Chapter 10
Infections of the Spinal Cord

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Abstract Infectious myelopathies can be caused by viral, bacterial, fungal, and parasitic agents. In this chapter, the most common causes of infectious and tropical myelopathies will be reviewed. HIV and HTLV-1 retroviruses have been associated with subacute and chronic myelopathy; herpesviruses may cause radiculomyelitis and transverse myelitis; enterovirus and flavivirus seem to have a tropism for the anterior horns of the spinal cord. Paralytic poliomyelitis can occur as a complication of poliovirus infection in around 1–2 % of cases. Enterovirus 71 has been identified as the etiologic agent of a poliomyelitis-like syndrome. The *Flaviviridae* family includes some mosquito-borne virus such as dengue, Japanese encephalitis, West Nile and Murray Valley viruses, and tick-borne virus and has also been associated with a flaccid poliomyelitis-like syndrome. Tuberculous myelopathy may develop as a secondary extension of vertebral body tuberculosis (Pott disease), as a downward extension of tuberculous meningitis, and even as a primary tuberculous lesion. Spinal schistosomiasis is a common cause of acute myelopathy in tropical regions, and acute transverse myelitis, conus medullaris syndrome, and lower limb myeloradiculopathy are the most common spinal syndromes. Other parasitary diseases that may affect the spinal cord include gnathostomiasis, cysticercosis, hydatid disease, and paragonimiasis. Invasive fungus may provoke a spinal cord compression syndrome from osteomyelitis, epidural abscess, or paravertebral lesions.

Keywords Gnathostomiasis • Epidural abscess • HTLV-1 virus • Infectious myelopathy • Poliomyelitis • Schistosomiasis • Spinal cord infection • Tropical spastic paraparesis • Vacuolar myelopathy • Viral myelitis

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Table 10.1 Acute transverse myelitis diagnostic criteria

Bilateral, not necessarily symmetric, spinal cord dysfunction affecting sensory, motor, and autonomic systems
Clearly defined sensory level
Progression to nadir of clinical symptoms between 4 h and 21 days after the onset of symptoms
Detection of an inflammatory process of the spinal cord in the CSF and/or MRI:
(a) Pleocytosis on the CSF with lymphocytic predominance
(b) Spinal cord MRI showing an enhancing spinal cord lesion
Exclusion of other etiologies including compressive, tumor, vascular, and postirradiation causes

CSF cerebrospinal fluid, *MRI* magnetic resonance imaging

Introduction

Infectious myelopathies can be caused by viral, bacterial, fungal, and parasitic agents. In addition, several infectious tropical diseases are an important cause of myelopathy in endemic regions and also a potential etiology of spinal cord dysfunction in returned travelers [1].

Some viral infections may preferentially involve the anterior horns of the spinal cord leading to a syndrome of acute flaccid paralysis, whereas others may cause an acute transverse myelitis syndrome with focal inflammation, functional transection of the spinal cord, and motor and sensory dysfunction below the level of the injury [2].

Myelitis is a medical emergency and prognosis depends on rapid suspicion, diagnosis, and therapy. Spinal cord magnetic resonance imaging (MRI) is a very helpful diagnostic technique that may reveal the location and extension of the inflammatory and infectious process. Cerebrospinal fluid (CSF) analysis should be performed to differentiate between viral, bacterial, parasitic, and other inflammatory causes such as multiple sclerosis. In this chapter, the most common causes of infectious and tropical myelopathies will be reviewed.

Parainfectious Myelitis

Acute transverse myelitis is a segmental or focal spinal cord damage provoked by an acute inflammatory process and is characterized by the presence of acute or subacute sensory, motor, and autonomic dysfunction including urinary, intestinal, and sexual sphincter abnormalities [3]. A systemic infection process or vaccination may precede acute transverse myelitis in 50 % of cases. This condition has been called parainfectious transverse myelitis, and its diagnostic criteria are summarized in Table 10.1. Probable pathogenic mechanisms include the activation of the host's immune system through molecular mimicry and the development of autoantibodies against pathogen proteins cross-reacting with host antigens located in the spinal cord. Between half and one third of these patients may develop severe sequela in spite of rapid treatment. Pulses of intravenous steroids are the

mainstay of treatment, although some refractory cases have been treated with intravenous immunoglobulins, plasma exchange, and even cyclophosphamide or rituximab.

Viral Myelitis

Although viral infections may cause a parainfectious acute transverse myelitis, some viruses are indeed neuroinvase and may provoke a myelopathy. Retroviruses such as human immunodeficiency virus (HIV) and human T-cell leukemia/lymphoma virus type 1 (HTLV-1) have been associated with subacute and chronic myelopathy, whereas Herpesvirus family more commonly causes white matter inflammation and transverse myelitis, and enterovirus and flavivirus seem to have a neurothropic affinity for the anterior horns of the spinal cord.

Retroviruses

Human Immunodeficiency Virus

HIV primary infection has been associated with several neurological disorders including mononeuropathy, inflammatory demyelinating polyneuropathy, motor neuron disease, polymyositis, mononeuritis multiplex, HIV-associated neuromuscular weakness syndrome, immune reconstitution inflammatory syndrome, meningoencephalitis, and acute transverse myelitis [4]. Pathogenic mechanism of HIV acute transverse myelitis is not fully understood, although direct cytopathic HIV effect and immune-mediated toxicity have been proposed. A rapid improvement of HIV primary infection-related myelopathic symptoms has been observed after starting highly active antiretroviral therapy and steroids [5].

HIV can also cause a chronic progressive myelopathy called HIV-associated vacuolar myelopathy, which is clinically characterized by progressive – frequently symmetric – leg weakness, lower limb paresthesias, gait disturbance, and bladder and bowel sphincter dysfunction. Lower limb spasticity is more prominent than muscle weakness and in some cases gait ataxia, and lower limb dyssynergy can be observed. Pathological brisk reflexes in both upper and lower limbs, extensor plantar responses, and impairment of vibratory and position sense are usually found. Increased reflexes may not be found when a coexistent peripheral neuropathy is present. HIV-associated vacuolar myelopathy predominates in the middle and lower thoracic spinal cord and is characterized pathologically by loss of myelin and microvacuolation due to intramyelin swelling [6]. Lateral and posterior columns are usually much more involved than the anterior horns. Axons are usually preserved whereas intranuclear viral inclusions and inflammation are not usually detected [4].

Pathogenesis is unknown. Although the virus is unable to infect neurons directly, it can still injure these structures by a variety of mechanisms, many of which are yet to be elucidated. HIV-associated vacuolar myelopathy can be observed pathologically in approximately half of patients with AIDS, but only 10–20 % may develop clinical symptoms. Nevertheless, since introduction of highly active antiretroviral therapy, the incidence of HIV-associated vacuolar myelopathy has diminished significantly.

Spinal cord MRI may be normal or show some degree of spinal atrophy or even show similar findings to those observed in combined subacute degeneration. Vacuolar myelopathy is a diagnosis of exclusion that should be questioned when the CSF is significantly inflammatory. This chronic myelopathy is not associated with a sensory level or an acute onset, as in acute transverse myelitis, and when found, an alternative diagnosis to vacuolar myelopathy should be ruled out. Differential diagnosis should exclude other causes of HIV-associated myelopathy, including opportunistic infections such as viral (herpes, cytomegalovirus, HTLV-1), bacterial (*Treponema pallidum*, *Mycobacterium tuberculosis*), fungal (*Cryptococcus neoformans*), and parasitic diseases (*Toxoplasma gondii*), and even vascular, neoplasic, inflammatory, and other disorders (cobalamin deficiency) [7, 8].

Human T-Cell Leukemia/Lymphoma Virus Type 1

HTLV-1 is a human type C retrovirus that belongs to the Retroviridae family. At least 20 million people worldwide are infected by the HTLV-1. Sub-Saharan Africa, Middle East, Melanesia, Japan, Central and South America, and the Caribbean region are the main endemic areas. HTLV-II, a related type C retrovirus, affects predominantly American Indians and parenteral drug abusers [9].

HTLV-1 virus has several modes of transmission. It can be transmitted via sexual intercourse, mainly occurring from male to female; from mother to child, due to prolonged breastfeeding; and via contaminated blood products (blood transfusion) and sharing of needles and syringes. Intravenous exposure to blood is the most efficient mode of HTLV-1 transmission [10].

Most of HTLV-1-infected patients may remain lifelong asymptomatic carriers. Nevertheless, between 0.5 and 4 % may develop a progressive spastic paraparesis called tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM), and an additional 2–5 % may develop adult T-cell leukemia/lymphoma (ATLL). TSP/HAM is at least three to four times more frequent in females and occurs in adults with a mean age at onset of 40–50 years. Incidence of TSP/HAM in endemic areas is around 2 cases/100,000 inhabitants per year. Onset may occur between months and years after the initial infection, and approximately 50 % of TSP/HAM patients may suffer from clinical progression during the first decade after starting symptoms [9].

Classical TSP/HAM is characterized by a slowly and progressive spastic paraparesis with lower limb weakness and sensory symptoms, back pain, sphincter

Table 10.2 Neurological and systemic conditions associated to HTLV-1 infection

Neurological manifestations
Cognitive dysfunction
Tropical spastic paraparesis
Autonomic involvement
Amyotrophic lateral sclerosis-like syndrome
Cerebellar syndrome
Cranial nerve neuropathy (mainly facial palsy)
Axonal sensory-motor neuropathy
Polymyositis
Ophthalmic complications
Retina vasculitis
HTLV-1- associated uveitis
Optic neuritis
Systemic complications
Sjögren syndrome/xerostomy
Arthritis and poly-arthralgias
Periodontal disease
Bronchoalveolitis
Infective dermatitis
Predisposition to helminthic and bacterial infections
Strongyloides stercoralis coinfection

disturbances (neurogenic bladder/bowel), and sexual dysfunction. Patients may present with urinary urgency, incontinence, and urinary retention early in the course of the disease, and in some cases, urinary symptoms and erectile dysfunction may precede the development of TSP/HAM in some years [11]. On neurological exploration, symmetric and proximal weakness of the legs, hypoesthesia and reduced vibration sense, spasticity, hyperreflexia, clonus, and Babinski sign can be detected. More severe patients are wheelchair bound, and disability and falls are common. Clinical spectrum of HTLV-1 infection is much wider than previously thought, and an association between HTLV-1 viral burden and some inflammatory conditions has been observed [11]. A list of systemic and neurological complications associated to HTLV-1 infection is shown in Table 10.2.

Pathogenesis of TSP/HAM may be dependent upon both viral and immunological factors. Its lifelong persistence in CD4+ lymphocytes determines a prolonged interaction between the virus and the host's immune system. HTLV-I proviral DNA and mRNA load are significantly raised in TSP/HAM patients compared to asymptomatic carriers. This antigenic load activates T cells CD8+ specific for Tax-protein, which upregulate pro-inflammatory cytokines [12].

Pathological studies have shown a chronic inflammation with perivascular lymphocytic cuffing and mild parenchymal lymphocytic infiltrates in the spinal cord. There is a predilection of HTLV-1 neuro-inflammation for the lower thoracic spinal cord. Perivascular lymphocytic infiltration with CD4+ lymphocytes can be seen on earlier infiltrates. In advanced stages of the disease, CD8+ T lymphocytes;

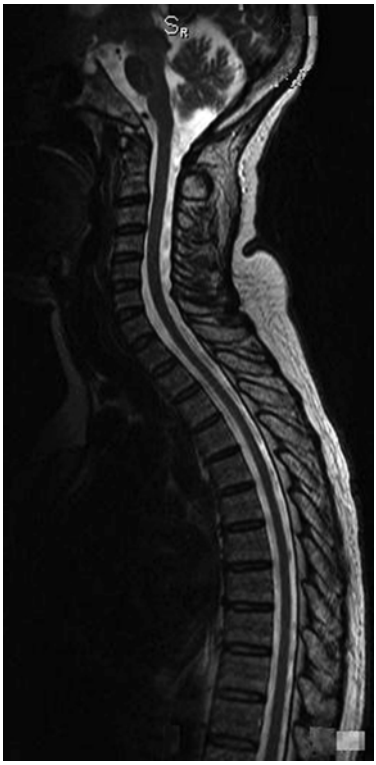

Fig. 10.1 Spinal cord MRI, T2-weighted imaging of a patient affected by HTLV-1 tropical spastic paraparesis. Atrophy of the thoracic spinal cord

pyramidal, spinocerebellar, and spinothalamic tract damage; axonal and myelin degeneration; and spinal cord atrophy predominate [9].

Antibodies directed against HTLV-1 antigens are usually present in both blood and CSF. Enzyme-linked immunosorbent assay (ELISA) is used for screening, and confirmation is done by Western blot technique. CSF may demonstrate a mild lymphocytic pleocytosis, a mild to moderate increase of protein concentration and oligoclonal bands. Peripheral atypical lymphocytes and a high HTLV-1 proviral load can be observed in the blood. Polymerase chain reaction (PCR) in peripheral blood mononuclear cells allows for distinction between HTLV-1 and II and permits the quantification of proviral load.

Spinal cord MRI may show atrophy on the cervical and thoracic regions in the chronic stage (Fig. 10.1). High intensity signal on T2-weighted imaging, and heterogeneous enhancement of gadolinium on T1-weighted imaging, has been observed in the lower cervical and thoracic spinal cord in the initial stages of the disease. Brain MRI may also detect subcortical and periventricular white matter lesions in around 50 % of TSP/HAM patients [11].

Repeated courses of steroids (intravenous methylprednisolone) are used to treat symptoms at initial presentation. Alpha interferon, plasma exchange, intravenous immunoglobulins, danazol, pentoxifilline, zidovudine, lamivudine, monoclonal

antibodies (daclizumab), and valproic acid have been used in open trials in a small number of patients. Alpha interferon may cause a reduction in HTLV-I proviral load. Nevertheless, their clinical efficacy is limited, and symptomatic treatment remains the mainstay of therapy. There is an overactivity of the detrusor muscle and a dyssynergy of the bladder sphincter in the TSP/HAM, and urinary tract infections are common and complicated by vesicoureteral reflux. Neurogenic bladder should be managed by means of intermittent catheterization associated with anticholinergic drugs. Constipation, neurogenic pain, and spasticity are other relevant issues that should be treated in the chronic stage of the disease [12].

Enterovirus

Enteroviruses are RNA viruses that belong to the Picornaviridae family. They are transmitted by direct contact as they reproduce in both the gastrointestinal and the upper respiratory tracts [13]. Most enteroviral infections are asymptomatic, but some of them may cause herpangina, myocarditis, pericarditis, and hand-foot-mouth disease. In addition, they are the most common cause of viral meningitis and can also provoke an acute myelitis affecting the anterior spinal cord horn.

Poliovirus

After performing massive worldwide polio immunization campaigns, the number of polio cases has just dropped down dramatically. Global expansion of eradication programs resulted in a reduction of paralytic disease from an estimated annual pre-vaccine level of at least 600,000 cases to fewer than 1,000 cases in 2010 [14]. Nevertheless, poliomyelitis still remains endemic in some regions of Pakistan, Afghanistan and Nigeria, and isolated cases in Central and sub-Saharan African countries have been reported. In addition, polio outbreaks attributed to circulating vaccine-derived poliovirus have been described. Vaccine-derived polioviruses causing paralytic disease have undergone recombination with human enterovirus C species [15, 16].

Paralytic poliomyelitis can occur as a complication of poliovirus infection in around 1–2 % of cases. Most infected people have a mild viral infection and only 5 % may even present with mild systemic symptoms. Several challenges to a final eradication of paralytic poliomyelitis persist today and include the following: (1) the reinfection of polio-free areas, (2) the continued transmission of wild polioviruses in endemic reservoirs, (3) the appearance of outbreaks due to circulating vaccine-derived polioviruses, and (4) the persistent excretion of vaccine-derived poliovirus by a few vaccinees with B-cell immunodeficiency [14].

Poliovirus affects the cells of the anterior horns of the spinal cord and provokes a clinical syndrome of acute and asymmetric flaccid paralysis. On examination, motor weakness, proximal more than distal, areflexia, and fasciculation can be

observed, whereas sphincter function and sensory modalities are preserved. Lower limbs are involved more frequently than the upper ones, although a bulbar form of polio has also been described. Risk of developing paralysis is associated with age, with higher risk in adult life, intermediate risk in children, and low risk in infants [13].

After a period of stability subsequent to acute polio infection, some patients have presented an exacerbation of muscle weakness and fatigue. This syndrome has been called post-polio syndrome, and its diagnosis requires the presence of a lower motor neuron disorder and exclusion of other disorders as cause of the new symptoms. It has been hypothesized that the muscle-related effects of post-polio syndrome may be associated with an ongoing process of denervation and reinnervation, reaching a point at which denervation is no longer compensated for by reinnervation. An inflammatory process might be the cause of this denervation. Post-polio patients should be advised to avoid both inactivity and overuse of weak muscles [17].

Enterovirus 71

Enterovirus 71 (EV71) has been identified as the etiologic agent of a poliomyelitis-like syndrome. EV71 infections usually manifest as mild case of hand-foot-mouth disease/herpangina affecting children and have a peak incidence during the summer and seasonal variations. Epidemic outbreaks have happened throughout the world, and mainly in Malaysia, Singapore, Taiwan, and Australia [18]. Severe complications of EV71 infection include shock, cardiopulmonary manifestations such as neurogenic pulmonary edema, cardiac dysfunction, increased vascular permeability, and neurological involvement [19].

Neurological syndromes observed in EV71 infection include meningitis, meningoencephalomyelitis, poliomyelitis-like syndrome, Guillain-Barré syndrome, acute transverse myelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, and brainstem encephalitis. EV71 may affect the CNS causing an enteroviral encephalomyelitis involving the central midbrain, posterior portion of the medulla oblongata and pons, bilateral dentate nuclei of the cerebellum, and the ventral roots of the cervical spinal cord [20].

Fever exceeding 38 °C and a characteristic mucocutaneous rash can be followed by acute flaccid paraplegia 3–5 days later. Lymphocytic pleocytosis (between 10 and 100 cells/ul) can be found on the CSF. Brain MRI may show hyperintensity lesions on T2-weighted and fluid-attenuation inversion recovery images in the lower brainstem and deep cerebellar nuclei and even on the ventral cervical roots [21]. Bilateral hyperintense lesions in the anterior horn regions of the cord on T2-weighted images can be observed in acute myelitis patients. Fever lasting more than 3 days, peak temperature ≥38.5 °C, and history of lethargy have been identified as independent risk factors for neurological involvement as evidenced by CSF pleocytosis [18]. There is no efficacy therapy for EV71 myelitis; the antiviral drug pleconaril has been used in some cases with modest effects against this virus.

Other Non-polio Enterovirus

Coxsackie A9, B4, and B3 and echovirus 11 and 12 are other common causes of acute flaccid paralysis in the infancy, although Coxsackie meningomyelitis can also happen in elderly people. These non-polio enteroviruses have probably surpassed poliovirus as other causative agents of viral myelitis after starting polio vaccination programs all over the world.

Flavivirus

The *Flaviviridae* family are RNA viruses that include some mosquito-borne virus such as dengue virus, Japanese encephalitis virus, yellow fever virus, West Nile virus (WNV) and Murray Valley encephalitis virus, and tick-borne virus. Flavivirus are a cause of encephalitis in the tropics but they have been associated with a flaccid poliomyelitis-like syndrome [22–24]. These flavivirus may have a special affinity to gray matter including the anterior horn cells. Neurotoxic cytokines are believed to play a role in regional inflammation of the nerve roots in flavivirus polio-like syndrome. MRI of the spinal cord may show marked contrast enhancement of the affected nerve roots in flavivirus polyradiculitis [25]. In some cases, anterior horn cell involvement of the spinal cord has been associated with extensive bilateral thalamic destruction, both of which are well recognized complications of flavivirus infection [22].

Treatment for flavivirus myelitis is supportive, and although several drugs have been used in the acute stage of infection, including ribavirin, steroids, alpha interferon, and intravenous inmunoglobulins, they have not proven any clear effectiveness.

West Nile Virus

West Nile virus is a mosquito-borne flavivirus that is increasingly spread in the Western hemisphere in the last decades. WNV may cause high fever, malaise, headache, backache, arthralgia, myalgias, retro-orbital pain, and a maculopapular rash. Approximately 1 % of infected people may present with meningitis or encephalitic syndrome, and only 10 % of these may have flaccid paralysis [26]. Postmortem examinations of patients with WNV infection have showed a pronounced tropism for the gray matter of the spinal cord, as in other naturally occurring WNV infection in vertebrates, such as monkeys, horses, and birds, causing poliomyelitis [27].

WNV-associated poliomyelitis-like patients may have an acute flaccid and asymmetric paralysis, absent deep tendon reflexes in affected limbs, preserved sensation, bowel or bladder dysfunction, and respiratory failure. These patients usually have associated signs of meningitis, encephalitis, or respiratory distress from involvement of spinal motor neurons supplying the phrenic nerves to the diaphragm. However, acute flaccid paralysis may also occur in the absence of fever or meningoencephalitis [26].

Inflammation of the spinal cord gray matter may extend into the ventral nerve roots and provoke a myeloradiculitis. This fact may explain the appearance of asymmetric acute flaccid paralysis involving one (monoparesis) to four limbs (quadriparesis), seen in many patients with WNV infection. Although isolated radiculopathy is rarer, patients with monoparesis or asymmetric weakness in the arms or legs have been reported.

A positive serum M immunoglobulin (IgM) antibody to WNV indicates a recent infection. CSF may show a positive WNV IgM antibodies, increased leukocytes (usually >200 cells/mm^3) and protein levels, and normal glucose. Around half of WNV meningitis patients may have at least 50 % neutrophils in their initial CSF specimen [28], followed by a shift to lymphocytosis.

Spinal cord MRI may show abnormal signal intensity areas that may be more pronounced in the ventral horns and enhancement around the conus medullaris and cauda equina [29]. In myeloradiculitis cases, MRI may detect enhancement of the ventral nerve roots. A complete resolution of these abnormalities has been observed during MRI follow-up in some patients.

Neurological recovery is usually incomplete with a poorer prognosis for recovery of physical function in patients with acute flaccid paralysis [30].

Dengue Virus

Dengue is a mosquito-borne viral disease that is endemic in almost all tropical and subtropical countries. It is caused by one of four related dengue virus (DENV) serotypes, single-stranded RNA viruses, members of the *Flaviviridae* family. Dengue is the second most common mosquito-borne disease affecting humans after malaria. Although most DENV infections are asymptomatic, symptomatic DENV infections can present as dengue fever and dengue hemorrhagic fever [31].

Spinal cord involvement following DENV infection has been reported during the infectious and post-infectious stages [32, 33]. Direct virus invasion and immune-mediated factors are pathogenic mechanisms involved in each one of these stages, respectively [34]. Post-dengue acute transverse myelitis may present as acute weakness and numbness of the lower limbs and urinary retention. Post-infectious immune-mediated myelitis has been described to occur 1–2 weeks after the onset of dengue symptoms, whereas parainfectious myelitis usually occurs within the first week of infection. CSF intrathecal synthesis of DENV-specific IgG antibodies have been detected in dengue myelitis patients [35]. Spinal cord MRI may be normal or show high-signal areas in T2-weighted imaging. Therapy is supportive.

Herpesvirus

Herpes family viruses include herpes simplex virus 1 (HSV1) and 2 (HSV2), varicella zoster virus (VZV), cytomegalovirus, and Epstein-Barr virus. These viruses may remain latent for years after initial infection. They usually provoke

white matter inflammation of the spinal cord and clinically may present as acute transverse myelitis [36].

HSV1 and HSV2

HSV1, HSV2, and VZV establish a latent infection in the dorsal root ganglia for the entire life of the host. HSV1 usually enters the host through oral mucosa. HSV1 can cause encephalitis, corneal blindness, and in some rare cases myelitis in children [36]. HSV2 causes genital herpes and is the causative agent for most HSV-associated myelitis in adults.

After initial infection, HSV2 enters the sensory nerves and reaches the dorsal root ganglia where, once incorporated into cell genoma, it remains latent for years. When reactivated, viral particles transported back to the dermatome may provoke a vesicular rash and asymptomatic shedding of viral particles. During reactivation, newly HSV2 replicated virus can spread axonally into the spinal cord and may cause a lumbosacral myeloradiculitis called Elsberg syndrome [37, 38]. The conus medullaris and lower thoracic cord are predominantly affected. Urinary retention, constipation, erectile dysfunction, back and anogenital dull pain, paresthesias and tingling in lumbosacral dermatomes, and leg muscle flaccid paresis in various combinations can be found. HSV1, VZV, cytomegalovirus, and Epstein-Barr virus can also provoke lumbosacral radiculomyelitis.

A more severe HSV2 ascending necrotizing myelitis has been described in immunosuppressed patients. Diabetes, HIV infection, and neoplasm seem to predispose to cervicothoracic ascension of HSV2 necrotizing myelitis [39]. In these cases, acute flaccid paraplegia with absent reflexes can be found.

The CSF may show mild to moderate lymphocytic pleocytosis, usually less than 200 cell/uL, and elevation of protein. Necrotizing myelitis may also show polymorphonuclear pleocytosis. The diagnosis of HSV infection is based on CSF DNA amplification by PCR and can be complemented by culture from vesicular fluid or less successfully from CSF or by increasing antibody titers.

MRI may show varying degrees of root or lower spinal cord edema with enlargement and hyperintensity on T2-weighted images, accompanied by contrast enhancement in acute infection but may be normal in other cases. MRI reports of HSV sacral radiculitis or radiculomyelitis are sparse [37].

Treatment with intravenous acyclovir for 14 days may shorten the symptomatic period. However, myelopathic deficits may persist despite antiviral treatment. A recurrence of symptoms may occur in up to 30 % of patients during the first year after herpetic meningitis or radiculomyelitis [40].

Varicella Zoster Virus

VZV infection causes chickenpox and herpes zoster. After chickenpox primary infection, VZV can be latent in the cranial nerve or sensory dorsal root ganglia and reactivate several decades later to produce herpes zoster vesicles that involve a

specific dermatome. VZV myelitis/myeloradiculitis may occur during reactivation and usually affect elderly, immunocompromised, or AIDS patients [41]. Rare cases of VZV myelitis of the cervical spinal cord in immunocompetent patients have also been reported [42]. Varicella myelitis is very rarely observed in healthy adults [43].

Myelitis may develop several days/weeks after the eruption of vesicles, although VZV myelitis cases without vesicle eruption have been described. A progressive asymmetric paraparesis with lower limb sensory loss affecting pain and temperature sensory modalities and sphincter function impairment are common. Mononuclear pleocytosis and raised proteins can be found on the CSF, and diagnosis can be confirmed by detection of both VZV-DNA on PCR and IgM-type anti-VZV antibodies in the CSF. Detection of anti-VZV antibodies in the CSF is the most sensitive method of diagnosing VZV infection of the CNS. Spinal cord MRI may detect T2 abnormalities on T2-weighted imaging in the spinal level corresponding to the dermatome involved. Symptoms may improve after treatment with parenteral acyclovir [44].

Cytomegalovirus

Cytomegalovirus may cause a lumbosacral polyradiculomyelitis with focal necrosis of the myelin in immunosuppressed patients and mainly in AIDS patients with a CD4 count below 100 cells/uL [45]. Less frequently, a necrotizing myelitis in the absence of radiculitis may happen. Rare cases have also been reported in immunocompetent patients [46, 47]. Polymorphonuclear pleocytosis and elevated protein concentration can be seen on CSF [48]. PCR has been found to be the most reliable method for the diagnosis of CMV myelitis. Spinal cord MRI usually shows spinal cord and roots swelling, adherence of the spinal roots to thecal sac, variable degrees of meningeal thickening, and irregular contrast enhancement. Prognosis is usually poor. Ganciclovir plus foscarnet has been recommended as therapy.

Epstein-Barr Virus

Epstein-Barr virus is the etiologic agent of infectious mononucleosis. Neurological manifestations of EBV infection include encephalitis, cerebellitis, aseptic meningitis, myelitis, and Guillain-Barré syndrome and affect mainly children and young adults. Reactivation on the CNS can occur also in immunosuppressed patients. As EBV does not invade neurons, an immune-mediated mechanism has been proposed. Spinal cord involvement includes myeloradiculitis, encephalomyeloradiculitis, and acute transverse myelitis [49–51].

CSF is usually inflammatory, with mononuclear pleocytosis in 80 % of cases, and 70 % have abnormal MRI findings [52]. The detection of EBV DNA in the CSF by means of PCR technique supports the diagnosis of EBV infection. There is no definitive treatment for EBV myelitis, and steroids and immunoglobulins have been used empirically.

Lyssavirus: Rabies

Rabies is a viral zoonosis that causes approximately 100,000 deaths per year worldwide, and most deaths occur in developing countries. Furious rabies is a life-threatening condition in humans that is provoked by an RNA lyssavirus carried in dogs and bats. The virus is transmitted to humans by infected saliva through the bite of a rabid animal, and the incubation period averages 1–3 months. Dogs are the major vector, especially in developing countries. Once symptoms develop, the disease is invariably fatal [53].

Here are the two classic forms of the disease. The most common is the furious or encephalitic rabies, which is characterized by hyperexcitability, autonomic dysfunction, hydrophobia, and aerophobia. Human paralytic rabies, a form that is not easily identified in clinical practice, may occur in one third of patients. Clinical presentation, a flaccid paralysis in the bitten limb which ascends symmetrically or asymmetrically, resembles Guillain-Barré syndrome or even an acute poliomyelitis and proceeds to encephalopathy [54].

Pathogenic mechanisms responsible for the motor weakness are not clear. Rabies should be ruled out in all patients with a history of animal bite that develop an acute myelopathy or encephalopathy. Rabies diagnosis relies on clinical history, serological antibodies in blood and CSF, and virus amplification and molecular analyses by PCR technique. Molecular analyses of rabies viruses isolated from both furious and paralytic rabies patients have shown only minor genetic variations with no specific patterns in glyco- (G), phospho- (P), and nucleoprotein (N) sequences. Longer survival period in paralytic rabies has been hypothesized to be related to unidentified mechanisms on neuronal gene expression, required for virus transcription/replication and for maintaining neuronal survival [55]. Treatment is supportive.

Bacterial Myelopathies

Spinal Cord Tuberculosis

CNS may be involved in between 1 and 10 % of *Mycobacterium tuberculosis* infections. The most common presentation is tuberculous meningitis, although it also may present as parenchymal tuberculomas, chronic spinal arachnoiditis, intradural spinal granulomas, myelopathy, or even spinal cord infarction. Risk factors of neuro-tuberculosis (TB) are immunosuppression states and chronic malnutrition. Patients coinfected with HIV and tuberculosis may be at higher risk of CNS involvement, although HIV infection does not appear to modify the clinical manifestations of TB radiculomyelitis. In developing countries, neuro-tuberculosis may occur in the context of primary dissemination in young adults, and only half of these patients may present with pulmonary symptoms at onset [56].

Tuberculous myelopathy may develop as a secondary extension of vertebral body tuberculosis (Pott disease), as a downward extension of tuberculous meningitis, and even as a primary TB lesion. In addition, radiculomyelopathy may also develop during appropriate treatment of intracranial TB [57].

Pott disease may be the most frequent cause of TB myelopathy, and bacilli may spread through the vertebral venous system involving the anterior segments of the thoracic and lumbar spine and provoking the collapse of infected vertebral bodies and secondary damage of the spinal roots and spinal cord.

Spinal forms associated to TB meningitis include granulomatous myeloradiculitis, chronic adhesive spinal cord arachnoiditis, intramedullary tuberculomas, intradural extramedullary granulomas, and even spinal cord infarction associated with spinal artery vasculitis [58, 59].

In tuberculous myeloradiculitis, the space between the spinal dura mater and the leptomeninges may be occupied by a thick exudate that may cause encasement of the spinal cord and impingement of the spinal roots. Granulomatous reaction of spinal leptomeninges is associated with vasculitis caseation, histiocyte proliferation, and tubercle formation [60]. Blood vessels may be impaired by necrotizing granulomas or by arteritis. Syringomyelia is another recognized complication.

Epidural tuberculoma and intramedullary tuberculomas may present as a subacute myelopathy depending on the location, level, and extension of the granuloma. TB myeloradiculitis is characterized by a subacute onset of paraparesis that may slowly progress over weeks. Neurological symptoms include root pain, numbness and paresthesias, muscle weakness, and bladder sphincter disturbances; paralysis develops after a few days. Absent reflexes, flaccid weakness of the lower limbs, and extensor plantar response can be found on examination.

Diagnosis of spinal TB is based on clinical and CSF findings, as well as typical CT or MRI appearance. CSF may reveal lymphocytic pleocytosis, hypoglycorrhachia, and high level of proteins as a result of CSF flow block. Around two thirds of patients have positive CSF acid-fast stain and Lowenstein cultures, and less than half may have a positive tuberculin skin test. Sensitivity of these tests in the absence of TB meningitis needs further elucidation.

Spine MRI and myelo-CT in Pott disease may show contrast enhancement with vertebral body collapse and variable degrees of spinal cord compression. Tuberculomas may show a pattern of contrast-enhanced T1 hypointense rings with high signal centrally on T2-weighted image. Granulomatous myeloradiculitis findings include obliteration of the subarachnoid space, loss of the outline in the cervicothoracic spinal cord, matting of the nerve roots in lumbar region, and a nodular, thick, or linear intradural gadolinium-enhanced pattern. In the chronic advanced stage, signs of arachnoiditis such as matted nerve roots and even syringomyelic cavity can be detected [57].

Early diagnosis and treatment is necessary to avoid progression of disability. A four-drug regimen for 2 months followed by 10 months of rifampin and isoniazid is recommended. The value of adjunctive surgery remains uncertain, although localized areas of adhesive arachnoiditis or cord compression from a cyst and instability of vertebral bodies may be surgically treated with good results [61].

Spirochetes: Neurosyphilis and Lyme Borreliosis

The incidence of primary and secondary syphilis has increased over the past decade, and the presenting clinical features have changed since the beginning of the HIV epidemic. *Treponema pallidum* disseminates to the CSF and meninges very early in the infection. Spirochetes can be identified in the CSF in primary syphilis, and in many cases, the spirochetes may be spontaneously cleared from the CSF. Following neuroinvasion, early neurosyphilis may involve the CSF, meninges, and cerebral or spinal cord vasculature. Asymptomatic neurosyphilis is characterized by persistent asymptomatic meningitis with mild abnormalities in the CSF, and spirochetes may or may not be identified in the CSF. Syphilitic meningitis and meningovasculitis are common forms, and vasculitis may affect the spinal cord in some rare cases [62].

Brain and spinal cord parenchyma are affected in the late forms of neurosyphilis that occur years to decades after initial infection. General paresis and *tabes dorsalis* are the classic syndromes of late neurosyphilis, and their incidence has dropped down after the discovery and extensive use of penicillin. *Tabes dorsalis* is a chronic and progressive spinal cord disorder affecting the posterior columns, which is characterized clinically by sensory ataxia, loss of vibration and pain sensation, and bowel and bladder dysfunction. Neurological examination may reveal increased reflexes, insensitivity to deep pain and sensory ataxia, and Charcot joints. Optic atrophy and Argyll-Robertson pupils may also be present. In the last decades, syphilitic meningomyelitis seems to be more common than *tabes dorsalis* [63].

Other less common spinal cord neurosyphilitic syndromes are hypertrophic pachymeningitis, motor neuron disease associated to syringomyelia, and Charcot deformations of the vertebra with compressive spinal cord syndrome.

Diagnosis is based on a positive peripheral serology and CSF assessment. Venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests are sensitive in the early stages of syphilis and may become negative in the late stages. Treponemal-specific test is used for confirmation, and titers remain positive in later stages. A positive serum test requires further confirmation of neurosyphilis by means of CSF analysis. A reactive CSF-VDRL has been considered as diagnostic of neurosyphilis, although this test may be nonreactive in some patients so a negative test does not exclude neurosyphilis diagnosis. The CSF-RPR is as sensitive and specific as the CSF-VDRL. Treponemal tests, such as the fluorescent treponemal antibody-absorbed (FAT-ABS) test, are used to exclude the diagnosis of neurosyphilis. FAT-ABS should be used when CSF-VDRL is negative in spite of a serological evidence for syphilis and a compatible clinical picture [64]. Mild pleocytosis can be found in the CSF. Spinal cord atrophy and high intensity area abnormalities spanning the posterior column of the spine can be found [64].

Tabes dorsalis should be treated with intravenous aqueous penicillin (4 million units every 4 h during 14 days). For those allergic patients, ceftriaxone 2 g intravenously for 14 days has been recommended. Clinical symptoms may worsen when staring antimicrobial therapy due to a sudden increase of spirochete lysis and antigen level rise. This condition is called Jarisch-Herxheimer reaction. A lumbar

puncture should be repeated at 6-month interval after therapy, and patients should be retreated if CSF white blood cell count is not normal 6 months after treatment or the CSF-VDRL titer has a fourfold increase. In HIV-infected individuals, the CSF-VDRL may normalize more slowly after treatment [64, 65].

Spinal cord involvement may also occur in Lyme neuroborreliosis, particularly at the level of the affected segment in patients with the so-called Garin-Bujadoux-Bannwarth meningoradiculitis, characterized by severe radicular pain, often mimicking a mechanical radiculopathy, involving one or a few dermatomes, and accompanied by cerebrospinal fluid lymphocytosis. Despite being a painful condition, motor findings with weakness and atrophy are prominent while sensory loss is infrequent.

Spinal Epidural Abscess

Epidural abscess is a medical and neurosurgical emergency that results in severe morbidity and high mortality if diagnosis and treatment are delayed. Incidence of spinal epidural abscess may range between 0.2 and 2.8 per 10,000. Gram-positive bacteria cause epidural abscesses much more frequently than gram-negative. *Staphylococcus aureus* is the most common cause of epidural abscess and occur in between 50 and 70 % of the identified cases, whereas *Streptococcus* species have been isolated in less than 10 % [66]. The most common isolated gram-negative organisms are *Pseudomonas aeruginosa* and *Escherichia coli*.

Infection may originate and spread directly from a near focus of osteomyelitis or hematogeneously from a more distal focus such as skin furuncles, pulmonary and other viscera infections, or surgical instrumentation. These pyogenic infections frequently may seed the anterior epidural space via spread from bone and soft tissue foci, whereas the posterior epidural space via hematogenous dissemination. The thoracic region is the most frequently involved [67].

Risk factors associated with epidural abscess include spinal abnormality, spinal trauma, spinal surgery or procedure, immunosuppression, diabetes mellitus, alcoholism, hemodialysis [68], malignancy, AIDS, bacteremia, and use of intravenous drugs. In around one third of cases, a mild back trauma was identified as preceding clinical symptoms. Fever is present in less than 70 % of cases. Clinical symptoms include focal back pain, motor weakness and spasm, radicular pain, and sensory and sphincter disturbances [69].

Inflammatory biomarkers including C-reactive protein and erythrocyte sedimentation rate are usually elevated, and blood cultures may be positive in around half of the patients. Neuroimaging studies of the spinal cord may show the extension and localization of the epidural abscess. CT scan is useful to assess the degree of bone involvement, whereas spinal MRI usually better describes the extension and degree of compression of the spinal cord (Fig. 10.2). Spinal tap should be not performed to avoid the risk of introducing bacteria into the CSF.

Once diagnosed, patient should perform emergent surgical drainage and debridement, spinal decompression, and prolonged antibiotic therapy for 6–8 weeks.

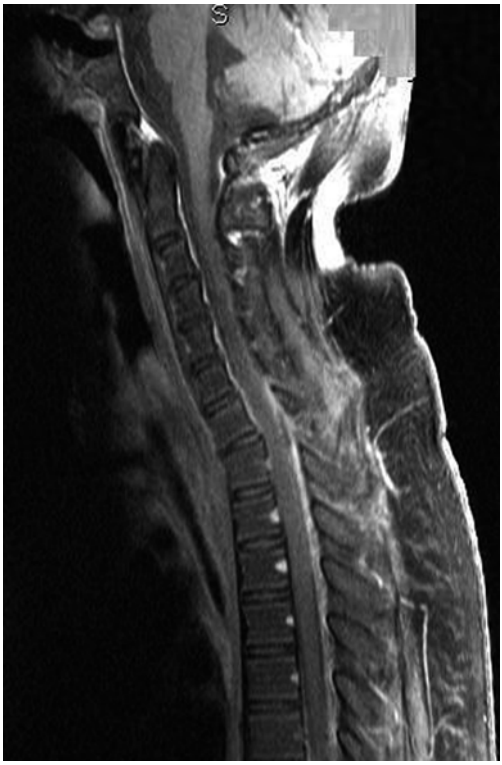

Fig. 10.2 Spinal cord MRI, T1-enhanced weighted imaging. Epidural cervical abscess with diffuse enhancement of contrast

Empiric parenteral antimicrobial therapy should include vancomycin to cover methicillin-resistant *Staphylococcus aureus* and an antibiotic for aerobic gram-negative bacilli such as a cephalosporin with antipseudomonal activity (e.g., ceftazidime or cefepime). Specific antibiotic therapy should be started once cultures were available and on the basis of organisms and susceptibility. In those patients who are critically ill or who have a longitudinal epidural spread, conservative therapy should be considered. Even with best treatment, mortality is still high and may range between 10 and 25 % of cases and has been associated with a delay in surgical therapy. Severity of neurological symptoms at time of surgical drainage has been considered a predictor of mortality and disability [67].

Other Pyogenic Infections of the Spinal Cord

Brucellosis is an infection caused by *Brucella melitensis* that is endemic in the Mediterranean area and Middle East countries. Spondylitis is the most frequent brucellosic vertebral infection in adults, and the lumbar region is more commonly affected; vertebral lesions may occur at several levels in some cases. Brucellosic

epidural abscess is a relatively common complication accompanying brucellosis spondylitis. Extradural thoracic and lumbar spinal compression by *Brucella* epidural abscess has been reported [70, 71], and clinical symptoms are unspecific and include fever and lumbar back pain. Epidural abscess may also cause symptoms of myelopathy or radicular pain by compression, and arachnoiditis and multilevel radiculitis due to lumbar epidural abscess may also occur. Differential diagnosis includes other pyogenic spondylitis causes including TB, salmonella, nocardia, and others.

Tropical and Parasitary Myelopathies

Spinal Schistosomiasis

Schistosomiasis is a helminthic infection that affects to more than 230 million people worldwide. *Schistosoma mansoni*, *Schistosoma haematobium*, *Schistosoma japonicum*, *Schistosoma intercalatum*, and *Schistosoma mekongi* are the five species that may infect humans. *S. mansoni* is endemic in South America, the Caribbean region, Africa, and the Middle East. *S. haematobium* is spread in many African and Middle Eastern countries, and *S. japonicum* is endemic in Japan, China, and the Philippines [72].

Schistosomes are blood-dwelling flukes that live in blood vessels of vertebrates including humans and other mammals. Freshwater snails are intermediate host, and cercaria released from snails perforate the skin of human beings and through lymphatic and hematogenous spread settle in the portal circulation. *S. mansoni* and *S. japonicum* inhabit, respectively, the inferior and superior mesenteric vein tributaries whereas *S. haematobium* inhabits the bladder veins. The female worm usually releases hundreds of eggs each day that are excreted in stool (*S. mansoni*) or urine (*S. haematobium*) [73].

Spinal schistosomiasis is a common cause of acute myelopathy in tropical regions. *S. mansoni* and *S. haematobium* are responsible for most cases of spinal schistosomiasis. Around 6 % of neurological patients admitted to a Brazilian hospital with a non-traumatic myelopathy were due to *S. mansoni* spinal schistosomiasis [74]. Schistosomal myelopathy is more common in young people who are exposed to freshwater. Spinal schistosomiasis occurs in the early stage of the infection and systemic symptoms of schistosomiasis are usually absent.

Spinal schistosomiasis occurs as a consequence of the immunogenic interaction between schistosome egg deposition in the spinal cord and the inflammatory response reaction of the host around them. The host's response may vary from a minimal inflammatory reaction to the scattered ova in the absence of neurological manifestations to severe reactions resulting in space-occupying granulomatous mass and spinal cord tissue necrosis. The shape and size of the ova are other factors that may explain the increased frequency of *S. mansoni* infection in spinal

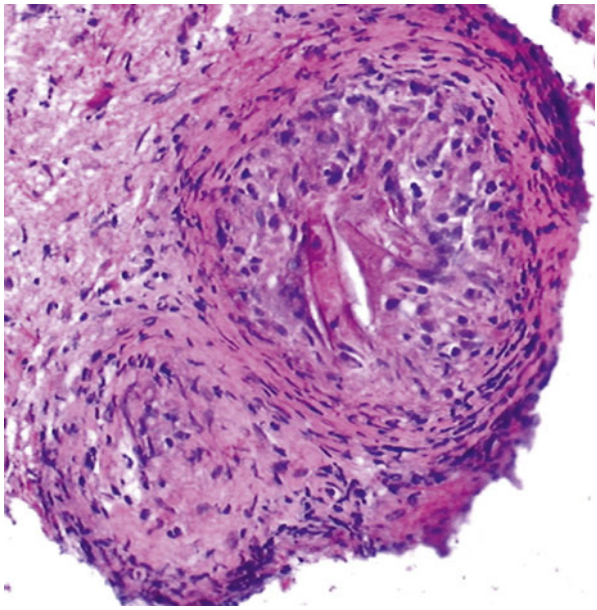

Fig. 10.3 Spinal cord biopsy of a patient with schistosomal myelopathy showing several granulomas around *S. mansoni* eggs

schistosomiasis (Fig. 10.3). *S. mansoni* and *S. haematobium* eggs are larger than the *S. japonicum* ones and are retained much more frequently in the spinal cord. The higher size of *S. mansoni* ova, 60 um in width by 150 um in length, and its lateral spine may limit their progress along the vertebral venous plexus to the brain [73].

The schistosome eggs and even the adult worm may also reach the spinal venous system retrogradely via the Batson's valveless venous plexus that connects the deep iliac veins and the inferior vena cava with the spinal cord's venous system. Schistosomal myelopathy is more frequent in the lumbosacral and lower thoracic regions of the spinal cord. The carriage of the ova into the spinal veins may be facilitated by Valsalva intra-abdominal pressure maneuvers such as defecation and coughing [73].

Schistosomal acute transverse myelopathy, conus medullaris syndrome, and lower limb myeloradiculopathy are the most commonly found syndromes. Schistosome myelitis may start as a flaccid paraplegia with sphincter dysfunction, and lower thoracic spinal cord and conus medullaris are frequently involved [74, 75].

Cauda equina's roots are frequently affected in schistosomal myeloradiculopathy. Granulomatous masses localized in the conus medullaris, lower thoracic level, and spinal lumbar and sacral roots may provoke an asymmetric lower limb weakness, sensory symptoms in lumbosacral dermatomes, and sexual dysfunction and neurogenic bladder. Back pain, tingling, lower limb paresthesias, and urinary retention may appear several days before weakness onset [75].

Less frequent clinical pictures are painful radiculopathy, chronic asymmetric myeloradiculopathy, cervical intramedullary schistosomiasis, and spinal cord compression due to extra-axial granulomas [73].

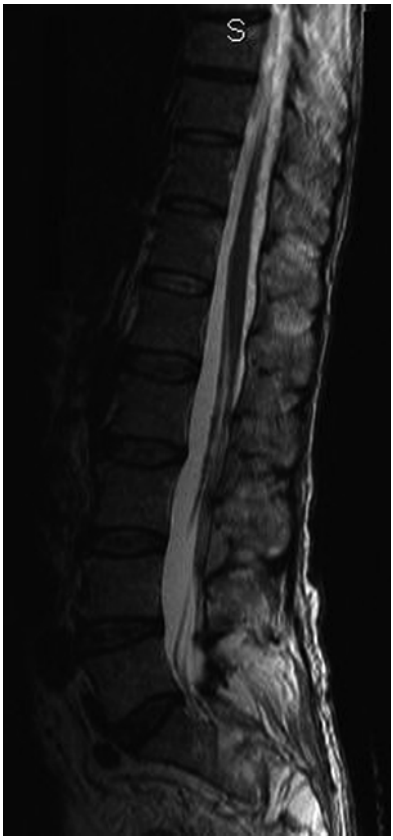

Fig. 10.4 Lumbosacral MRI of a patient affected by a schistosomal myeloradiculopathy showing arachnoiditis and adherence of the lumbar and sacral roots

Swelling of conus medullaris; enlargement of the spinal cord at the thoracic level, usually below T8 level; and thickening of spinal roots and cauda equina can be detected on spinal MRI [76] (Fig. 10.4). Granulomas of conus medullaris heterogeneously enhance gadolinium contrast on T1-weighted imaging. Although enlargement may be evident at the thoracic level, the abnormal T2 high signal may frequently extend to the lumbar and sacral spinal cord, or even to the lower cervical level [77].

Parasitological examinations are of limited value in the diagnosis of schistosomal myelopathy, and schistosome ova may be observed in stool, urine, and/or rectal mucosa (rectal biopsy) in less than 40 % of these patients. A low parasite burden and a day-to-day variation in stool egg count and clustering of eggs within the stool may explain the large number of negative result cases on parasitological examination.

Serological techniques that may detect antibodies against schistosome crude egg and soluble worm antigens in blood and CSF are hemagglutination, indirect immunofluorescence, and ELISA tests. The analysis of the CSF may show lymphocytic pleocytosis, presence of eosinophils, and an increased concentration of proteins

Table 10.3 Clues to the diagnosis of spinal cord schistosomiasis

(a) Person from schistosomiasis endemic area or any returned traveler exposed recently to freshwater in endemic areas who present with acute transverse myelitis, conus medullaris, and/or cauda equine myelopathy
(b) Spinal cord MRI showing swelling of conus medullaris, thickening of spinal roots and cauda equina, and gadolinium enhancement
(c) CSF analysis showing lymphocytic pleocytosis, increased protein concentration, and presence of eosinophils
(d) ELISA, hemagglutination, and/or indirect immunofluorescence tests detect positive antibodies against schistosome
(e) Schistosome eggs are observed in stool and/or rectal biopsy in a person with myelopathy

[72]. In those people living in endemic areas, neither ova detection nor a positive antibody test confirms the schistosomal etiology of a myelopathy. Schistosome antibodies remain positive for life, and a positive immune reaction in endemic regions is considered evidence of exposure. Some clues for the diagnosis of schistosomal myelopathy are summarized in Table 10.3.

Definitive diagnosis can be made in some cases by performing a biopsy of the spinal cord's leptomeninges. Schistosome ova in various stages of evolution, with surrounding inflammatory reaction and demyelination near the ova, can be found on pathological specimens. Schistosome granuloma is characterized by a necrotic center that contains schistosome eggs surrounded by giant cells and lymphocytes and an outer layer of eosinophils, plasma cells, and fibroblasts [74].

Combined therapy with steroids and praziquantel are used to treat acute schistosomal myelopathy [78]. Steroids may reduce the intensity of inflammatory reaction, diminish the edema around granulomas, and suppress granuloma formation. Oxamniquine has also been used to treat *S. mansoni* infection, and artemisinin derivatives may be helpful to kill immature schistosomules.

Although mass exeresis, decompressive laminectomy, and liberation of lumbosacral roots have been used in severe spinal schistosomiasis cases, there is no clinical trial that has compared the efficacy of the best spinal surgical intervention against conventional pharmacological treatment. Surgical decompression should be indicated only in selected cases presenting with rapid deterioration of lower limb strength and evidence of extra-axial spinal cord compression due to tumor-like lesions.

Gnathostomiasis

Gnathostomiasis is a parasitic disease caused by *Gnathostoma spinigerum* which is endemic in Southeast Asia (China, Japan, Korea, and Thailand), Mexico, and Peru. It may be transmitted when human beings eat undercooked fish or poultry and by drinking copepod-contaminated freshwater. The primary intermediate host is the freshwater copepod of the genus Cyclops; secondary intermediate hosts are fish,

ducks, pigs, and water snakes. Adult larva inhabits definitive host's stomach. Once ingested raw or undercooked infested fish or poultry, the larvae cross the intestinal wall and migrate to the subcutaneous tissues.

Intermittent, painful, subcutaneous swellings usually occur when humans are infected. Neurological complications of gnathostomiasis include headache, hydrocephalus, seizures, brain hemorrhage, transverse myelitis, and painful radiculomyelitis. *Gnathostoma spinigerum* is not indeed a neurotrophic parasite, although it may accidentally enter into the CNS, migrating on peripheral nerves and spinal roots and provoking a radiculitis and/or radiculomyelitis [79]. Severe neurogenic and radicular pain in the lower limbs and trunk, paraparesis, and neurogenic bladder can occur during this accidental migration. Transverse myelitis can occur as a consequence of larvae's migration and necrosis across the spinal cord and the leptomeningeal inflammation secondary to the host's immunological response.

CSF may show a pattern of eosinophilic meningitis. The CSF usually is xanthochromic, and pleocytosis (500–2,000 white cell count) with predominance of eosinophils (20–70 %), raised proteins (>100 mg/dL), and normal levels of glucose may be a clue for the diagnosis. A positive serological test using the immunoblotting test in the CSF and serum is usually positive for *G. spinigerum*. Spinal cord MRI may show spinal cord swelling, edema, leptomeningeal gadolinium enhancement, and the presence of multiple hemorrhagic tracts [80].

Recovery of the parasite from the tissue provides definitive diagnosis. Patients should be initially treated with steroids to reduce the inflammatory reaction of the spinal cord, and then albendazole or ivermectin. Albendazole alone may exacerbate neurological symptoms as a result of larvae death in the spinal cord, so prednisolone or dexamethasone is used to reduce edema.

Spinal Neurocysticercosis

Cysticercosis is a common parasitic disease, caused by the larval stage of the tapeworm *Taenia solium*. Cysticercosis is endemic in many Central and South American countries, Southeast Asia, and sub-Saharan Africa. Spinal cord involvement may occur in 1–5 % of neurocysticercosis patients and affect much more frequently the subarachnoid space than the medullary parenchyma. Many of these patients may have an already known intracranial neurocysticercosis in which a migration of subarachnoid cyst from the basilar cisterns has occurred. Intramedullary cysts are much less common [1]. Subarachnoid infestation coexists with cyst located on the brain cisterns, a fact that supports the hypothesis of dissemination via the CSF. However, intramedullary cysts may also reach the spinal cord via hematogenous dissemination.

Spinal cord compression by spinal subarachnoid cysts may cause a chronic progressive paraparesis, myeloradiculopathy, or a cauda equina syndrome and may mimic a spinal neoplasm. Spinal cysticercosis may also provoke a chronic adhesive arachnoiditis characterized by neurogenic pain, motor weakness, spasticity, and

sphincter disturbances. The rare cases of intramedullary cysticercosis may present as an acute transverse myelitis [81].

CSF may show eosinophilia and increased protein concentration. Spinal cysticercosis should be treated with steroids and albendazole, although decompressive surgery may be needed to treat compressive arachnoiditis [82].

Hydatid Disease

Hydatidosis, the cystic infection caused by the cestoce *Echinococcus granulosus*, may also involve the spinal cord in some exceptional cases. *E. granulosum* is endemic in the Mediterranean area, South America, Middle East, and New Zealand. Humans are infected via fecal-oral route, and once ingested, the eggs hatch and form larvae that migrate across the intestinal wall and will generate large hydatid cysts in the liver. Canines are the definitive hosts.

Case reports of spinal echinococcosis have been described, affecting the extradural or intradural extramedullary space; intramedullary echinococcosis is even rarer [83]. Hydatid disease may affect bones in 0.5–2 % of infected patients, half of them occurring in spinal vertebrae provoking spondylitis mainly in the thoracic (50 %) and lumbar spine. The cysts may grow progressively and provoke a mass effect, bone destruction, and host's inflammatory reaction. Spinal cord MRI may show characteristic cysts, and serological analysis may confirm the diagnosis. Prognosis is poor due to high recurrence index, and treatment is based on albendazole plus spinal decompressive surgery [84].

Other Parasitary Diseases

In China, paragonimiasis can cause myelopathy due to extradural compression or less frequently due to intramedullary granulomas [85]. Paragonimiasis can be acquired on having consumed badly cooked or raw crabs parasited by the larva of *Paragonimus westermani. Toxoplasma gondii* spinal cord abscesses have been described in immunosuppressed patients [86]. Acute disseminated encephalomyelitis associated with acute *Toxoplasma gondii* infection has also been reported in immunocompetent children [87]. Visceral *larva migrans* syndrome due to *Toxocara canis* or *Ascaris suum* infection has been reported to cause myelitis in Japan [88, 89].

Clinically, these parasitic infections of the spinal cord can appear in the shape of a slow and progressive myelopathy, a myeloradicular syndrome, or as an acute transverse myelitis. Medullary inflammation and the host's immune reaction with the formation of granulomas are pathogenic mechanisms. Eosinophils can be detected in the blood or CSF. The analysis of tools and the determination of specific antibodies can help in the diagnosis. MRI may reveal spinal cord swelling with or without gadolinium enhancement.

Fungal Myelopathies

Opportunistic fungi such as *Aspergillus* sp., *Zygomycetes*, or *Candida* sp. may infect mainly immunosuppressed patients suffering hematologic malignancies such as acute myeloid leukemia, lymphoma, or hematopoietic stem cells transplants, AIDS, chronic use of steroids, or after transplantation. Pathogenic fungi (*Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Scedosporium prolificans*) may also provoke CNS infections in immunocompetent people [90].

CNS fungal infections may present as chronic meningitis or focal brain lesions. In these cases, fungi usually reach the CNS via hematogenous dissemination from the lungs, heart (mycotic endocarditis), or skin. Fungal infections of the spinal cord are uncommon and affect more frequently immunocompromised hosts, pregnancy, and patients that underwent cardiovascular surgery. However, fungal chronic epidural abscess and spinal cord infection has been reported also in healthy people.

Most fungus may provoke a spinal cord compression syndrome from osteomyelitis, epidural abscess, or paravertebral lesions. Many cases of spinal cord fungal infections may be related to local invasion of the spinal epidural space from vertebral osteomyelitis or by lesions extending through the intervertebral foramina (Fig. 10.5). Spinal fungal infection may present clinically as epidural abscess, chronic arachnoiditis, myelitis, intramedullary granulomas, or vasculopathy associated with spinal cord infarction. In occasions, the fungi can invade the epidural space provoking granulomatous meningitis with intramedullary or extradural granulomas.

Invasive spinal cord aspergillosis typically occurred in terminal and immunosuppressed patients. Nevertheless, the spectrum of hosts and clinical presentations is increasing, due to better medical treatments that prolong the survival of the patients [91]. Invasive aspergillosis may provoke a meningovascular infiltration and a necrotic endarteritis with thrombosis and ischemia leading to vessel occlusion and spinal cord infarctions. Cases of medullary inflammation and spontaneous cord transection due to invasive spondylitis by *Aspergillus* have been described in both immunosuppressed children (leukemia) and also in immunocompetent ones [92].

Candida albicans can also provoke intramedullary, vertebral, and paravertebral abscesses. Epidural abscess caused by *Candida albicans* has been reported in chronic renal failure patients [93]. However, *Candida albicans* spondylodiscitis and subdural spinal granuloma may occur in healthy people [94, 95].

Cryptococcus neoformans is particularly common in bird feces, such as pigeon droppings. Cases of compressive myelopathy due to cryptococcal granulomas arisen from vertebral osteomyelitis or from another infection spread by contiguity from the intervertebral foramina have been reported. Intra- and/or extra-spinal granulomas may also be the consequence of chronic granulomatous meningitis. Cryptococcosis may mimic spinal tuberculosis and is a diagnostic dilemma in countries with high burden of tuberculosis [96]. Intramedullary cryptococcomas of the spinal cord may resemble a spinal tumor [97]. Cryptococcus myeloradiculitis has also been reported in HIV-infected patients.

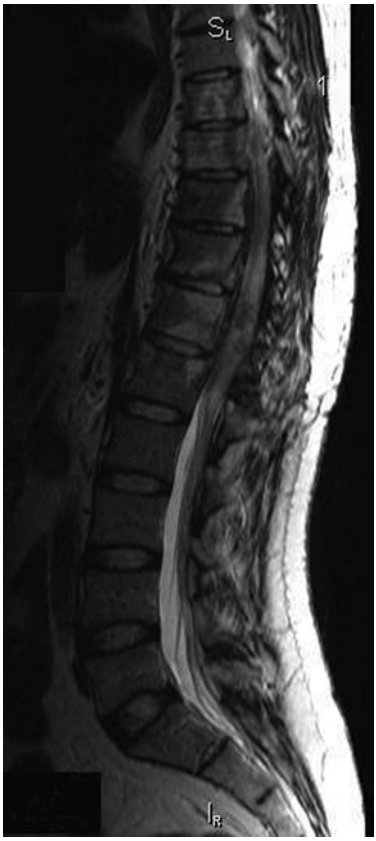

Fig. 10.5 Spinal cord MRI, T2-weighted imaging, of a patient affected by chronic fungal spinal infection due to *Scedosporium prolificans*

Blastomycosis can also imitate vertebral tuberculosis, provoking osteolytic injuries, abscesses, granulomas, and compressive meningitis of the spinal cord [98]. Intramedullary blastomycosis has also been described in children [99]. *Coccidioides immitis* is a dimorphic fungus common in Central and South America. Coccidioides infection can provoke chronic meningitis, tumorlike lesions, hydrocephalus, and spinal arachnoiditis. Coccidioidomicosis can provoke destructive lesions of the vertebral bodies and formation of paraspinal granulomatous masses [100].

Spinal cord fungal infections have high mortality, so aggressive and early treatment should be initiated. Surgical debridement and specific treatment such as intravenous liposomal amphotericin B, 5-fluocytosine, and azoles (voriconazole, posaconazole, itraconazole, fluconazole) have been used with variable results.

Conclusion

Infectious diseases are one of the main causes of acute spinal cord injury. Virus, bacteria, and parasites can provoke acute and chronic infectious myelopathies. Early diagnosis and suspicion is needed to prevent severe sequela and disability.

A detailed neurological examination and assessment of spinal cord syndrome should be followed by a complete spine cord MRI and CSF analysis. Tropical diseases are an emerging etiology of infectious myelopathy, even in non-endemic countries. Teaching programs in neuro-infection and tropical neurology are needed and they should cover this particular topic.

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