of meningovascular forms. Meningovascular syphilis is characterized by chronic meningeal inflammation and endarteritis obliterans of small vessels. Rarely meningovascular syphilis may lead to cord infarction.[35]

Tabes dorsalis manifests with subacute to chronic onset of sensory ataxia, loss of vibration, loss of deep pain sensation, and lancinating pains. Physical examination usually demonstrates hyperreflexia, sensory ataxia, insensitivity to deep pain, Charcot joints, and Argyll Robertson pupils.[36] MRI demonstrates cord atrophy and nonenhancing T2 hyperintense signal abnormalities spanning the posterior aspect of the cord.[37] Pathologic changes of tabes dorsalis are found predominantly in the dorsal roots and posterior columns below the midthoracic level, with lymphocytic inflammatory changes, astrocytic gliosis, and demyelination involving fasciculus gracilis and Lissauer tract.[38] The precise pathophysiology remains unclear.

In addition to classical tabes dorsalis and cord infarction from meningovascular syphilis, *T. pallidum* may lead to several other forms of myelopathy. Exceptionally rare syphilitic spinal forms include hypertrophic pachymeningitis, spinal cord gumma, anterior horn cell syndrome, and syringomyelia; and through indirect mechanisms, aortic aneurysm with secondary anterior cord syndrome and Charcot deformations of vertebra with cord compression. In the current era, *meningomyelitis* is the most common syphilitic involvement of the spinal cord.[39] It presents on average 6 years after infection with progressive, at times asymmetric, spastic paraparesis. Imaging characteristics are variable, ranging from central cord T2 hyperintensity with gadolinium enhancement to more superficial pial enhancement with reversal of the typical T2 and T1 postcontrast signal.[39] Several case reports have noted recovery clinically and radiographically, making this an important diagnosis to consider and treat.[40]

Diagnosis is made by peripheral serology and CSF evaluation. Serologic screening assays using nontreponemal antigens to detect antibodies found on the membranes of *T. pallidum*, the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, are sensitive in early infection but may become negative later in the disease. A treponemal-specific test is performed for confirmation, and results will remain positive even in late disease. The treponema pallidum enzyme immunoassay has become the preferred test in high-volume centers in the United States.[41] If serum treponemal test results are negative, syphilis is excluded and other etiologies should be sought. If serum test results are positive, the confirmation of neurosyphilis generally requires CSF examination. The CSF profile is mildly inflammatory. A positive CSF VDRL confirms the diagnosis, but its sensitivity is low, so a negative test result does not exclude the diagnosis. If CSF VDRL is negative but serologic evidence for syphilis and a compatible clinical syndrome is present, CSF fluorescent treponemal antibody absorption testing can be used to confirm, as it is highly sensitive (but not specific).[42]

T. pallidum is exquisitely sensitive to penicillin. However, during initiation of treatment, clinical symptoms may worsen secondary to a sudden increase in pathogenic antigens due to lysis of the spirochetes (Jarisch-Herxheimer reaction). This is particularly important for

KEY POINTS

- *T. pallidum* can cause endarteritis obliterans of small vessels, including spinal vessels.
- Nontreponemal serologic tests for syphilis, such as Venereal Disease Research Laboratory and rapid plasma reagin, may become negative in late stages of syphilis.
- The Jarisch-Herxheimer reaction is a prototype worsening of clinical symptoms with initiation of antimicrobial treatment as spirochetes lyse and antigen levels rise.

KEY POINTS

- The classic triad of neuroborreliosis includes peripheral facial nerve palsies, aseptic meningitis, and painful radiculitis.
- Most patients with CNS tuberculosis have no pulmonary symptoms at the time of neurologic manifestation.

syphilitic myelitis, which is often preemptively treated with corticosteroids.

Lyme Disease

Borrelia is another genus of spirochetes that frequently affects the nervous system. *Borrelia burgdorferi* is transmitted to humans by the *Ixodes* tick species and is endemic to North America, Europe, and Asia. Early infection is usually associated with erythema migrans. The classic triad of early neurologic involvement includes peripheral facial palsy, aseptic meningitis, and painful radiculitis. Transverse myelitis is a rare manifestation of early Lyme disease, usually as a segmental lesion at the level of a painful radiculitis (ie, Bannwarth syndrome). More commonly reported in Europe, it constitutes a small (4% in one series) proportion of early neurologic Lyme involvement.[43] A more chronic and progressive myelopathy in late Lyme disease has also been described in Europe. In the United Sates, transverse myelitis is restricted to case reports and generally occurs in early disseminated disease.[44]

Lyme disease should be suspected in the patient with a history of a tick bite who has traveled to or resides in an endemic area, and especially in the patient with a history or the presence of the typical erythema migrans lesion. By the time of neurologic involvement, serologic evidence of infection will be present in almost all cases. In the United States, an ELISA is used for screening and a Western blot for confirmation. PCR has not been validated in CSF and is not useful in most cases. CSF evaluation typically demonstrates lymphocytic pleocytosis, elevated protein concentration, normal glucose concentration, and increased IgG index. An increased CSF to serum ratio of Lyme-specific immunoglobulin is highly supportive of CNS Lyme disease. Imaging of the spine is usually normal but may demonstrate a segmental T2-weighted cord lesion at the level of meningeal and radicular root enhancement.[44,45] For transverse myelitis associated with Bannwarth meningoradiculitis, IV ceftriaxone is the agent of choice, usually given for 14 to 28 days with a short course of oral or IV corticosteroids.[46]

Tuberculosis

Mycobacterium tuberculosis (TB) is a slow-growing aerobic organism that may cause chronic infection of the CNS. The World Health Organization reported 8.8 million cases and 1.1 million deaths attributed to TB in 2010. CNS TB, primarily in the form of tuberculous meningitis, accounts for 1% of TB cases and 6% of extrapulmonary TB. In developed countries, TB usually presents as reactivation in adult immigrants from endemic countries. In the CNS, this usually takes the form of meningitis from the rupture of a meningeal focus into the subarachnoid space. In developing countries, other CNS complications, such as parenchymal tuberculoma or spinal arachnoiditis, may occur as part of primary dissemination in children and young adults. Risk factors for CNS involvement include malnutrition, immunosuppression, and extremes of age. HIV coinfection does not appear to alter the clinical course of CNS TB in developed countries, but patients in developing countries with HIV show less inflammation on CSF and imaging studies and have less favorable response to treatment.[47] Notably, fewer than half of patients with CNS TB have pulmonary symptoms at presentation.

The most common cause of myelopathy in patients with TB is vertebral body infection, or Pott disease. Spreading through the vertebral venous system, it involves predominantly anterior segments of thoracic and lumbar spine, leading to collapse of these vertebral

bodies with secondary spinal root and cord injury. Most patients with this syndrome present with back pain, leg weakness, and a gibbus deformity.

TB less commonly leads to intramedullary or intradural extramedullary tuberculomas, granulomatous myeloradiculitis, spinal artery vasculitis with cord infarct, or acute disseminated encephalomyelitis.[48,49] These forms of TB typically occur in association with meningitis but may present with only myelopathic symptoms. Epidural or intramedullary tuberculomas usually present with subacute myelopathic symptoms, depending on the specific location of the space-occupying granuloma. In granulomatous myeloradiculitis, TB enters the CNS through the hematogenous route and then spreads within the CNS via the subarachnoid space. Patients usually experience a subacute (1 to 2 month) prodrome followed by a relatively rapid culmination of symptoms, including radicular pain, paresthesia, flaccid weakness with extensor plantar responses, and bladder dysfunction.[50]

CSF typically reveals moderate lymphocytic pleocytosis, low glucose concentration, and at times markedly high protein concentrations indicating spinal block. CSF acid-fast stains and cultures are positive in up to 80% of TB meningitis with optimal sampling and processing, but the sensitivity for spinal involvement in the absence of meningitis is not well established. Tuberculin skin test results may be positive in only 40% of these patients.[51] MRI in Pott disease reveals T1 hypointensity with T2 hyperintensity with contrast enhancement, progressing to vertebral body collapse and cord compression. Tuberculomas show contrast-enhancing T1 hypointense rings with high T2 signal centrally. In granulomatous myeloradiculitis, MRI may reveal contrast enhancement and thickening of the meninges and spinal roots. Pathology is characterized by granulomatous inflammation with thick exudates engulfing the meninges and nerve roots. In some cases, spinal involvement may lead to syringomyelia. Blood vessels may also be directly involved by the necrotizing granulomas or a vasculitic process induced by the local proinflammatory cytokine milieu.

Treatment of spinal TB is similar to that for TB meningitis, namely a four-drug regimen for 2 months followed by 7 to 10 months of isoniazid and rifampin. In patients who are ambulatory at diagnosis (primarily vertebral disease with pain), medical therapy has been shown to be equally effective to combined medical and surgical therapy.[52] However, with neurologic compromise, instability of vertebral bodies, or failure of medical therapy, adjunctive surgery is often necessary. Depending on the duration, location, and spinal level, patients have varying outcomes with lumbar involvement showing more improvement than thoracic.

Pyogenic Bacteria

Myelopathy may occur with pyogenic infection through different pathogenic mechanisms. Vertebral osteomyelitis may lead to structural spine collapse or extension of the infection into the epidural space causing an epidural abscess. Rarely, an intramedullary abscess may occur from primary hematogenous seeding.[53]

Pyogenic infections of the spine have an incidence of 2.4 per 100,000 population. Of these, myelopathic or radicular signs develop in about 30%.[54] Epidural abscess in the setting of osteomyelitis is usually caused by hematogenous spread of the pathogen to the vertebra during periods of bacteremia. Alternatively, bacteria may spread from local soft tissues, viscera, or surgical instrumentation. Direct seeding of the epidural space usually involves the posterior epidural

KEY POINTS

- Tuberculosis may cause necrotizing granulomatous vasculitis, including spinal vessels.
- Pyogenic infections usually seed the anterior epidural space via direct extension from bone and soft-tissue foci, and the posterior epidural space via hematogenous dissemination.

KEY POINTS

- Most patients with pyogenic epidural abscesses are not febrile.
- Erythrocyte sedimentation rate or C-reactive protein are elevated in almost all patients with pyogenic epidural abscess.
- Epidural abscess is a surgical emergency with over 20% mortality.
- Schistosomiasis is the most common parasitic cause of myelopathy worldwide.
- *Schistosoma mansoni* eggs are usually found in stool and those of *Schistosoma haematobium* in urine.
- Schistosomiasis-related myelopathy is caused by chronic inflammation directed at the eggs of the organism.

space, while infections related to osteomyelitis or soft-tissue infections usually involve the anterior epidural space.[55]

The most important risk factors for epidural abscess include diabetes mellitus, alcohol abuse, trauma or instrumentation, skin infection, and a history of IV drug use. The thoracic region is most frequently involved.[56] Patients usually present with focal back pain over the site of infection, usually associated with muscle spasms. Fever is present in fewer than half of the patients.[54] Epidural abscesses are most frequently caused by gram-positive organisms with *Staphylococcus aureus* isolated in over 70% and *Streptococcus* species isolated in 7% of cases.[56] The most frequent gram-negative organisms identified are *Escherichia coli* and *Pseudomonas aeruginosa*.

Erythrocyte sedimentation rate or C-reactive protein is elevated in almost 100% of patients. Blood cultures are positive in about 60% of patients. Rapid spine imaging is critical. MRI is the modality of choice, but CT may be better for characterizing bony involvement. Lumbar puncture is relatively contraindicated because it has low yield and poses a risk of introducing bacteria into the CSF.[55]

The treatment of choice for epidural abscess is emergent drainage and prolonged antibiotics. Medical therapy alone is considered only in patients with longitudinally extensive epidural involvement, or in critically ill patients. Even with proper treatment, mortality is 10% to 23%. The severity of neurologic deficits at the time of surgery is the strongest predictor of mortality. A delay in surgical treatment by more than 12 hours after development of neurologic deficits leads to no or minimal recovery of neurologic deficits (**Case 6-3**).[55]

PARASITIC CAUSES

Schistosomiasis

Schistosoma is a genus of the trematode parasite (fluke) that commonly causes myelopathy or encephalopathy among infected hosts. It is endemic to most tropical regions of the world, and over 200 million people are infected, although the species that typically cause neurologic disease are concentrated in Central and South America (*Schistosoma mansoni*) and sub-Saharan Africa (*S. mansoni* and *Schistosoma haematobium*).[57] Fresh water snails serve as intermediate hosts and higher vertebrates as definitive hosts. Cercariae (larvae) released from snails penetrate the skin of vertebrates, and through hematogenous and lymphatic spread settle in the portal circulation. *Schistosoma* mate in the liver before migrating to the mesenteric and vesicular veins, where females release eggs by the hundreds each day, leading to excretion in stool (*S. mansoni*) and urine (*S. haematobium*). Retrograde migration of eggs from the portal venous system through the valveless pelvic and epidural venous plexus leads to deposition around CNS tissue and generation of a granulomatous inflammatory response (arterial dissemination has also been described).

Most reported cases of spinal cord schistosomiasis are caused by *S. mansoni*, usually in adolescents and young adults. Patients present with subacute lower back pain radiating to the lower limbs, followed by weakness, dermatomal sensory abnormalities, and bowel and bladder dysfunction.[58] The lower cord (especially T11-L1) and cauda equina are most commonly affected, but cervical and thoracic cord involvement occurs. Physical examination reveals variable degrees of myelopathy and/or radiculopathy. Most patients have no extra CNS symptoms at time of onset.

MRI usually shows cord enlargement, intramedullary T2-weighted hyperintense signal within the lower thoracolumbar cord or conus medullaris/cauda equina, and heterogeneous

Case 6-3

A 77-year-old previously healthy man presented with low-grade fevers, chest pain, back pain, and lower-extremity numbness. While trying to move a boulder in his yard 1 week earlier, he developed chest pain that evolved into rib pain over 2 days. He presented to the emergency department, where chest x-rays and ECG were unremarkable. He was treated with cephalexin for a cellulitis of his finger. He noted unsteadiness on his feet the next day and then developed lower-extremity numbness, prompting a return to the emergency department. His temperature was 37.8°C (100°F). He was found to have thoracic spine tenderness and over the next 3 days developed bilateral lower-extremity weakness and urinary retention. Laboratory studies were significant for an elevated erythrocyte sedimentation rate and white blood cell count differential with a leftward shift. MRI demonstrated an epidural fluid collection and evidence of osteomyelitis at T7-8 (**Figure 6-3**). He was taken urgently to the operating room for decompression, and intraoperative cultures grew *S. aureus*. Blood cultures and transthoracic echocardiogram results were negative. He completed a prolonged course of IV antibiotics, and his symptoms improved gradually although 2 years later he had residual gait unsteadiness.

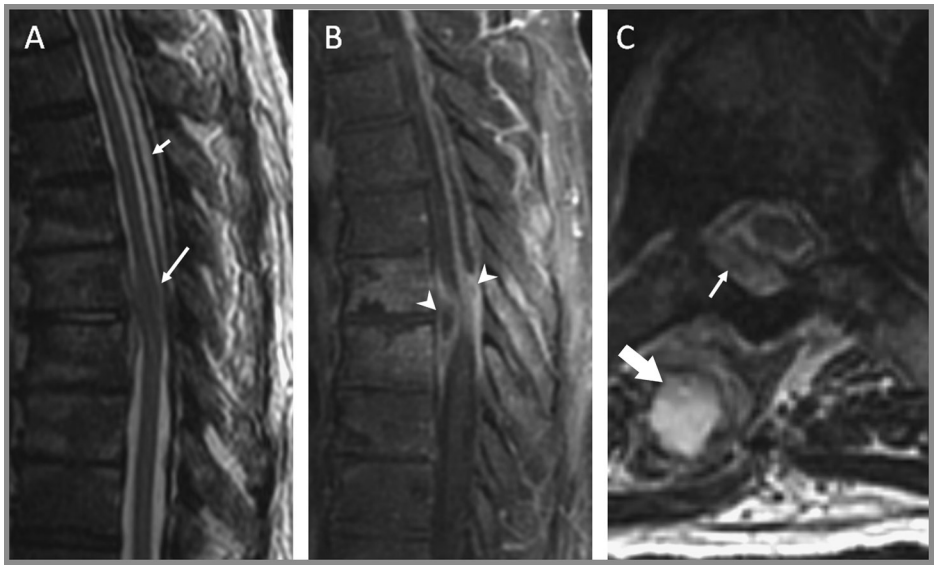

FIGURE 6-3 Epidural abscess. Sagittal (*A*) and axial (*C*) T2-weighted and sagittal T1-weighted (*B*) MRI with contrast of the thoracic and lumbar spine demonstrate focal T2 changes in the bone and disk that vividly enhance, consistent with osteomyelitis. *B,* Focus of enhancing fluid collection (*arrowheads*) surrounding the cord and exerting mass effect (*thin arrow in panel C*). The posterior fluid collection demonstrates significant cephalic extension. *C,* A large enhancing mass within the paraspinal muscle consistent with an abscess (*thick arrow*).

Comment. This case demonstrates ambiguous symptoms in an initially well-appearing patient who rapidly deteriorated and had to be rushed to the operating room. Clinicians should maintain a high index of suspicion for epidural abscess in patients with atypical back pain, especially with an elevated erythrocyte sedimentation rate or C-reactive protein. Patients usually present with pain and radicular symptoms and are likely to have no fever. Invasion of the anterior epidural compartment usually indicates a neighboring osteomyelitis or soft-tissue infection as in this case. *Staphylococcus* is the most likely pathogen, as demonstrated here. Lumbar puncture is relatively contraindicated. Treatment almost always involves surgery in addition to prolonged antibiotics.

contrast enhancement of the cord or roots. Diagnosis is based on three features: (1) a lower spinal cord or cauda equina lesion, (2) evidence of schistosomal infection (ova in stool or urine, rectal biopsy, or serologic), and (3) exclusion of other causes.[59] Microbiology expertise should be sought when considering the diagnosis for optimization of sampling and processing, and

KEY POINTS

- In schistosomiasis, blood and CSF eosinophilia is classic but not universal.
- Response to treatment is part of diagnostic criteria for toxoplasmosis.
- Neurocysticercosis sometimes invades the subarachnoid space but rarely involves the spine.

even then only 50% of patients will have positive parasitology in stool. Blood or CSF eosinophilia is characteristic but may be absent. Peripheral serology (ELISA, indirect hemagglutination, or immunofluorescence) may be particularly useful for establishing exposure in travelers but has little utility in patients from endemic areas because of high seroprevalence. Serologic tests in CSF are more specific. Identification of parasite antigens in peripheral plasma or CSF using monoclonal antibodies or PCR show promise as more specific tests but are not widely available.[60] Tissue biopsy remains the gold standard for diagnosis but is avoided in CNS disease because of morbidity.

Treatment includes praziquantel (various dosing regimens have been used without randomized trials to define clear guidelines), which does not destroy eggs but stops egg production; and concurrent corticosteroids to reduce the inflammatory response and edema, usually with a several-month taper. Rarely, surgery for decompression may be necessary with fulminant or medically refractory cases. Clinical and radiographic recovery occurs in most patients treated early (**Case 6-4**).[58,61]

Other Parasites

Other parasites are rare causes of myelopathy. *Toxoplasma gondii* is a ubiquitous intracellular protozoan that most often causes asymptomatic infection, but reactivation of dormant cysts can cause disease in immunocompromised patients. The most frequent manifestation is multifocal cerebral mass lesions in patients with advanced HIV, but similar lesions may occasionally be found in the spinal cord, typically with concurrent brain involvement. Diagnosis is usually made in patients with HIV with cerebral and spinal cord inflammatory mass lesions, positive peripheral IgG serology (sensitive but not specific), positive CSF toxoplasma PCR (specific but not sensitive), and response to treatment. The organism is exquisitely sensitive to a combination of pyrimethamine (supplemented by folinic acid) and sulfadiazine or clindamycin.[62]

Neurocysticercosis is caused by the cystic larval form of the cestode *Taenia solium*, which is endemic in Central and South America, sub-Saharan Africa, and South and Southeast Asia. Neurologic disease is common but usually involves the brain parenchyma, ventricles, or cerebral subarachnoid space. Only 1.2% to 5.8% of neurocysticercosis cases involve the spinal cord, predominantly in the subarachnoid space but rarely as intramedullary cysts, which can mimic neoplasm. The subarachnoid cysts most likely migrate from the basilar cisterns, and up to 75% of cases occur in patients with known intracranial neurocysticercosis.[63] The cysts are initially mobile, but when degeneration begins they become fixed anywhere along the length of the thecal sac.[64] Diagnosis is based on demographics and imaging, with supportive serology. CSF typically shows high protein concentration and eosinophilia. Spinal cysts are treated with a combination of albendazole and corticosteroids, sometimes requiring surgery for decompression or hydrocephalus.[63]

Hydatid disease is a cystic infection caused by the cestode *Echinococcus*. Most CNS hydatid disease occurs in the brain as a result of the species *Echinococcus granulosum*, which is endemic to the Middle East, South America, New Zealand, and the Mediterranean. Spinal involvement is rare and may affect the vertebra, extradural or paraspinal structures, or intradural extramedullary space, with only a few intramedullary cysts reported in the literature.[65] Canines are definitive hosts for the tapeworms, and humans are infected via the fecal-oral route. Once ingested, the eggs hatch and form oncosphere larvae,

Case 6-4

A 29-year-old man from Brazil presented to a local emergency department after 3 weeks of worsening lower back pain radiating to his bilateral knees. The pain was moderately responsive to nonsteroidal anti-inflammatory medication but worsened over the week prior to presentation, and he developed right-leg numbness and weakness. On the day of presentation he developed urinary retention and bowel incontinence. On examination he had full strength, decreased sensation to light touch and pinprick in a saddle distribution as well as distal lower extremities, and reduced reflexes in the lower but not upper extremities. Hematologic studies and liver function tests were normal. MRI of the spine showed patchy enhancement of the lower spinal cord and cauda equina (**Figure 6-4**). CSF studies were significant for elevated protein (114 mg/dL), normal glucose, and mild pleocytosis (28 cells/μL) with lymphocytic predominance and increased eosinophils. Stool screening for ova and parasites was negative. He was treated with ivermectin, praziquantel, and high-dose corticosteroids.

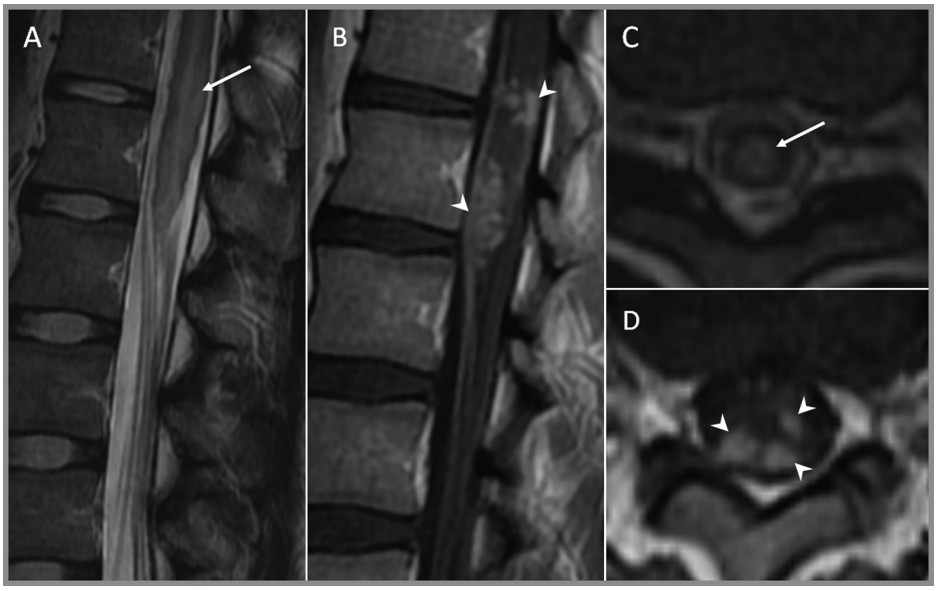

FIGURE 6-4 Schistosomal lumbosacral myeloradiculitis. *A*, *C*, Sagittal and axial T2-weighted and T1-weighted MRI with contrast of the thoracic and lumbar spine demonstrates diffuse intramedullary T2 cord changes (*arrows*). *B*, Contrast studies demonstrate clustering and largely peripheral nodular enhancement of the lower spinal cord including conus (*arrowheads*). *D*, Thick nodular root enhancement within cauda equina is shown (*arrowheads*).

Serology was ultimately positive for IgG against schistosomal antigens (results obtained 2 weeks after presentation). He regained bowel and bladder function. He had temporary worsening when corticosteroids were tapered after 1 month but tolerated a longer taper with only mild residual distal lower-extremity paresthesia.

Comment. This case illustrates a stereotypic presentation of schistosomiasis, which should be ruled out in any patient from endemic regions with subacute back pain accompanied by sensory deficits and weakness. Most of the patients are young, and the pain initially responds well to nonsteroidal anti-inflammatory drugs, as was seen in this case. The symptoms arise from the inflammatory response to the parasite eggs, which tend to migrate to the lower cord via the venous system. Cauda equina symptoms and these imaging findings are typical for this infection. The patient's CSF had elevated eosinophils, which should increase the index of suspicion for parasitic infections. As described above, most of these patients do well on combination therapy against the parasite and corticosteroids to mitigate the inflammatory response to the eggs.

which migrate across the intestinal wall and form hydatid cysts in the liver and other tissues, including the CNS. These cysts may grow extremely large, and pathology is caused by a combination of mass effect, bony destruction, and host inflammatory response. MRI reveals characteristic cysts causing mass effect

TABLE 6-5 Fungal Causes of Myelopathy

Fungus	Pathology	Clinical Clues	Diagnosis	Treatment
Cryptococcus neoformans	Granulomatous meningitis and myeloradiculitis	Ubiquitous, encephalopathy, high CSF opening pressure	CSF India ink stain, CSF antigen	Amphotericin B + flucytosine, then fluconazole; shunt
Coccidioides immitis	Osteomyelitis	Southwest United States, Latin America; pulmonary symptoms; spares disks	CSF antibodies	Fluconazole; voriconazole, intrathecal amphotericin B (second-line alternatives)
Blastomyces dermatitidis[a]	Granulomatous osteomyelitis	North America; pulmonary symptoms; fistula formation	CSF culture	Surgery and amphotericin B, followed by azole
Aspergillus species	Focal vascular invasion and hemorrhages	Ubiquitous, exposure to steroids, pulmonary symptoms	Non-CNS histology or culture, serum or CSF galactomannan, serum β-D-glucan	Voriconazole; amphotericin B

[a] This is a rare cause; other rare fungal causes of osteomyelitis include *Candida* and *Histoplasma capsulatum*.

KEY POINTS

- Gnathostoma causes injury via direct destruction of tissue as larvae migrate.
- *Aspergillus* invades blood vessels and causes thrombosis and hemorrhages.

on the cord, and serologic testing is also available. Treatment includes surgical decompression and albendazole, but recurrence is the norm.[66]

Gnathostoma spinigerum is a nematode endemic to Southeast Asia transmitted to humans via undercooked infested fish, reptiles, or poultry. Larvae may invade spinal roots, causing severe radicular pain, and then travel rostrally, causing radiculomyelitis through direct mechanical disruption of tissues as well as the inflammatory response to its secretions. Diagnosis is made by history of endemic exposure, biopsy of skin lesions, eosinophilic CSF profile, and serologic testing. Treatment usually includes surgical resection of the larvae followed by albendazole or ivermectin.[67] *Angiostrongylus cantonensis* is another nematode that is a common cause of eosinophilic meningitis, but an extremely rare cause of myelitis in endemic areas (Southeast Asia, Pacific Basin, and Caribbean).[68]

FUNGAL CAUSES

Fungal infections of the CNS are usually associated with some degree of immune incompetence. Fungal CNS syndromes vary with the type of pathogen and immune state. Molds (most commonly *Aspergillus*) tend to cause focal CNS disease in mildly immunosuppressed patients, with vascular invasion leading to thrombosis and hemorrhage in patients with more profound immunocompromise. Yeasts (most commonly cryptococcus) cause a chronic basal meningitis and granuloma formation. While CNS involvement typically manifests as meningitis or brain lesions, spinal cord disease occurs in the form of epidural abscess, chronic arachnoiditis, intramedullary granuloma, frank myelitis, or vasculitis with cord infarction.[69] Most cases are related to regional spine invasion from vertebral osteomyelitis. **Table 6-5** lists specific pathogens. Fungal causes of transverse myelitis are extremely rare.

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