Infectious Myelopathies

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews infectious etiologies of spinal cord dysfunction, emphasizing the importance of recognizing common clinicoradiographic syndromes and interpreting them in the context of exposure risk and individual host susceptibilities.**

RECENT FINDINGS: **This article discusses the shifting spectrum of neurologic infectious diseases, the growing population of patients who are immunocompromised, and the emergence of effective antiretroviral therapies. In addition, it discusses new molecular and serologic tests that have the potential to enhance our ability to rapidly and accurately diagnose infectious diseases of the spine.**

SUMMARY: **When evaluating patients with suspected infectious myelopathies, it is imperative to narrow the range of pathogens under consideration. The geography, seasonality, and clinicoradiographic presentation and immunocompetence status of the patient define the range of potential pathogens and should guide testing and initial management.**

INTRODUCTION

Prompt and thorough investigation of spinal cord dysfunction is important as severe impairment may accrue rapidly without a clear diagnostic and treatment plan. Spinal cord dysfunction of any cause, whether extrinsic or intrinsic, focal or diffuse, is referred to as *myelopathy*. *Myelitis* usually designates inflammation of the spinal cord itself. The corollary terms for root pathology are *radiculopathy* and *radiculitis*. Infections can result in spine pathology through direct invasion of neural structures, secondary inflammation, or compression, as with an epidural abscess. Neuroinvasion can lead to downstream inflammatory changes, but inflammation can also result from immune-mediated mechanisms triggered by systemic infection in the absence of direct nervous system involvement by the pathogen. When this occurs contemporaneously with acute infection, the term *parainfectious* is used, whereas the term *postinfectious* refers to cases in which neurologic symptoms develop weeks after systemic infection.

Once infection has been identified as a probable cause, it is imperative to narrow the range of potential pathogens under consideration. Knowing which microorganisms are likely and whether the presentation is primarily driven by direct infection or secondary immune-mediated mechanisms can prevent unnecessary testing, mitigate the risk of false-positive results, and guide appropriate empiric therapy.

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Dr Toledano discusses the unlabeled/investigational use of corticosteroids and IV immunoglobulin for the treatment of infectious myelopathies.

The traditional way of narrowing the differential diagnosis in neurology relies on history, examination, and imaging. Certain pathogens cause primarily intramedullary infection, whereas others are more likely to seed extramedullary sites. Some pathogens cause isolated myelopathy, but others (such as herpes simplex virus type 2 [HSV-2]) are more likely to affect both the cord and roots, leading to myeloradiculitis. Some infections preferentially involve anterior horn cells, leading to a syndrome of acute flaccid myelitis, whereas others affect the cord more diffusely, leading to spastic paresis and sensory dysfunction below the level of the lesion. Pyogenic bacteria are more likely to be associated with fever and to seed structures adjacent to the cord, resulting in compressive myelopathy. Both syphilis and varicella-zoster virus (VZV)

TABLE 4-1 **Global Distribution of Select Microorganisms Associated With Myelopathy and Radiculopathy**

Microorganism	Location of highest endemicity
Viruses	
Human T-cell lymphotropic virus type 1 (HTLV-1)	South America; the Caribbean; Japan; Papua New Guinea; the Melanesian islands; the Middle East; and West, Central, and Southern Africa
Poliovirus	Afghanistan and Pakistan
Rabies *Lyssavirus*	Worldwide but most common in Africa, Central and South America, and Asia
Bacteria	
Borrelia species	Northeast, mid-Atlantic, and northern Midwest of the United States; Europe
Brucella species	North Africa, the Mediterranean Basin, Middle East, Indian subcontinent, Mexico
Mycobacterium tuberculosis	Central and South America, sub-Saharan and Northern Africa, Indian subcontinent, Southeast Asia, Micronesia, China, Eastern Europe
Fungi	
Blastomyces dermatitidis	Areas of the United States and Canada surrounding the Ohio and Mississippi River Valleys and the Great Lakes
Coccidioides species	Southwestern United States, Mexico, and South America
Histoplasma capsulatum	Most commonly reported in the United States, particularly areas around the Ohio and Mississippi River Valleys; also in Central and South America, Africa, Asia, and Australia
Parasites	
Angiostrongylus cantonensis	Southeast Asia and the Pacific Basin
Echinococcus species	South America, the Middle East, Eastern Mediterranean, Western China, and the former Soviet Union
Gnathostoma spinigerum	Southeast Asia
Schistosoma haematobium	Sub-Saharan Africa and the Middle East
Schistosoma japonicum	China, the Philippines, and Indonesia
Schistosoma mansoni	Sub-Saharan Africa, South America, and some of the South Caribbean Islands
Taenia solium (neurocysticercosis)	South and Central America, sub-Saharan Africa, India, and Southeast Asia

can rarely be associated with spinal cord ischemia. Certain retroviruses result in slowly progressive myelopathies, whereas herpesviruses tend to be associated with more rapid progression. Familiarity with these clinicoradiographic presentations can help narrow the differential, although, admittedly, this approach is limited as individual pathogens can have multiple manifestations.

Another important tool is microbiology. Exposure is a precondition to infection, and certain host factors can predispose individuals to specific microorganisms or increase their risk of developing manifestations of chronic infection. Age, geography (TABLE 4-1), seasonality, and psychosocial factors define the range of potential pathogens. If a patient is immunocompromised, the nature of the immunodeficiency (whether cellular or humoral, for example) also helps narrow the differential (TABLE 4-2) (CASE 4-1). All patients with suspected central nervous system (CNS) infection should be tested for human immunodeficiency virus (HIV), which predisposes patients to opportunistic infection and can itself cause myelopathy.

The selection of microbiologic diagnostic tests should be guided by the abovementioned considerations. Ignoring these can result in failure to test for the offending pathogen. Conversely, overtesting increases the risk of false-positive results and can result in unnecessary exposure to antimicrobials and delays in establishing the correct diagnosis. CSF analysis can be useful for differentiating between viral, bacterial, fungal, and parasitic etiologies (TABLE 4-3). Familiarity with the role and accuracy of each test for identifying specific pathogens is crucial for diagnosis and interpretation of results (TABLE 4-4). A variety of assays that target multiple microorganisms are becoming increasingly available. Some rely on nested multiplex nucleic acid amplification to simultaneously test for up to 14 pathogens. Others, such as 16s rRNA polymerase chain reaction (PCR) are used to detect the presence of any bacteria in the sample. Metagenomic next-generation sequencing of CSF or brain tissue samples can potentially detect the presence of DNA or RNA sequences of all previously catalogued and sequenced pathogens (TABLE 4-5[1]). Utility, availability, and cost vary for these tests, but the tests are likely to become incorporated into diagnostic algorithms in the near future.

KEY POINTS

- Infections can result in spine pathology through direct invasion of neural structures or by immune-mediated mechanisms triggered by systemic infection in the absence of neuroinvasion.
- Although considerable overlap exists, recognizing common clinicoradiographic syndromes is critical when generating a differential diagnosis for infectious myelopathies.

INTRAMEDULLARY SPINAL CORD INFECTIONS

Most intramedullary cord infections are associated with some degree of inflammation; thus, the term myelitis can be broadly applied. Rarely though, as in the case of HIV-associated vacuolar myelopathy, inflammation appears to play no pathogenic role. Many infections affect both cord and root, leading to myeloradiculitis. Some infections preferentially affect the gray matter (poliomyelitis), whereas others affect primarily the white matter (leukomyelitis), sometimes even remaining confined to specific columns or tracts. However, in many cases, the extent of inflammation or limitations in imaging may render these distinctions obscure. The term *transverse myelitis* has evolved to have multiple meanings and often mixes clinical and pathologic entities, limiting its utility as a clinicoradiographic descriptor. Although rare, some microorganisms can cause an intramedullary abscess.

Myelitis

Viruses are a common cause of infectious myelitis. Spinal cord injury can be caused either by direct neural invasion or via immune-mediated parainfectious or postinfectious mechanisms.

HERPESVIRUSES. The herpesviruses are a family of DNA viruses that are ubiquitous worldwide and include herpes simplex virus type 1 (HSV-1), HSV-2, VZV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Although they cause nervous system disease in a minority of patients who are infected, their pervasiveness makes them one of the more common infectious causes of myelitis and myeloradiculitis (TABLE 4-6).

VARICELLA-ZOSTER VIRUS. VZV causes a diverse spectrum of neurologic complications. Primary infection causes chickenpox, after which the virus establishes latent infection in the dorsal root ganglia. When reactivated, the virus travels along the sensory nerve to the surface, leading to a vesicular rash, or herpes zoster. Retrograde travel can lead to meningoencephalitis or myelitis, particularly in immunocompromised hosts. The myelitis can be localized to the same segment as the rash or can involve the cord more diffusely. Thoracic involvement is most common.[2] Patients usually present over days to weeks with

TABLE 4-2 **Microorganisms Associated With Immunodeficiency**

Immunodeficiency	Microorganism
Cell-mediated dysfunction (eg, human immunodeficiency virus [HIV], DiGeorge syndrome, Hodgkin lymphoma, glucocorticoids, tacrolimus, methotrexate, mycophenolate mofetil, cyclophosphamide)	Viral: varicella-zoster virus (VZV) (herpes zoster and disseminated infection), cytomegalovirus (CMV), JC virus Bacterial: *Staphylococcus aureus, Mycobacterium tuberculosis, Nocardia* species, *Listeria monocytogenes*; coinfection with *Treponema pallidum* common in patients with HIV Fungal: *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides* species Parasitic: *Toxoplasma gondii* (HIV)
Neutropenia (eg, intensive chemotherapy, hematopoietic cell transplantation, solid organ transplantation)	Viral: herpes simplex virus types 1 and 2, VZV (herpes zoster and disseminated infection), CMV, Epstein-Barr virus Bacterial: *Staphylococcus epidermidis, S. aureus, Streptococcus* species, *Pseudomonas aeruginosa* Fungal: *Aspergillus* species, *Candida* species Parasitic: *T. gondii*
Humoral immune dysfunction (eg, primary hypogammaglobulinemias, complement deficiency, multiple myeloma, Waldenström macroglobulinemia, lymphoma, chronic lymphocytic leukemia, B-cell–depleting therapies, splenectomy)	Viral: Enteroviruses, VZV (herpes zoster) Bacterial: encapsulated bacteria (*Streptococcus pneumoniae*, *Neisseria meningitides*, *Haemophilus influenzae*)
Tumor necrosis factor-α inhibitors	Viral: VZV (herpes zoster) Bacterial: *Mycobacterium tuberculosis*, *Nocardia* species, *L. monocytogenes* Fungal: *H. capsulatum*, *B. dermatitidis*, *Coccidioides species*, *C. neoformans*, *Aspergillus* species
Barrier disruption (eg, shunts/drains, neurosurgical intervention, lines)	Bacterial: *Cutibacterium acnes*, skin/gut-derived bacteria Fungal: *Candida* species

progressive asymmetric paraparesis and sensory disturbances. MRI usually shows an expansile T2-hyperintense lesion with associated gadolinium enhancement, which can be longitudinally extensive. Multifocal segmental lesions can also occur, although are less common.

CSF commonly demonstrates a lymphocytic pleocytosis, and VZV PCR can be diagnostic, although sensitivity is variable and decreases steadily 1 week from symptom onset.[3] CSF VZV serology, and in particular a low serum to CSF VZV IgG ratio confirming intrathecal production, has considerably higher sensitivity. A presumptive diagnosis can be made in patients presenting with myelitis following a characteristic dermatomal rash even if PCR is negative. Conversely, VZV myelitis can occur in the absence of antecedent herpes zoster.[2] Additionally, it must be noted that CSF pleocytosis and even VZV PCR positivity can occur in patients with herpes zoster without clinical meningoencephalomyelitis.[4,5] Treatment is with IV acyclovir and corticosteroids. Postinfectious aquaporin-4-IgG–seropositive neuromyelitis optica spectrum disorder (NMOSD) myelitis has been reported following herpes zoster, and this should be considered in the appropriate clinical setting.[6]

KEY POINTS

- The sensitivity of CSF varicella-zoster virus polymerase chain reaction starts decreasing steadily the further away from symptom onset. A low serum to CSF IgG ratio demonstrating intrathecal production of antibodies is more sensitive.
- Varicella-zoster virus myelitis can occur in the absence of a characteristic herpes zoster rash.

EPSTEIN-BARR VIRUS. EBV establishes latency in lymphocytes and can become reactivated in the setting of immune compromise. Primary infection in early adulthood can be asymptomatic or present as mononucleosis, which is characterized by fever, pharyngitis, fatigue, lymphadenopathy, and splenomegaly. Myelopathy is rare and usually occurs in the setting of primary infection; it is frequently accompanied by encephalopathy.[7,8] It remains unclear whether the mechanism of injury is direct viral invasion or an immune-mediated parainfectious process. Cases of acute disseminated encephalomyelitis (ADEM) have been reported following primary infection, including cases associated with anti–myelin oligodendrocyte glycoprotein (MOG) antibodies.[9] Heterophile antibody positivity or the presence of viral capsid antigen IgM antibodies is helpful in establishing acute systemic infection. Caution is needed when interpreting CSF PCR results as EBV DNA detection does not necessarily indicate CNS infection. CSF EBV DNA can be detected in the setting of CNS inflammation or infection by a different pathogen, presumably because of trafficking of latently infected leukocytes into the intrathecal space.[10,11] CSF EBV PCR positivity can also occur in the setting of CNS lymphoproliferative disorders. Treatment is supportive, but immunotherapies such as corticosteroids and IV immunoglobulin (IVIg) are frequently used.

OTHER MICROORGANISMS. Other viruses, as well as some atypical bacteria, can also cause isolated myelitis.

HUMAN IMMUNODEFICIENCY VIRUS. Although most HIV-associated myelopathies occur late in the course of the disease, acute myelitis can rarely occur in the setting of recent HIV infection and seroconversion.[12] Rare cases of myelitis have also been described in the setting of discordant HIV viral loads between CSF and plasma. This phenomenon occurs because of the disparate effectiveness of combination antiretroviral therapy between the CNS and blood compartments, leading to unchecked infection in the CNS or CSF viral escape.[13] Changing the antiretroviral regimen to optimize CNS penetrance usually leads to improvement of symptoms.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2. Rare reports of myelitis, including a case of necrotizing myelitis, have been reported in association with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the pathogen that

causes COVID-19.[14] Both parainfectious and postinfectious cases have been reported, and the virus was not detected in CSF.[15] Neural injury secondary to the hypercytokinemia that is one of the hallmarks of COVID-19 has been postulated as a potential mechanism, although the nature of the association remains to be elucidated.

MYCOPLASMA PNEUMONIAE. *M. pneumoniae* is an atypical bacterium commonly associated with upper respiratory tract infections and acute bronchitis (TABLE 4-7). CNS manifestations are rare and likely caused by parainfectious or postinfectious immune-mediated mechanisms rather than direct infection. Tellingly, the onset of neurologic symptoms is usually days to weeks following respiratory infection. Most cases of myelitis occur in the setting of ADEM, but isolated myelitis has been reported.[16] MRI usually shows longitudinally extensive

CASE 4-1

A 34-year-old man with chronic myelogenous leukemia (status post–day 60 after allogeneic hematopoietic stem cell transplantation on tacrolimus for graft versus host disease prophylaxis) presented with a 3-week history of fevers, encephalopathy, right-sided greater than left-sided weakness, and urinary retention. Antimicrobial prophylaxis included valacyclovir, posaconazole, penicillin, and inhaled pentamidine, with plans to transition to trimethoprim-sulfamethoxazole following engraftment.

On neurologic examination, he was inattentive and oriented to person and location only. He had a right homonymous hemianopia. Strength in the right hemibody was 3/5, with an upper motor pattern of weakness. Strength in the left hip flexor was 4/5. Deep tendon reflexes were hyperactive (3+) on the right. Babinski sign was present bilaterally.

Brain MRI demonstrated a hemorrhagic lesion in the left occipital lobe as well as several lesions with restricted diffusion, some with a ring pattern but no enhancement (FIGURE 4-1). MRI of the cervical spine showed several T2-hyperintense lesions (contrast was not given). CSF demonstrated lymphocytic pleocytosis, and CSF *Toxoplasma gondii* polymerase chain reaction (PCR) was positive. He was started on pyrimethamine and sulfadiazine, with clinical and radiographic improvement seen over the next few months.

COMMENT

This case highlights the importance of reviewing antimicrobial prophylaxis in patients who are immunocompromised. *Toxoplasma* encephalitis was suspected despite atypical features (lack of enhancement, hemorrhagic lesion, spinal cord involvement) as the patient was not on *Toxoplasma gondii* prophylaxis. *Toxoplasma* encephalitis is rare in hematopoietic stem cell transplantation but can occur in patients who have received allogeneic hematopoietic stem cell transplantation and are seropositive, especially within the first 100 days after transplantation. Because of its potential for myelosuppression, trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia is usually avoided until engraftment. Delayed engraftment (or intolerance to trimethoprim-sulfamethoxazole) can increase the risk of *Toxoplasma* encephalitis.

T2 signal change with white or gray matter involvement. Not surprisingly, detection of *M. pneumoniae* by CSF PCR is rare, as direct infection is not thought to be the primary mechanism of CNS injury. Diagnosis of recent systemic infection can be difficult given the lag between infection and onset of neurologic symptoms. PCR is insensitive, and antibody titers may reflect past infection or cross-reactivity with other pathogens.[17,18] A fourfold rise in IgG titers when comparing acute and convalescent serum is diagnostic, but this may not always be demonstrable by the time neurologic symptoms develop. The role of antibiotics is unclear, and symptoms are usually managed with corticosteroids or IVIg.

TREPONEMA PALLIDUM. Syphilitic meningomyelitis, although rare, is the most common spinal cord manifestation of syphilis, a sexually transmitted disease caused

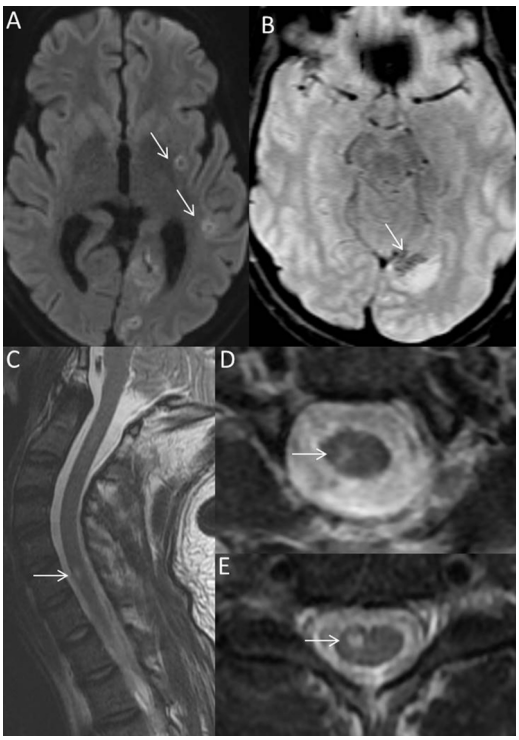

FIGURE 4-1
Imaging of the patient in CASE 4-1. *A*, Axial diffusion-weighted imaging shows diffusion-restricting lesions with a ring pattern *(arrows)*. *B*, Axial gradient recalled echo (GRE) sequence shows a hemorrhagic lesion in the left occipital lobe (*arrow*). Sagittal (*C*) and axial (*D*, *E*) T2-weighted images show intramedullary lesions (*C, D, E, arrows*).

by the spirochete *T. pallidum*. Neurosyphilis, particularly late forms (eg, tabes dorsalis, general paresis), was common in the preantibiotic era. In the current era, early forms (asymptomatic, meningitic, meningovascular) are more commonly encountered, frequently in patients with HIV coinfection. Meningomyelitis presents, on average, 6 years after infection, with progressive asymmetric spastic paresis, bladder dysfunction, and sensory disturbances. Spinal cord MRI shows longitudinally extensive T2 hyperintensity with pial gadolinium enhancement,[19] although patchy parenchymal enhancement has also been described and imaging findings are nonspecific.[20]

The first step in establishing the diagnosis of neurosyphilis is confirming infection with *T. pallidum* with serum treponemal and nontreponemal testing. Nontreponemal tests, such as rapid plasma reagin (RPR) or the Venereal Disease Research Laboratory (VDRL) test are almost always reactive in early disease but may be nonreactive in late neurosyphilis, particularly in tabes dorsalis. Treponemal tests detect antibodies to *T pallidum* and remain positive for life. If serum treponemal tests are negative, the diagnosis of syphilis is excluded. In the setting of positive serum tests, a reactive CSF VDRL is diagnostic of neurosyphilis, but a nonreactive VDRL does not rule out the diagnosis. CSF pleocytosis or an elevated protein in the correct clinical setting may be diagnostic. Treatment is with 14 days of IV penicillin G.

Myeloradiculitis

Some microorganisms can preferentially affect the nerve roots. Root involvement with or without associated myelitis can help narrow the differential diagnosis.

HERPES SIMPLEX VIRUS TYPE 2. HSV-2 lays dormant in the sacral dorsal root ganglia, reactivating to cause recurrent genital lesions. Retrograde migration up the cauda equina to the conus and lower spinal cord can cause myeloradiculitis. Symptoms typically involve an anogenital vesicular rash followed by pain, paresthesia, progressive flaccid paraparesis, and urinary retention. Upper motor neuron signs may be present on examination and suggest lower thoracic spinal cord

TABLE 4-3 Characteristic CSF Profiles by Etiology

	Protein	CSF to serum glucose ratio	Nucleated cells (cell predominance)	Lactate
Normal	15-45 mg/dL	>0.6	<5 cells/mm^3	<3.6 mmol/L
Pyogenic bacteria[a]	Increased	Low	Increased (neutrophilic)[b]	Increased
Viral	Normal to slightly increased	Normal	Increased (lymphocytic)[c]	Normal
Tuberculosis	Increased	Low	Increased (lymphocytic)	Can be increased
Fungal	Increased	Low	Increased (lymphocytic)[d]	Can be increased
Parasitic	Increased	Normal	Normal/increased (eosinophilic)[e]	Unknown

[a] Lumbar puncture is not recommended in patients with known or suspected epidural abscess both because it is low yield and because of increased risk of introducing bacteria into CSF.
[b] Partially treated meningitis/*Listeria monocytogenes* can be associated with lymphocytic pleocytosis.
[c] Cytomegalovirus and West Nile virus may present with neutrophilic pleocytosis.
[d] *Coccidioides* species can present with eosinophilic pleocytosis; *Blastomyces, Candida,* and *Aspergillus* species can cause neutrophilic pleocytosis.
[e] Eosinophilic pleocytosis is not always present; lymphocytic and neutrophilic predominance is also seen.

involvement. CSF normally shows a lymphocytic pleocytosis, and MRI of the lumbosacral spine may show signal change and enlargement of the lower cord with nerve root enhancement. Diagnosis is usually established by demonstrating the presence of HSV-2 DNA by PCR. Patients who are immunocompromised should receive IV acyclovir for 10 to 14 days. Oral antiviral therapy may be considered in those who are immunocompetent. Adjunctive corticosteroids are frequently used. The clinical entity of rapidly progressive lumbosacral myeloradiculitis is known as Elsberg syndrome. Although commonly associated with HSV-2, other viruses (including VZV) can present as Elsberg syndrome, but an infectious agent is not always identified.[21]

CYTOMEGALOVIRUS. A painful ascending lumbosacral myeloradiculitis is also the most common manifestation of CMV spinal cord infection, although isolated thoracolumbar myelitis has also been reported.[22] CMV is a lymphocytic infection usually acquired in childhood or early adulthood. The virus then becomes latent in mononuclear cells and can become reactivated later in life. Primary CMV infection is usually asymptomatic, although a mononucleosislike syndrome can occur. CMV nervous system infection occurs almost exclusively in patients who are immunocompromised in the setting of reactivation of latent disease, although postinfectious myelitis has been reported with primary infection.[23] The CSF of immunocompromised patients with myeloradiculitis or myelitis usually shows a neutrophilic predominant pleocytosis with hypoglycorrhachia. Treatment is with ganciclovir, but outcomes are variable.

LYME DISEASE. Painful meningoradiculitis with or without medullary involvement is the most common spinal manifestation of Lyme disease, although frank myelitis is rare.[24] Lyme disease is a tick-borne infection caused by several species in the spirochete family Borreliaceae. In the United States, neuroinvasive disease is caused almost exclusively by *Borrelia burgdorferi* and is seen in the summer and fall months in the northeastern states and Great Lakes region. The constellation of painful radiculitis accompanied by facial nerve palsy and CSF pleocytosis is known as Bannwarth syndrome and appears to be more common in Europe.[25] Neurologic symptoms usually occur weeks after the initial tick bite. Frequently, but not always, they follow the classic symptoms of fever and characteristic target rash (erythema migrans). Lymphocytic or monocytic pleocytosis without hypoglycorrhachia is common, although CSF parameters may be normal. Diagnostic testing relies on detection of antibodies to *B. burgdorferi* using the standard two-tiered testing algorithm, which starts with an initial enzyme immunoassay.[26] Positive samples require supplemental IgM or IgG immunoblot testing. A newer algorithm involving two different sequential enzyme immunoassays may be more sensitive for early disease but is not yet widely available. Although CSF analysis is not required to establish neuroborreliosis in symptomatic patients who are seropositive, demonstration of intrathecal production of antibodies against *B. burgdorferi* with a serum to CSF IgG index can be helpful in select clinical confounding cases.[27] *B. burgdorferi* PCR is insensitive and has low overall utility. Recommended treatment in the United States for CNS involvement is IV ceftriaxone for 2 to 4 weeks.[28]

SCHISTOSOMIASIS. Parasitic infections can also present with myeloradiculitis (TABLE 4-8). Schistosomiasis is a disease caused by five species of parasitic

KEY POINTS

- The myelitis associated with *Mycoplasma pneumoniae* is likely caused by parainfectious or postinfectious immune-mediated mechanisms.
- Meningomyelitis is the most common spinal cord manifestation of syphilis.
- Treponemal tests remain positive for life following infection. Negative treponemal tests essentially rule out a diagnosis of syphilis.
- Elsberg syndrome is characterized by subacute onset of sacral myeloradiculitis and is commonly associated with herpes simplex virus type 2.
- Meningoradiculitis is the most common spinal manifestation of *Borrelia burgdorferi*.

trematode worms of the genus *Schistosoma*. Neuroschistosomiasis, characterized by either myelopathy or encephalitis, is one of the most severe manifestations of the disease. Schistosomiasis accounts for 1% to 4% of spinal cord lesions in sub-Saharan Africa, although this is likely an underestimation.[29] Myelopathy occurs primarily with *Schistosoma haematobium* and *Schistosoma mansoni*, which are endemic to sub-Saharan Africa and the Middle East; *S. mansoni* is also endemic to parts of South America and some of the South Caribbean Islands.

TABLE 4-4 **Laboratory Testing of Select Microorganisms Associated With Myelopathy and Radiculopathy**

Microorganism	Laboratory tests (sample type)	Comments
Viruses		
Enteroviruses	Polymerase chain reaction (PCR) (CSF, nasopharyngeal, stool)	
Epstein-Barr virus	PCR (CSF, blood), serology (blood), heterophile antibody test (blood)	CSF PCR can be positive in the setting of central nervous system inflammation or infection by another pathogen
Flaviviruses	Serology (blood, CSF), PCR (CSF, blood)	In general, serology more sensitive than PCR, but PCR useful in patients with congenital or acquired humoral deficiency because of cross-reactivity confirmatory testing can be done with plaque reduction neutralization test
Cytomegalovirus	PCR (CSF, blood), serology (blood), serum IgG avidity testing (blood)	Serology: IgG appears within weeks following primary infection and remains positive for life; IgM is positive during primary infection but can be persistently positive or positive during reactivation; serum IgG avidity assay can disambiguate between primary and past infection when both IgM and IgG are positive
Herpes simplex virus types 1 and 2	CSF PCR	
Varicella-zoster virus	CSF PCR, serum to CSF IgG ratio	CSF PCR sensitivity decreases >1 wk from symptom onset
Bacteria		
Borrelia burgdorferi	Traditional algorithm is enzyme immunoassay followed by Western blot; modified algorithm is two sequential enzyme immunoassays; serum/CSF IgG index	Modified algorithm may be more sensitive for early disease but not yet widely available; CSF PCR is insensitive
Brucella species	Culture (blood, CSF, tissue), serology (blood)	PCR not widely available
Mycobacterium tuberculosis	Culture (blood, CSF, tissue), acid-fast bacilli stain, PCR (CSF, tissue), histopathology	Interferon gamma release assays can confirm exposure, but a negative test does not rule out the diagnosis

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Schistosoma japonicum, which is found in China, the Philippines, and Indonesia, usually causes encephalitis but can rarely cause myelopathy. Infection is acquired in freshwater ponds, lakes, and rivers contaminated by free-swimming parasite larvae (cercariae) shed from snails. Cercariae penetrate the skin and develop into worms that reside in blood vessels, mate, and produce eggs that travel through the venous system and lodge in tissues. Myelopathy is thought to occur via embolization of eggs through retrograde venous flow into the Batson venous

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Microorganism	Laboratory tests (sample type)	Comments
Treponema pallidum	Treponemal tests (fluorescent treponemal antibody absorption, treponema pallidum agglutination assay, enzyme immunoassay), nontreponemal tests (rapid plasma reagin [RPR], Venereal Disease Research Laboratory test)	A negative CSF Venereal Disease Research Laboratory test does not rule out neurosyphillis
Fungi		
Aspergillus species	Antigen: galactomannan (CSF, blood, bronchoalveolar lavage [BAL]), (1,3)-β-D-glucan (CSF, blood, BAL), culture (CSF, BAL, blood, tissue), PCR (CSF, BAL, tissue), histopathology	Galactomannan can be falsely positive in patients receiving piperacillin-tazobactam and IV immunoglobulin (IVIg); (1,3)-β-D-glucan not specific for *Aspergillus*; limited availability of PCR; low sensitivity and specificity
Blastomyces dermatitidis and *Histoplasma capsulatum*	Antigen (blood, urine, CSF), serology (blood, CSF), PCR (CSF, BAL, tissue), culture (CSF, BAL), histopathology	Serology and antigen studies are more sensitive than PCR
Coccidioides species	Serology (CSF, blood), antigen (CSF, blood, urine), PCR (CSF, tissue), culture (CSF, tissue), histopathology	
Cryptococcus species	Antigen (CSF, blood), culture (CSF, blood)	Antigen most sensitive and specific test
Parasite		
Taenia solium (neurocysticercosis)	Serology enzyme-linked immunoelectrotransfer blot or enzyme-linked immunosorbent assay (ELISA) (blood, CSF), histopathology	Enzyme-linked immunoelectrotransfer blot test of choice; more sensitive in serum; sensitivity reduced if single or calcified lesion
Schistosoma species	Microscopy (stool, urine), serology (blood, CSF), histopathology	
Toxoplasma gondii	CSF PCR, histopathology	CSF PCR is diagnostic but lacks sensitivity; serology confirms past exposure

CSF = cerebrospinal fluid; IgG = immunoglobulin G; IgM = immunoglobulin M.

TABLE 4-5 **Assays Targeting Multiple Microorganisms**[a]

Assay	Function	Pros/cons
Meningitis/encephalitis panel	Real-time multiplex polymerase chain reaction (PCR) that can simultaneously detect 14 pathogens: *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, cytomegalovirus, varicella-zoster virus, herpes simplex virus types 1 and 2, human herpesvirus 6, Enterovirus, human parechovirus, and *Cryptococcus neoformans*/*Cryptococcus gattii*	Fast turnaround time with potential to decrease unnecessary antimicrobial exposure Sensitivities and specificities comparable to individual pathogens but low sensitivity for *Cryptococcus* species Standalone herpes simplex virus PCR has higher sensitivity compared to panel No antibiotic susceptibilities
16S rRNA PCR with reflex sequencing (CSF or tissue sample)	Detection of 16S rRNA gene polymerase, which is highly preserved in bacteria (including mycobacteria), is followed by sequencing of the amplified DNA, enabling a diagnosis	Useful for identifying bacteria in patients who have already received antibiotics Can be run on paraffin-embedded tissue No antibiotic susceptibilities
Fungal 18S and 28S rRNA/internal transcribed spacer (ITS1 and ITS2) PCR with reflex sequencing (CSF or tissue sample)	Detection of highly preserved fungal ribosomal genes is followed by sequencing of the amplified DNA, enabling diagnosis	Fast turnaround time compared to fungal cultures Useful when fungal elements are seen on paraffin-embedded tissue but fresh tissue sample no longer available
(1,3)-β-D-Glucan (serum or CSF)	(1,3)-β-D-Glucan is a cell wall polysaccharide present in most fungi (except *Cryptococcus* species, the Zygomycetes, and *Blastomyces dermatitidis*)	Sensitivity and specificity in serum varies depending on population (highest among patients with hematopoietic stem cell transplantation) Few studies assessing utility in CSF Not sufficient to rule out central nervous system fungal infection if negative Exposure to antibiotics such as piperacillin-tazobactam and ampicillin can cause false-positive results
Metagenomic next-generation sequencing (CSF or tissue sample)	All DNA and RNA in CSF or brain tissue sample are sequenced without need for prior culturing; results can be compared to databases of all known microorganisms	Potential to detect any pathogen (bacteria, virus, fungus, parasite) in a clinical sample, including unsuspected pathogens Sensitivity likely low for pathogens for which PCR is insensitive A negative result does not rule out infection

CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; rRNA = ribosomal ribonucleic acid.
[a] Modified with permission from Yost MD, Toledano M.[1] © 2020 Springer Nature.

plexus, a valveless paravertebral venous system that connects the deep pelvic veins to the internal vertebral venous plexus. The eggs result in venous congestion and granulomatous inflammation leading to myeloradiculitis. Patients usually present with subacute lumbar pain, paraparesis, sensory loss, and urinary retention. Symptoms can arise months to years after infection, so eliciting a history of exposure may be challenging, particularly in nonendemic regions.[30] MRI often shows medullary expansion of the conus medullaris or lower thoracic cord associated with intramedullary, meningeal, or root nodular enhancement.[31] Patients may demonstrate peripheral or CSF eosinophilia. Definitive diagnosis is by visualization of the eggs on histopathology, but positive serology, antigen detection, or demonstration of eggs in stool or urine by microscopy can support the diagnosis in the correct clinical setting. Praziquantel and corticosteroids are used for treatment, although decompressive surgery is required in some cases. Neurologic sequelae are common.

FUNGI. Infiltrative meningoradiculitis and meningomyeloradiculitis can occur with the endemic mycoses caused by the dimorphic fungi *Histoplasma capsulatum* and *Blastomyces dermatitidis*, usually in the setting of chronic meningitis (CASE 4-2).[32] Opportunistic fungi such as *Cryptococcus* can also rarely cause infiltrative meningomyeloradiculitis (TABLE 4-9).[33] MRI in these cases typically shows leptomeningeal and root enhancement with or without cord signal change. Similarly, atypical bacteria such as *Mycobacterium tuberculosis*, *Brucella*, and *T. pallidum* can cause granulomatous myeloradiculitis in the setting of meningitis.

Leukomyelitis

Certain pathogens can preferentially affect the white matter of the spinal cord, causing a leukomyelitis (*leukos* means white in Greek). Infections that primarily affect the lateral columns result in spastic paraparesis, whereas those with prominent dorsal column involvement result in sensory ataxia.

Herpesviruses Associated With Myelopathy and Radiculopathy TABLE 4-6

Herpesvirus	Clinical characteristics	Treatment
Herpes simplex virus type 2	Sacral myelopolyradiculitis; can be associated with vesicular rash along sacral dermatomes; isolated myelitis (rare)	Acyclovir or valacyclovir, adjunctive corticosteroids
Varicella-zoster virus	Longitudinally extensive or multifocal myelitis, myeloradiculitis, or spinal cord infarct; thoracic most common	IV acyclovir with or without adjunctive corticosteroids
Cytomegalovirus	Painful myeloradiculitis in patients who are immunocompromised because of virus reactivation; postinfectious myelitis following primary infection, can present as poliomyelitis	Ganciclovir and/or foscarnet; immunomodulatory therapies for postinfectious cases
Epstein-Barr virus	Probable parainfectious/postinfectious encephalomyelitis with or without radiculopathy following primary infection	Supportive treatment; immunomodulatory therapies
Herpes simplex virus type 1	Rare reports of myelitis, mostly in immunocompromised hosts	IV acyclovir
Human herpesvirus 6	Few case reports in patients following allogeneic hematopoietic stem cell transplantation	Ganciclovir, foscarnet, cidofovir

LATERAL COLUMN PREDOMINANT. Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects 5 million to 20 million individuals worldwide.[34,35] It is endemic to southern Japan, the Caribbean, South America, Papua New Guinea, the Melanesian islands, and the Middle East as well as West, Central, and Southern Africa. The virus is transmitted by breast-feeding, sharing of needles, sexual intercourse (with male-to-female transmission being more efficient than the reverse), and blood transfusions and, rarely, via transplanted organs.[36]

The two main diseases associated with HTLV-1 are adult T-cell leukemia and HTLV-1–associated myelopathy (HAM), also known as tropical spastic paraparesis (TSP).

HAM/TSP affects between 0.25% and 4% of HTLV-1 carriers, depending on the population studied, and is more common in females.[37] The onset of myelopathy ranges from 4 months to 30 years after infection, but it almost never develops in children; the peak incidence is around the fifth decade of life.[37] Virus acquisition through blood transfusion or organ donation may be associated with more severe disease.[38] HAM/TSP has been described as a two-phase disease consisting of an acute inflammatory phase and a chronic neurodegenerative phase. The exact mechanism of injury is unknown, but the presence of lymphocytic infiltrate in the CNS suggests that an aberrant immune response to HTLV-1 is likely responsible, at least in the early inflammatory phase. Pathologic studies show inflammation and demyelination of the lateral corticospinal, spinocerebellar, and spinothalamic tracts, with relative sparing of the dorsal columns.[39] MRI of the spine may show T2-hyperintense lesions with or without associated gadolinium enhancement, followed by spinal cord atrophy in later stages. Unlike other parainfectious myelitis, HAM/TSP is characterized by the onset of slowly progressive proximal greater than distal spastic paraparesis (upper limbs are usually spared). Back pain and early bladder involvement are common.

Clinical diagnostic criteria have been proposed.[40] Detection of HTLV-1 antibodies is required for the diagnosis of HAM/TSP but lacks specificity. An elevated HTLV-1 proviral load in peripheral blood mononuclear cells can be supportive. CSF protein concentration and lymphocyte count can be normal or mildly elevated, and oligoclonal bands may be present. Elevated HTLV-1 proviral load in CSF

TABLE 4-7 Atypical Bacteria Associated With Myelopathy and Radiculopathy

Bacteria	Spinal manifestation	Treatment
***Borrelia* species**	Meningoradiculitis rarely with associated myelitis	Ceftriaxone
***Brucella* species**	Spondylodiskitis, intramedullary and extramedullary abscess, granulomatous meningoradiculitis, arachnoiditis	Ceftriaxone plus rifampin and doxycycline
Mycobacterium tuberculosis	Spondylodiskitis (Pott disease), intramedullary and extramedullary tuberculoma, granulomatous myeloradiculitis, tuberous arachnoiditis causing myeloradiculopathy, spinal artery vasculitis with spinal cord ischemia	Isoniazid, rifampin, pyrazinamide, ethambutol for 2 months, followed by isoniazid and rifampin for 7-10 months; corticosteroids
Mycoplasma pneumoniae	Probable immune-mediated longitudinally extensive myelitis	Corticosteroids, IV immunoglobulin (IVIg)
Treponema pallidum	Meningomyelitis, hypertrophic pachymeningitis with polyradiculopathy, meningovascular syphilis resulting in spinal cord ischemia, spinal gummas	IV penicillin G

lymphocytes compared to matched peripheral blood mononuclear cells may be more specific and help predict progression, but the assay is not widely available.[41]

Treatment is mainly supportive. Corticosteroids are often used as some studies have shown that they slow progression and improve pain; however, no randomized clinical trials have been conducted, and improvement may not be sustained.[37]

A phase 1–2a study of mogamulizumab, an anti-CCR4 (chemokine receptor type 4) monoclonal antibody with efficacy in adult T-cell leukemia, was associated with improvement in some clinical parameters as well as reduction in proviral load, but larger studies are needed to establish efficacy.[42] The general outcome is progression to disability, but significant variation exists in the rate of progression.

LATERAL AND DORSAL COLUMN INVOLVEMENT. Vacuolar myelopathy is the best characterized spinal cord abnormality associated with HIV infection, occurring late in the course of the disease as an acute immunodeficiency syndrome (AIDS)–defining illness.[43] It is characterized pathologically by white matter vacuolization of the posterior and lateral columns. HIV antigens and inflammation are usually absent. Although it shares features with the subacute combined degeneration seen with cobalamin deficiency, the pathophysiology remains poorly understood. The disease is usually most prominent in the thoracic cord and causes spastic paraparesis and profound sensory ataxia. MRI may be normal or may show T2 hyperintensity in the affected tracts. Initiation of combined antiretroviral therapy is the only effective treatment.

Tabes dorsalis, characterized by degeneration of the posterior column and dorsal root ganglia, occurs in the setting of chronic untreated syphilis. Typically, patients develop severe sensory ataxia and lancinating pain. Charcot joints and Argyll Robertson pupils are often associated. Although common in the preantibiotic era, tabes dorsalis is only rarely seen in contemporary practice.

Poliomyelitis and Acute Flaccid Myelitis

The word *poliomyelitis* specifies inflammation of the gray matter within the spinal cord (*poliós* means gray in Greek).

Parasitic Infections Associated With Myelopathy and Radiculopathy TABLE 4-8

Parasite	Spinal manifestation	Treatment
Angiostrongylus cantonensis	Myeloradiculitis	Albendazole, adjunctive corticosteroids
***Echinococcus* species**	Spondylodiskitis, epidural hydatid cysts	Albendazole, surgery
Gnathostoma spinigerum	Eosinophilic myeloradiculitis	Supportive care; use of antihelminthic agents remains controversial
***Schistosoma* species**	Sacral myeloradiculitis, intramedullary or extramedullary granuloma	Praziquantel
Taenia solium	Subarachnoid lesions, intramedullary lesion	Corticosteroids with or without surgery for arachnoiditis; albendazole with or without corticosteroids for intramedullary disease
Toxoplasma gondii	Intramedullary lesion(s)	Sulfadiazine plus pyrimethamine plus leucovorin

POLIOVIRUS. Poliomyelitis is historically connected with the poliovirus, a picornavirus of the genus *Enterovirus* that infects the anterior horn cells, manifesting as acute flaccid paralysis. A worldwide vaccination program has virtually eradicated wild-type virus, and as of 2019, poliomyelitis was endemic only in Afghanistan and Pakistan. Outbreaks of vaccine-derived poliomyelitis caused by circulating poliovirus derived from strains in the oral poliovirus vaccine have occurred in locations with low population immunity.[44] Vaccine-associated paralytic poliomyelitis can also rarely occur in patients who are immunodeficient, particularly those with B-cell depletion and hypogammaglobulinemia.[45,46]

Poliovirus infection occurs via the fecal/oral route. Only a small fraction of those infected develop paralytic disease. The onset of weakness typically coincides with signs and symptoms of viral meningitis and muscle pain. The distribution and extent of weakness may vary, ranging from monoparesis to (usually asymmetric) quadriparesis. Reflexes are decreased or absent, and the sensory examination is normal. CSF may or may not demonstrate pleocytosis, and, although CSF PCR rarely detects the virus, it can sometimes be detected in stool or nasopharyngeal samples. MRI may show T2 hyperintensity primarily affecting the gray matter of the affected spinal cord levels. Treatment is supportive.

ACUTE FLACCID MYELITIS. Other enteroviruses can also be associated with poliomyelitis. Since 2012, the United States has experienced a biennial spike in cases

CASE 4-2

A 72-year-old man presented with a 4-month history of lumbar pain with radicular features and urinary retention. He also reported headache, fatigue, and myalgia. He had reportedly completed treatment for pulmonary histoplasmosis 5 years earlier.

Neurologic examination was notable for bilateral proximal greater than distal lower extremity weakness, which was 4/5 in affected muscles; absent deep tendon reflexes; and decreased sensation to pinprick up to the left thigh and right knee.

MRI of the thoracic and lumbar spine revealed leptomeningeal enhancement around the thoracic cord and conus medullaris as well as smooth enhancement of the roots without clumping (FIGURE 4-2). CSF analysis revealed a protein of 127 mg/dL, lymphocytic pleocytosis with 94 cells/mm^3, and a low glucose of 21 mg/dL. Urine *Histoplasma* antigen was strongly positive. CSF *Histoplasma* serology, polymerase chain reaction (PCR), and fungal cultures were negative, but *Histoplasma* antigen was positive. CSF and blood (1,3)-β-D-glucan were positive. Imaging and symptoms improved significantly after completing induction with IV liposomal amphotericin B.

COMMENT

Establishing the diagnosis of central nervous system histoplasmosis can be difficult. Antigen testing in urine, blood, and CSF should be conducted, along with serology in CSF and blood. Although specific, PCR is less sensitive. (1,3)-β-D-Glucan is neither sensitive nor specific but can be supportive. Some patients exhibit low-level antigenuria following treatment of pulmonary or disseminated histoplasmosis, but a robustly elevated antigen level is indicative of active infection.

of (mostly) pediatric acute flaccid paralysis, termed *acute flaccid myelitis*.[47] These have coincided temporally and geographically with outbreaks of the nonpolio enterovirus D68. Both enterovirus D68 and enterovirus 71 have been associated with cases of flaccid paresis elsewhere in the world, and enterovirus 71 has been associated with cases of rhombencephalomyelitis in Southeast Asia.[48,49] Despite the strong epidemiologic link, the etiology of acute flaccid myelitis remains elusive. CSF enterovirus PCR has only rarely been positive in these patients, and less than half had enterovirus nucleic acid detected in respiratory or stool samples. Recently, a study identified high levels of CSF enterovirus-specific antibodies in patients with acute flaccid myelitis despite negative molecular testing, further supporting a causal role for nonpolio enteroviruses.[50] According to the 2020 consensus definition, a patient presenting with acute flaccid paresis and MRI spine showing predominantly gray matter involvement in one or more vertebral segments is considered a confirmed case.[47] CSF pleocytosis is not required. Currently no targeted therapies have demonstrated efficacy, although IVIg is often used. Plasma exchange and corticosteroids have also been suggested, but theoretical concerns exist about their use in the setting of potentially active viral infection.[51]

OTHER VIRUSES. Adenoviruses have also been associated with poliomyelitis.[52,53] In addition, flaviviruses, a family of arthropod-borne RNA viruses more commonly associated with meningoencephalitis, can also cause poliomyelitis (**TABLE 4-10**).

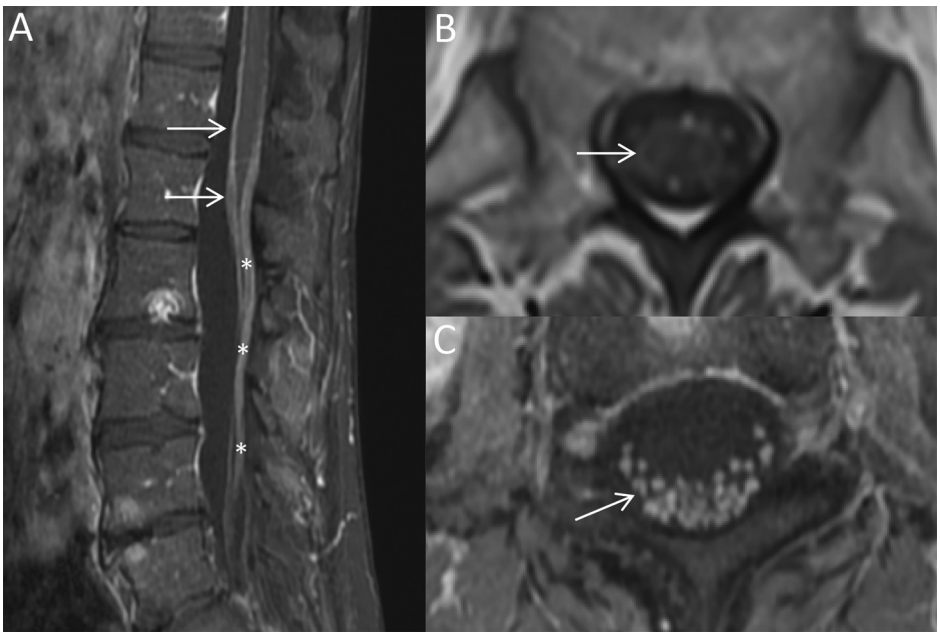

FIGURE 4-2
Imaging of the patient in CASE 4-2. Sagittal (*A*) and axial (*B*, *C*) postcontrast T1-weighted MRIs show smooth leptomeningeal enhancement of the thoracic cord and conus medullaris (*A*, *B*, *arrows*), as well as enhancement of the cauda equina roots (*A*, *asterisks*; *C*, *arrow*).

WEST NILE VIRUS. West Nile virus is now endemic throughout the continental United States. One percent of infections are neuroinvasive, including an acute poliomyelitis or ventral root infection that manifests as acute flaccid paralysis.[54] The latter commonly presents as acute flaccid monoparesis and fever with or without associated meningoencephalitis and occurs in summer and early fall, months in which the *Culex* mosquito thrives.

POWASSAN VIRUS. Powassan virus, which is carried by ticks and found in the Northeast and Great Lakes regions of the United States, can also cause flaccid paresis, usually between late spring and midfall, when ticks are most active (CASE 4-3).[55] Viremia is short-lived, and CSF PCR is an insensitive diagnostic test unless performed early in the course of the disease.[56] IgM-captured enzyme-linked immunosorbent assay (ELISA) in either blood or CSF during the acute phase is diagnostic. Although highly sensitive, the ELISA has poor specificity given significant cross-reactivity with other flaviviruses.[57] Confirmatory plaque reduction neutralization testing can be performed, although the clinical utility may be limited in the absence of targeted antiviral

TABLE 4-9 **Fungal Infections Associated With Myelopathy and Radiculopathy**

Microorganism	Spinal involvement	Systemic involvement	Treatment
Endemic fungi			
Blastomyces dermatitidis	Spondylodiskitis, intramedullary and extramedullary abscess, myeloradiculitis	Chronic pneumonia, verrucous lesions with irregular borders, subcutaneous nodules, prostatitis, osteomyelitis	Liposomal amphotericin B followed by an azole
Coccidioides species	Adhesive arachnoiditis, spondylodiskitis, intramedullary and extramedullary abscess	Pneumonia, fever, drenching night sweats, weight loss, arthralgia, erythema nodosum	Oral fluconazole for life
Histoplasma capsulatum	Meningoradiculitis, meningomyelitis, spondylodiskitis, intramedullary and extramedullary abscess	In pulmonary disease: fever, chills, myalgia, anorexia, cough, chest pain, chest x-ray showing mediastinal lymph nodes In disseminated disease: pancytopenia, hepatosplenomegaly, endocarditis, adrenal insufficiency, osteomyelitis	Liposomal amphotericin B followed by itraconazole
Opportunistic fungi			
Aspergillus species	Necrotizing myelopathy, intramedullary and extramedullary mass lesions, spondylodiskitis	Pneumonia associated with single or multiple nodules surrounded by ground-glass infiltrates (halo sign), cavitations, rhinosinusitis, endophthalmitis	Voriconazole or isavuconazole
Candida species	Spondylodiskitis, extramedullary abscess	Osteoarticular infections, endocarditis, endophthalmitis, peritonitis, pneumonia, mediastinitis	Liposomal amphotericin B with or without flucytosine
Cryptococcus species	Meningomyeloradiculitis, intramedullary/extramedullary mass lesions (cryptococcoma)	Asymptomatic focal pneumonitis, rarely symptomatic pneumonia, fever, night sweats	Liposomal amphotericin B followed by flucytosine

therapy. Serologic tests can be falsely negative in patients with congenital or acquired humoral deficiency (eg, patients on B-cell–depleting therapies such as rituximab), and PCR is usually needed to establish the diagnosis in these cases.[58]

RABIES. Paralytic rabies can also present with flaccid paresis. Rabies is caused by a number of different species of viruses in the Rhabdoviridae family, genus *Lyssavirus*, and usually transmitted to humans by bites from animal vectors. The onset of clinical disease is between 20 and 90 days from exposure. Although a majority of patients present with the more common encephalitic form, about 20% of patients develop paralytic rabies.[59] These patients typically have early progressive flaccid weakness that initially may affect only the bitten limb but invariably spreads to other limbs and bulbar muscles. Sphincter dysfunction, pain, piloerection, and sensory disturbances can occur, but hydrophobia is rare. Several tests are required to confirm the diagnosis, including virus isolation from saliva or skin via reverse transcriptase PCR or detection of antibodies in serum and CSF.[59] Once symptoms arise, no treatment has been found to be effective and the disease is invariably fatal.[60]

Spinal Cord Infarct

Although relatively rare, some microorganisms can be associated with spinal cord ischemic or hemorrhagic stroke.

Flaviviruses Associated With Myelopathy TABLE 4-10

Flavivirus	Mechanism	Area of involvement	Vector	Endemicity
West Nile virus	Neuroinvasive	Anterior horn cells and roots	*Culex* species mosquitoes	North America, the Caribbean, Africa, the Middle East, parts of Europe and the former Soviet Union
Powassan virus	Neuroinvasive	Anterior horn cells	*Ixodes* species ticks	Minnesota, Wisconsin, New York, Massachusetts, Ontario, Manitoba, Nova Scotia
St. Louis encephalitis virus	Neuroinvasive	Anterior horn cells	*Culex* species mosquitoes	North and South America, but most cases reported in the eastern and central United States
Tick-borne encephalitis virus	Probably neuroinvasive	Anterior horn cells	*Ixodes* species ticks	Baltic States, Russia, the Balkans, Nordic countries
Japanese encephalitis virus	Neuroinvasive	Anterior horn cells	*Culex* species mosquitoes	Temperate regions of China, Japan, the Korean peninsula, the Indian subcontinent, Southeast Asia
Dengue virus	Neuroinvasive parainfectious/ postinfectious	Longitudinally extensive or multifocal leukomyelitis	*Aedes* species mosquitoes	Central and South America, the Caribbean, Southeast Asia, the Pacific Islands; rarely, the southern United States
Zika virus	Neuroinvasive parainfectious/ postinfectious	Longitudinally extensive or multifocal leukomyelitis, anterior horn cells, roots	*Aedes* species mosquitoes	Outbreaks have occurred in Central, North, and South America; the Caribbean; Africa; Southeast Asia; and the Pacific Islands

VARICELLA-ZOSTER VIRUS. Pathologic studies of VZV meningoencephalomyelitis suggest the virus causes a necrotizing small vessel vasculitis with local demyelination and neuronal inclusions. A postviral (days to months) vasculopathy affecting larger caliber cerebral vessels has also been described.[2] Spinal cord ischemia, although rare, has been reported in association with VZV infection.[61]

TREPONEMA PALLIDUM. *T. pallidum* can cause an infection-associated inflammatory arteriopathy of the leptomeninges known as *meningovascular syphilis*, which can rarely result in spinal cord infarcts.[62]

BACTERIAL AND MYCOBACTERIAL MENINGITIS. Rarely, bacterial and mycobacterial meningitis can be associated with anterior spinal artery infarction.[63]

ASPERGILLUS. *Aspergillus* can cause necrotizing myelitis with associated spinal cord infarction, highlighting the angioinvasive nature of this opportunistic mold.[64] Typically, *Aspergillus* causes severe systemic infections in patients who are immunocompromised, especially those with severe neutropenia. As with most fungi, the route of infection is through inhalation into the lungs and paranasal sinuses. Immune suppression allows dissemination to extrapulmonary sites, including the CNS, where it more commonly presents with mass lesions. Detection of galactomannan, a major constituent of *Aspergillus* cell wall, in

CASE 4-3

A 56-year-old woman from Minnesota presented to the hospital in mid-October with new-onset fever, encephalopathy, and flaccid paresis of her right arm. At admission, her temperature was 39.2 °C (102.6 °F).

On neurologic examination, she was sleepy but easily arousable and oriented to person only. Strength in the right upper extremity was normal with the exception of her deltoid, biceps, and triceps, which were 3/5. Strength in the left arm and legs was normal. Deep tendon reflexes were absent in the right upper extremity but present elsewhere. Sensation appeared intact. Babinski sign was present on the right.

CSF revealed lymphocytic pleocytosis with normal glucose. Brain MRI showed T2 hyperintensities in the deep gray matter nuclei on the left, but MRI of the cervical spine was negative. Nerve conduction studies and EMG were consistent with a disorder of the anterior horn cells affecting right cervical myotomes (FIGURE 4-3). West Nile virus serology was negative. Powassan virus was positive via CSF enzyme-linked immunosorbent assay (ELISA) testing, later confirmed by plaque reduction neutralization testing.

COMMENT

This case highlights the importance of recognizing characteristic clinical patterns as well as the importance of paying attention to endemicity and seasonality. The patient presented with encephalomyelitis, acute flaccid monoparesis, and electrodiagnostic features suggestive of anterior horn cell disease, all of which are suggestive of *Flavivirus* infection. Mid-October is past mosquito season, making West Nile virus unlikely. Powassan virus, however, is endemic to the Upper Midwest and northeastern states and transmitted by ticks, which persist through early fall.

serum, bronchoalveolar lavage, or CSF can help establish the diagnosis. (1,3)-β-D-Glucan, a cell wall component of many fungi, can also be detected but is less specific. Histopathologic studies may be necessary for confirmation.

Intramedullary Abscess

Intramedullary abscess of the spinal cord is a rare clinical entity. This is partly because normal spinal cord tissue appears to be remarkably resistant to hematogenous spread from infection, which is a common cause of abscess formation. When hematogenous spread does occur, a predisposing spinal cord abnormality is common.[65] Another mechanism is contiguous spread of infection through a dermal sinus tract, more commonly in the lumbar region. In these cases, pathogens reflect the microorganisms colonizing the skin surrounding the sinus tract opening, including *Staphylococcus* species as well as gram-negative rods and anaerobes. Most patients present with weakness, back pain with radicular features, and bladder dysfunction. Fever occurs in less than 50% of patients.[65] MRI shows rim enhancement and surrounding edema and can be associated with internal restricted diffusion.

Empiric antimicrobial therapy should be based on the presumed mechanism of infection. Myelotomy and abscess drainage are usually required and help guide antimicrobial therapy. Ampicillin should be initiated empirically in cryptogenic cases to cover for *Listeria monocytogenes*.[65] Mortality occurs in less than 10% of cases, but residual neurologic deficits are common.[65]

A

NERVE CONDUCTIONS Temperature: 33.6 Â°C

Nerve	Type	Record Site	Rep Stim	Side	Normal Amp	Amp	Normal CV	CV	Distal Lat	Normal Lat	F-Wave Lat	F-Wave Est
Median	motor	abductor pollicis brevis		R	1.5	(> 4.0)	56	(> 48)	3.7	(< 4.5)	31.5	26.9
Ulnar	motor	abductor digiti minimi		R	2.0	(> 6.0)	63	(> 51)	2.7	(< 3.6)	29.3	23.3
Median	sensory	index		R	30	(> 15.0)	65	(> 56)	2.9	(< 3.6)		
Ulnar	sensory	fifth		R	16	(> 10.0)	65	(> 54)	2.7	(< 3.1)		

B

NEEDLE EMG

Muscle	Side	Ins Act	Spont Fib	Fasc	MUP Normal	MUP Activ	Recruitment Reduced	Recruitment Rapid	Duration Long	Duration Short	Amplitude High	Amplitude Low	Phases %	Phases Turns
Pronator teres	R	Increased	+++	0	------ None									
Triceps brachii	R	Increased	++	0			++		+/-					+
Cervical paraspinals	R	Increased	++	0			+						25%	
First Dorsal Interosseous	R	Increased	++	0	Normal	Poor								
Biceps brachii	R	Increased	+++	0			++		+				50%	++
Deltoid	R	Increased	++	0			++		+/-					+

FIGURE 4-3

Nerve conduction study and EMG results of the patient in CASE 4-3. *A*, Nerve conduction studies show low-amplitude compound muscle action potentials (CMAPs) in the right arm (*box*). *B*, Needle EMG demonstrates dense fibrillation potentials (*box*) and reduced motor unit action potential recruitment in right upper extremity muscles.

Microorganisms other than pyogenic bacteria that can cause intramedullary rim-enhancing lesions include *M. tuberculosis* (tuberculomas), endemic and opportunistic fungi, parasites, and CMV (TABLE 4-11).

EXTRAMEDULLARY INFECTION

Pyogenic bacteria are a common cause of extramedullary infection, but atypical bacteria, fungi, and parasites can also seed extramedullary sites, leading to compressive myelopathy and radiculopathy.

Spondylodiskitis and Spinal Epidural Abscess

Spondylitis (vertebral osteomyelitis) and infection of the adjacent intervertebral space (diskitis) most often occur as a result of hematogenous seeding from a distant focus of infection. Other routes of infection include direct inoculation from trauma or surgical procedure or contiguous spread from an adjacent soft tissue infection. Most cases occur in patients older than 50 years of age, and males are affected twice as often as females. Important risk factors include injection drug use, degenerative spine disease, prior spinal instrumentation, diabetes mellitus, infective endocarditis, dialysis, corticosteroid therapy, or any immunocompromised state.

Staphylococcus aureus accounts for more than 50% of cases in developed countries. Other causes include enteric gram-negative bacilli as well as pyogenic and nonpyogenic streptococci. *Pseudomonas aeruginosa*, coagulase-negative *Staphylococcus*, and *Candida* species are seen in association with line infections and injection drug use. *M. tuberculosis* still accounts for a substantial number of spinal

TABLE 4-11 **Etiologies of Spinal Cord Intramedullary Ring-Enhancing Lesions**

Viral

- **Cytomegalovirus**

Bacterial

- **Pyogenic bacteria**
- ***Mycobacterium tuberculosis* (tuberculoma)**
- ***Brucella* species**

Fungal

- **Endemic fungi**
  - *Blastomyces dermatitidis*
  - *Coccidioides* species
  - *Histoplasma capsulatum*
- **Opportunistic fungi**
  - *Aspergillus* species
  - *Cryptococcus* species (cryptococcoma)

Parasitic

- ***Schistosoma* species**
- ***Taenia solium* (neurocysticercosis)**
- ***Toxoplasma gondii***

cord infections worldwide, both in areas with high rates of disease (including sub-Saharan and North Africa, India, Southeast Asia, Micronesia, China, Eastern Europe, and Central and South America) and in countries with large populations from endemic regions. Although spinal manifestations of tuberculosis (TB) are protean, tuberculous spondylitis (Pott disease) is by far the most common. In developed countries, TB usually presents as reactivation in adults from endemic regions. *Brucella* and *Echinococcus* are rare causes of spondylodiskitis in endemic regions.[66-68] Endemic and opportunistic fungi are a rare but important cause of spondylodiskitis in those who are immunocompromised.

The main clinical presentation of spondylodiskitis is insidious neck or back pain, usually localized to the infected disk space. The pain is usually worse with activity and can be reliably exacerbated with percussion over the involved posterior spinous process. Fever is present in less than 50% of cases.[69] Leukocytosis is not always present, but elevations in erythrocyte sedimentation rate and C-reactive protein are observed in more than 80% of patients. Spondylodiskitis associated with TB, *Brucella*, or fungi has a more indolent course and is generally less painful than pyogenic spondylodiskitis. Consequently, many patients exhibit signs of nervous system compromise by the time of diagnosis.

Blood and urine cultures should be obtained in all patients suspected of having spondylodiskitis and are positive in up to 50% of patients. If blood cultures are positive for gram-positive organisms, evaluation for infective endocarditis should be considered in those with a history of valvular disease or new-onset heart failure. Although MRI cannot reliably distinguish between tuberculous and pyogenic spondylodiskitis, features favoring TB infection include intervertebral disk sparing, extensive paraspinal soft-tissue involvement, heterogeneous vertebral body enhancement, involvement of multiple vertebral bodies, and subligamentous spread.[70] Biopsy is warranted to establish a microbiologic diagnosis when blood and urine cultures are negative. If TB is suspected, tissue should be sent for acid-fast stain and mycobacterial culture. Existing molecular assays can simultaneously detect *M. tuberculosis* and rifampin resistance. Tissue microscopy usually reveals necrotizing granulomas.

Spinal epidural abscesses frequently arise in the setting of spondylodiskitis; thus, the two conditions share much of their epidemiology and microbiology. Hematogenous seeding of epidural fat, lymphatic spread from an oropharyngeal abscess, or direct invasion of the epidural space in the setting of surgery or penetrating trauma can also result in the formation of an epidural abscess.

Initial manifestations are similar to those of spondylodiskitis and characterized by localized pain and fever, but patients eventually develop radicular pain followed by frank myelopathic signs (**CASE 4-4**). Once weakness develops, deficits may become irreversible without intervention within 24 hours.[71] When suspected, MRI should be obtained and empiric antibiotic therapy initiated. Surgical decompression and drainage in addition to systemic antibiotic therapy (guided by culture and susceptibilities) are the treatments of choice in those with progressive neurologic deficits.

Treatment of spinal TB involves induction with a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by 7 to 10 months of isoniazid and rifampin. Medical management has been shown to be equal to combined medical and surgical management in patients with tuberculous spondylitis (Pott disease) who are ambulatory at the time of diagnosis.[72]

KEY POINTS

- Neuroschistosomiasis can present as an insidious lumbosacral myeloradiculitis.
- Human T-cell lymphotropic virus type 1–associated myelopathy presents with slowly progressive proximal greater than distal spastic paraparesis and early urinary retention.
- Human immunodeficiency virus–associated vacuolar myelopathy occurs most commonly in advanced infection, but the pathophysiology does not seem to be caused by viral cord infection or inflammation.
- Although tabes dorsalis was common in the preantibiotic era, it is only rarely seen in contemporary practice.
- The clinical presentation of poliomyelitis is usually monoparesis with reflex loss.
- Despite the strong epidemiologic link with enterovirus D68, the etiology of epidemic acute flaccid myelitis remains elusive.
- Viremia is short-lived with most flaviviruses, and polymerase chain reaction is insensitive. Blood or CSF IgM in the acute setting establishes the diagnosis.
- *Aspergillus* can present with spinal cord ischemia and hemorrhage.
- Ampicillin should be initiated empirically in cryptogenic spinal cord abscess for *Listeria* coverage.

Dural Disease and Arachnoiditis

Dural and arachnoid involvement by some pathogens can result in compressive myelopathy and radiculopathy, either exclusively or in addition to parenchymal inflammation caused by infiltrative disease.

TREPONEMA PALLIDUM. *T. pallidum* can cause hypertrophic pachymeningitis, which can present as polyradiculopathy. Focal meningeal inflammation from *T. pallidum* may lead to the formation of masslike lesions or gummas that can result

CASE 4-4

A 75-year-old man with a prosthetic mechanical aortic valve developed severe lumbar back pain days after successful cardioversion for incidentally discovered atrial fibrillation. A week later, he noted radicular features followed by a right footdrop. He denied fevers but reported having chills.

On examination, he had tenderness with percussion of his lumbar spine. C-reactive protein was elevated at 92 mg/L, and he had a mild leukocytosis at 11.3 cells/mm^3. MRI of the lumbar spine showed evidence of spondylodiskitis at L5-S1 and associated epidural abscess extending from the distal margin of the thecal sac to L1 (FIGURE 4-4). He was started on empiric antimicrobials and underwent lumbar decompression and washout. Blood and tissue cultures grew *Enterococcus faecalis*. Given his cardiac history, he underwent a transesophageal echocardiogram, which demonstrated endocarditis.

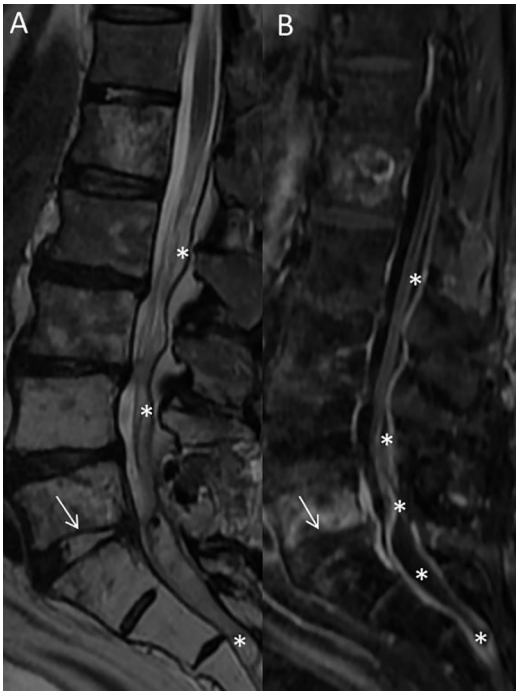

FIGURE 4-4
Imaging of the patient in CASE 4-4. Sagittal T2-weighted (*A*) and postcontrast T1-weighted (*B*) MRIs of the lumbar spine show L5-S1 disk edema with faint enhancement (*A, B, arrows*) as well as a rim-enhancing epidural fluid collection extending from the thecal sac to L1 (*A, B, asterisks*).

COMMENT

Focal spinal pain readily reproducible by percussion is suggestive of spondylodiskitis even in the absence of fever. The emergence of neurologic deficits is concerning for an evolving epidural abscess and demands prompt evaluation with MRI as delays in management can result in permanent disability. Cardiac history and detection of gram-positive organisms are indicative of possible endocarditis, and a transesophageal echocardiogram should be performed.

in compressive myelopathy or radiculopathy. MRI spine commonly reveals mass lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images, usually with adjacent parenchymal edema. The vast majority are associated with fairly homogeneous gadolinium enhancement, and the appearance can mimic a meningioma.[73]

COCCIDIOIDOMYCOSIS. Coccidioidomycosis is a fungal infection endemic to the southwestern United States characteristically associated with pulmonary infection. Meningitis is the most common CNS manifestation, but a compressive myelopathy can be seen in association with spinal block. The altered CSF dynamics are caused by adhesive arachnoiditis that results from the thick gelatinous exudate characteristic of this and other fungal diseases.[74]

MYCOBACTERIUM TUBERCULOSIS. *M. tuberculosis* can present in a similar fashion, typically as a subacute myeloradiculopathy (tuberculous spinal arachnoiditis). In these cases, the inflammatory exudates surround but do not necessarily infiltrate the spinal cord and nerve roots.[75] MRI spine may demonstrate nodular meningeal enhancement, nerve root thickening, and intramedullary signal change, with or without an associated syrinx.[75] CSF typically reveals moderate lymphocytic pleocytosis, hypoglycorrhachia, and a markedly elevated protein indicative of spinal block.

NEUROCYSTICERCOSIS. Unlike intracerebral disease, which predominantly involves the brain parenchyma, most spinal neurocysticercosis occurs in the subarachnoid space, although intramedullary involvement occurs in about 20% of cases.[76] Worldwide, cysticercosis remains the most common parasitic infection of the central nervous system. Although predominantly intracranial, neurocysticercosis can involve the spine in 1.5% to 3% of cases.[76] Neurocysticercosis is caused by infection by the eggs of the pork tapeworm *Taenia solium*, which is endemic to Central America, South America, sub-Saharan Africa, India, and East Asia.[77] Ingestion of cysticercal eggs in food contaminated by human feces results in absorption through the gut and migration to muscle, eye, or CNS.[77] Dissemination to the CNS occurs through small capillaries into the parenchyma or through the choroid plexus into the ventricles and subsequently the subarachnoid space. The signs and symptoms of neurocysticercosis are secondary to inflammation resulting from the degenerating cyst and lead to edema, or, in extraparenchymal disease, arachnoiditis or meningitis.

The signs and symptoms of spinal neurocysticercosis depend on a number of factors, including location (subarachnoid versus intramedullary), spinal level, and the presence or absence of inflammation and associated arachnoid scarring because of cyst degeneration.[76] Small intramedullary lesions often become symptomatic early and rapidly, whereas extramedullary lesions may present late and insidiously as the cyst grows large enough to compress the spinal cord or cauda equina roots.

Diagnosis is made by epidemiology and characteristic imaging features, and serologic testing can help support the diagnosis. Enzyme-linked immunoelectrotransfer blot is superior to the more widely available ELISA. Serum is more sensitive than CSF, whereas CSF examination generally plays a limited role in the diagnosis of neurocysticercosis. In cases of intramedullary disease, CSF can be normal or associated with mild protein elevation and pleocytosis. In the setting of arachnoiditis, marked protein elevation; monocytic, neutrophilic, or eosinophilic pleocytosis; and hypoglycorrhachia may be observed.

KEY POINTS

- **Tuberculous spondylitis (Pott disease) is the most common spinal manifestation of tuberculosis.**
- **Fever is present in less than 50% of patients with pyogenic spondylodiskitis or epidural abscess.**
- **Fungal and mycobacterial infection can cause adhesive arachnoiditis, resulting in spinal block and myelopathy with or without syringomyelia.**
- **Unlike intracerebral disease, which predominantly involves the brain parenchyma, most spinal neurocysticercosis occurs in the subarachnoid space, resulting in compressive myelopathy.**

Intramedullary cysts are treated with either albendazole or a combination of albendazole and praziquantel with adjunctive corticosteroids. Subarachnoid cysts may require higher doses and more prolonged treatment or may require surgical intervention. The inflammatory arachnoiditis resulting from cyst degeneration may limit recovery despite treatment.[76]

CONCLUSION

When evaluating patients with suspected infectious myelopathies and radiculopathies, it is important to narrow the range of pathogens under consideration. Specific clinicoradiographic features and careful attention to exposure, travel history, and immunocompetence can help narrow the differential. Direct infection is responsible for the neural injury in many cases; however, in others a parainfectious or postinfectious immune-mediated process is likely. Antimicrobial therapy is the mainstay of treatment, although effective antiviral therapies are lacking. Given that injury to the spinal cord usually involves both infectious and inflammatory mechanisms, strategies targeting each separately are often justified.

REFERENCES

1 Yost MD, Toledano M. Severe infections of the central nervous system. In: Rabinstein AA, ed. Neurological emergencies: a practical approach. Springer; 2020:121-149.

2 Gilden D, Nagel MA, Cohrs RJ. Varicella-zoster. Handb Clin Neurol 2014;123:265-283. doi:10.1016/B978-0-444-53488-0.00012-2

3 Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. Neurology 2008;70(11):853-860. doi:10.1212/01.wnl.0000304747.38502.e8

4 Haanpää M, Dastidar P, Weinberg A, et al. CSF and MRI findings in patients with acute herpes zoster. Neurology 1998;51(5):1405-1411. doi:10.1212/wnl.51.5.1405

5 Ahmed SV, Hamada H, Jayawarna C, Chandra S. Shingles with secondary asymptomatic CNS involvement! BMJ Case Rep 2012;2012:bcr0320126041. doi:10.1136/bcr.03.2012.6041

6 Mathew T, Thomas K, Shivde S, et al. Post herpes zoster infection neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2017;18:93-94. doi:10.1016/j.msard.2017.09.022

7 Majid A, Galetta SL, Sweeney CJ, et al. Epstein-Barr virus myeloradiculitis and encephalomyeloradiculitis. Brain 2002;125(Pt 1):159-165. doi:10.1093/brain/awf010

8 Merelli E, Bedin R, Sola P, et al. Encephalomyeloradiculopathy associated with Epstein-Barr virus: primary infection or reactivation? Acta Neurol Scand 1997;96(6):416-420. doi:10.1111/j.1600-0404.1997.tb00309.x

9 Nakamura Y, Nakajima H, Tani H, et al. Anti-MOG antibody-positive ADEM following infectious mononucleosis due to a primary EBV infection: a case report. BMC Neurol 2017;17(1):76. doi:10.1186/s12883-017-0858-6

10 Davies NWS, Brown LJ, Gonde J, et al. Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections. J Neurol Neurosurg Psychiatry 2005;76(1):82-87 doi:10.1136/jnnp.2004.045336

11 Martelius T, Lappalainen M, Palomäki M, Anttila VJ. Clinical characteristics of patients with Epstein Barr virus in cerebrospinal fluid. BMC Infect Dis 2011;11:281. doi:10.1186/1471-2334-11-281

12 Andrade P, Figueiredo C, Carvalho C, et al. Transverse myelitis and acute HIV infection: a case report. BMC Infect Dis 2014;14:149. doi:10.1186/1471-2334-14-149

13 Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis 2010;50(5):773-778. doi:10.1086/650538

14 Sotoca J, Rodríguez-Álvarez Y. COVID-19-associated acute necrotizing myelitis. Neurol Neuroimmunol Neuroinflamm 2020;7(5):e803. doi:10.1212/NXI.0000000000000803

15 Zachariadis A, Tulbu A, Strambo D, et al. Transverse myelitis related to COVID-19 infection. J Neurol 2020:1-3.doi:10.1007/s00415-020-09997-9

16 Tsiodras S, Kelesidis T, Kelesidis I, et al. Mycoplasma pneumoniae-associated myelitis: a comprehensive review. Eur J Neurol 2006;13(2):112-124. doi:10.1111/j.1468-1331.2006.01174.x

17 Nir-Paz R, Michael-Gayego A, Ron M, Block C. Evaluation of eight commercial tests for Mycoplasma pneumoniae antibodies in the absence of acute infection. Clin Microbiol Infect 2006;12(7):685-688. doi:10.1111/j.1469-0691.2006.01469.x

18 Lai CH, Chang LL, Lin JN, et al. High seroprevalence of Mycoplasma pneumoniae IgM in acute Q fever by enzyme-linked immunosorbent assay (ELISA). PLoS One 2013; 8(10):e77640. doi:10.1371/journal.pone.0077640

19 Kikuchi S, Shinpo K, Niino M, Tashiro K. Subacute syphilitic meningomyelitis with characteristic spinal MRI findings. J Neurol 2003;250(1):106-107. doi:10.1007/s00415-003-0921-7

20 Chilver-Stainer L, Fischer U, Hauf M, et al. Syphilitic myelitis: rare, nonspecific, but treatable. Neurology 2009;72(7):673-675. doi:10.1212/01.wnl.0000342460.07764.5c

21 Savoldi F, Kaufmann TJ, Flanagan EP, et al. Elsberg syndrome: A rarely recognized cause of cauda equina syndrome and lower thoracic myelitis. Neurol Neuroimmunol Neuroinflamm 2017;4(4):e355. doi:10.1212/NXI.0000000000000355

22 Hénin D, Smith TW, De Girolami U, et al. Neuropathology of the spinal cord in the acquired immunodeficiency syndrome. Hum Pathol 1992;23:1106-1114. doi:10.1016/0046-8177(92)90028-2

23 Karacostas D, Christodoulou C, Drevelengas A, et al. Cytomegalovirus-associated transverse myelitis in a non-immunocompromised patient. Spinal Cord 2002;40(3):145-149. doi:10.1038/sj.sc.3101265

24 Halperin JJ. Neuroborreliosis. Neurol Clin 2018; 36(6):821-830. doi:10.1007/s00415-016-8346-2

25 Stanek G, Strle F. Lyme disease: European perspective. Infect Dis Clin North Am 2008;22(2): 327-339, vii. doi:10.1016/j.idc.2008.01.001

26 Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995; 44(31):590-591.

27 Blanc F, Jaulhac B, Fleury M, et al. Relevance of the antibody index to diagnose Lyme neuroborreliosis among seropositive patients. Neurology 2007;69(10):953-958. doi:10.1212/01.wnl.0000269672.17807.e0

28 Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2007;69(1):91-102. doi:10.1212/01.wnl.0000265517.66976.28

29 Ferrari TCA, Moreira PRR. Neuroschistosomiasis: clinical symptoms and pathogenesis. Lancet Neurol 2011;10(9):853-864. doi:10.1016/S1474-4422(11)70170-3

30 Joshi TN, Yamazaki MK, Zhao H, Becker D. Spinal schistosomiasis: differential diagnosis for acute paraparesis in a U.S. resident. J Spinal Cord Med 2010;33(3):256-260. doi:10.1080/10790268.2010.11689703

31 Saleem S, Belal AI, El-Ghandour NM. Spinal cord schistosomiasis: MR imaging appearance with surgical and pathologic correlation. AJNR Am J Neuroradiol 2005;26(7):1646-1654.

32 Tan V, Wilkins P, Badve S, et al. Histoplasmosis of the central nervous system. J Neurol Neurosurg Psychiatry 1992;55(7):619-622. doi:10.1136/jnnp.55.7.619

33 Murai H, Tokunaga H, Kubo I, et al. Myeloradiculitis caused by Cryptococcus neoformans infection in a patient with ulcerative colitis: a neuropathological study. J Neurol Sci 2006; 247(2):236-238. doi:10.1016/j.jns.2006.05.050

34 Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012;3:388. doi:10.3389/fmicb.2012.00388

35 de Thé G, Bomford R. An HTLV-I vaccine: why, how, for whom? AIDS Res Hum Retroviruses 1993; 9(5):381-386. doi:10.1089/aid.1993.9.381

36 Tagaya Y, Matsuoka M, Gallo R. 40 years of the human T-cell leukemia virus: past, present, and future. F1000Res 2019;8. doi:10.12688/f1000research.17479.1

37 Bangham CR, Araujo A, Yamano Y, Taylor GP. HTLV-1-associated myelopathy/tropical spastic paraparesis. Nat Rev Dis Primers 2015;1:15012. doi:10.1038/nrdp.2015.12

38 Toro C, Rodés B, Poveda E, Soriano V. Rapid development of subacute myelopathy in three organ transplant recipients after transmission of human T-cell lymphotropic virus type I from a single donor. Transplantation 2003;75(1):102-104. doi:10.1097/00007890-200301150-00019

39 Nagai M, Osame M. Human T-cell lymphotropic virus type I and neurological diseases. J Neurovirol 2003;9(2):228-235. doi:10.1080/13550280390194028

40 De Castro-Costa CM, Araújo AQ, Barreto MM, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM). AIDS Res Hum Retroviruses 2006;22 (10):931-935. doi:10.1089/aid.2006.22.931

41 Enose-Akahata Y, Jacobson S. Immunovirological markers in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Retrovirology 2019;16 (1):35. doi:10.1186/s12977-019-0499-5

42 Sato T, Coler-Reilly ALG, Yagishita N, et al. Mogamulizumab (Anti-CCR4) in HTLV-1-Associated Myelopathy. N Engl J Med 2018; 378(6):529-538. doi:10.1056/NEJMoa1704827

43 Di Rocco A. Diseases of the spinal cord in human immunodeficiency virus infection. Semin Neurol 1999;19(2):151-155. doi:10.1055/s-2008-1040832

44 Platt LR, Estívariz CF, Sutter RW. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. J Infect Dis 2014;210 suppl 1:S380-S389. doi:10.1093/infdis/jiu184

45 Kew O, Morris-Glasgow V, Landaverde M, et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. Science 2002;296(5566): 356-359. doi:10.1126/science.1068284

46 Aylward RB, Alwan A. Polio in Syria. Lancet 2014;383(9916):489-491. doi:10.1016/S0140-6736(14)60132-X

47 McLaren N, Lopez A, Kidd S, et al. Characteristics of patients with acute flaccid myelitis, United States, 2015-2018. Emerg Infect Dis 2020;26(2): 212-219. doi:10.3201/eid2602.191453

48 Knoester M, Helfferich J, Poelman R, et al. Twenty-nine cases of enterovirus-D68-associated acute flaccid myelitis in Europe 2016: a case series and epidemiologic overview. Pediatr Infect Dis J 2019;38(1):16-21. doi:10.1097/INF.0000000000002188

49 Jang S, Suh SI, Ha SM, et al. Enterovirus 71-related encephalomyelitis: usual and unusual magnetic resonance imaging findings. Neuroradiology 2012;54(3):239-245. doi:10.1007/s00234-011-0921-8

50 Schubert RD, Hawes IA, Ramachandran PS, et al. Pan-viral serology implicates enteroviruses in acute flaccid myelitis. Nat Med 2019;25(11):1748-1752. doi:10.1038/s41591-019-0613-1

51 Murphy OC, Pardo CA. Acute flaccid myelitis: a clinical review. Semin Neurol 2020;40(2):211-218. doi:10.1055/s-0040-1705123

52 Ooi MH, Wong SC, Clear D, et al. Adenovirus type 21-associated acute flaccid paralysis during an outbreak of hand-foot-and-mouth disease in Sarawak, Malaysia. Clin Infect Dis 2003;36(5):550-559. doi:10.1086/367648

53 Haddad-Boubaker S, Joffret ML, Pérot P, et al. Metagenomic analysis identifies human adenovirus 31 in children with acute flaccid paralysis in Tunisia. Arch Virol 2019;164(3):747-755. doi:10.1007/s00705-018-04141-5

54 Sejvar JJ. West Nile virus infection. Microbiol Spectr 2016;4(3). doi:10.1128/microbiolspec.EI10-0021-2016

55 Picheca C, Yogendrakumar V, Brooks JI, et al. Polio-like manifestation of Powassan virus infection with anterior horn cell involvement, Canada. Emerg Infect Dis 2019;25(8):1609-1611. doi:10.3201/eid2508.190399

56 Lanciotti RS, Kerst AJ. Nucleic acid sequence-based amplification assays for rapid detection of West Nile and St. Louis encephalitis viruses. J Clin Microbiol 2001;39(12):4506-4513. doi:10.1128/JCM.39.12.4506-4513.2001

57 Shi PY, Wong SJ. Serologic diagnosis of West Nile virus infection. Expert Rev Mol Diagn 2003;3(6):733-741. doi:10.1586/14737159.3.6.733

58 Goates C, Tsuha S, Working S, et al. Seronegative West Nile virus infection in a patient treated with rituximab for rheumatoid arthritis. Am J Med 2017;130(6):e257-e258. doi:10.1016/j.amjmed.2017.01.014

59 Jackson AC. Human rabies: a 2016 update. Curr Infect Dis Rep 2016;18(11):38. doi:10.1007/s11908-016-0540-y

60 Zeiler FA, Jackson AC. Critical appraisal of the Milwaukee protocol for rabies: this failed approach should be abandoned. Can J Neurol Sci 2016;43(1):44-51. doi:10.1017/cjn.2015.331

61 Orme HT, Smith AG, Nagel MA, et al. VZV spinal cord infarction identified by diffusion-weighted MRI (DWI). Neurology 2007;69(4):398-400. doi:10.1212/01.wnl.0000266390.27177.7b

62 Terry PM, Glancy GR, Graham A. Meningovascular syphilis of the spinal cord presenting with incomplete Brown-Séquard syndrome: case report. Genitourin Med 1989;65(3):189-191. doi:10.1136/sti.65.3.189

63 Ng KS, Abdul Halim S. Anterior spinal cord syndrome as a rare complication of acute bacterial meningitis in an adult. BMJ Case Rep 2018;2018:bcr2018226082. doi:10.1136/bcr-2018-226082

64 Kleinschmidt-DeMasters BK. Central nervous system aspergillosis: a 20-year retrospective series. Hum Pathol 2002;33(1):116-124. doi:10.1053/hupa.2002.30186

65 Chan CT, Gold WL. Intramedullary abscess of the spinal cord in the antibiotic era: clinical features, microbial etiologies, trends in pathogenesis, and outcomes. Clin Infect Dis 1998;27(3):619-626. doi:10.1086/514699

66 Ulu-Kilic A, Karakas A, Erdem H, et al. Update on treatment options for spinal brucellosis. Clin Microbiol Infect 2014;20(2):O75-O82. doi:10.1111/1469-0691.12351

67 Pappas G, Papadimitriou P, Akritidis N, et al. The new global map of human brucellosis. Lancet Infect Dis 2006;6(2):91-99. doi:10.1016/S1473-3099(06)70382-6

68 Prabhakar MM, Acharya AJ, Modi DR, Jadav B. Spinal hydatid disease: a case series. J Spinal Cord Med 2005;28(5):426-431. doi:10.1080/10790268.2005.11753843

69 Torda AJ, Gottlieb T, Bradbury R. Pyogenic vertebral osteomyelitis: analysis of 20 cases and review. Clin Infect Dis 1995;20(2):320-328. doi:10.1093/clinids/20.2.320

70 Strauss SB, Gordon SR, Burns J, et al. Differentiation between tuberculous and pyogenic spondylodiscitis: the role of the anterior meningovertebral ligament in patients with anterior epidural abscess. AJNR Am J Neuroradiol 2020;41(2):364-368. doi:10.3174/ajnr.A6370

71 Khanna RK, Malik GM, Rock JP, Rosenblum ML. Spinal epidural abscess: evaluation of factors influencing outcome. Neurosurgery 1996;39(5):958-964. doi:10.1097/00006123-199611000-00016

72 MRC Working Party on Tuberculosis of the Spine, Darbyshire J. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. Int Orthop 1999;23(2):73-81. doi:10.1007/s002640050311

73 Marra CM. Neurosyphilis. Continuum (Minneap Minn) 2015;21(6 Neuroinfectious Disease):1714-1728. doi:10.1212/CON.0000000000000250

74 Gavito-Higuera J, Mullins CB, Ramos-Duran L, et al. Fungal infections of the central nervous system: a pictorial review. J Clin Imaging Sci 2016;6:24. doi:10.4103/2156-7514.184244

75 Garg RK, Malhotra HS, Gupta R. Spinal cord involvement in tuberculous meningitis. Spinal Cord 2015;53(9):649-657. doi:10.1038/sc.2015.58

76 Alsina GA, Johnson JP, McBride DQ, et al. Spinal neurocysticercosis. Neurosurg Focus 2002;12(6):e8. doi:10.3171/foc.2002.12.6.9

77 Del Brutto OH. Neurocysticercosis. Handb Clin Neurol 2014;121:1445-1459. doi:10.1016/B978-0-7020-4088-7.00097-3