2 Overview of Infective Syndromes of the Central Nervous System and Its Coverings: Decoding Chameleons and Mimics

Safiya Firoze, Hiba Sami, and Parvez A. Khan

Abstract

Infections of the central nervous system (CNS), which include those of the brain's cerebrum and cerebellum, spinal cord, optic nerves, and the membranes that cover them, are medical emergencies that are associated with high rates of morbidity, mortality, or long-term effects that can have detrimental effects on the quality of life of affected individuals. Acute CNS infections may be caused by microorganisms, such as bacteria, viruses, fungi, and parasites, or by trauma caused by fractures at the base of the skull or the cribriform plate, which can cause an opening between the CNS and the adjoining areas, such as sinuses, mastoid, middle ear, or nasopharynx, which may serve as a gateway for infections. Infections in the CNS can manifest as a subarachnoid space infection, such as meningitis, or a parenchymal infection, such as encephalitis, myelitis, or abscess. It is most usually disseminated hematogenously but it can also spread directly from nearby structures (otitis, sinusitis, and dental abscess) as well as invasive and non-invasive trauma (cranial fractures, foreign bodies, and ventricular shunt). CNS infection clinical syndromes may include acute meningitis: characterized by an acute onset of fever, headache, vomiting, meningismus, and impaired mental status in bacterial and viral infections; fast progression over hours to days; subacute or chronic meningitis: found in tuberculosis or fungal infections, with a low-grade fever that develops gradually over weeks; acute encephalitis that is caused by viruses manifests itself in two ways: (a) diffuse: changed mental condition and (b) focal: viral tropism for a single place; and encephalopathy caused by a systemic infection, such as Shigella, typhoid,

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malaria, Rickettsia, or endocarditis. Symptoms range from mild to severe and are frequently linked to mood swings.

Keywords

Central nervous system · Meningitis · Encephalitis · Myelitis · Abscess

2.1 Introduction

The brain (cerebellum and cerebrum), spinal cord, optic nerves, and their encasing membranes make up the central nervous system (CNS). The stiff boundaries of the cranium and spinal canal of the vertebral column safeguard these structures. The meninges are three layers of continuous protective tissues that surround the spinal cord and the cerebral cortex, the outermost, gray tissue layer of the brain. The pia mater is the deepest meningeal layer that directly covers the cerebral cortex. The arachnoid and dura mater, respectively, are the terms for the middle and outermost layers (Archibald and Quisling 2013).

2.2 Meningitis

2.2.1 The Meninges: Anatomical and Functional Attributes

The meninges are three layers of continuous protective tissues (Fig. 2.1) that surround the spinal cord and the cerebral cortex, the outermost, gray tissue layer of the brain. The pia mater is the deepest meningeal layer that directly covers the cerebral cortex. The arachnoid and dura mater, respectively, are the terms for the middle and outermost layers of the meninges. A number of compartments, including sinuses for venous drainage, are formed by the dura mater (Archibald and Quisling 2013). These sinuses are entered by arachnoid villi, which are a part of the arachnoid. The Virchow–Robin spaces are connected with the subpial space. The subarachnoid space is not connected to these two compartments, which transmit different vessels to and from the brain parenchyma. While the subarachnoid space is continuous and situated between the pia mater and the arachnoid, the subdural space is situated between the arachnoid and the dura mater. The epidural gap is the space between the dura and the skull. The infection continues to be close to the initiating factor. The majority of infections that spread into the epidural spaces are spread from a nearby source of infection, and the infection remains around the original nidus of infection. Subdural infections, on the other hand, are frequently linked to extracerebral sources, and these infections can also spread broadly inside the subdural compartment, far from the initiating source. The four ventricles of the brain's choroid plexuses continually produce cerebrospinal fluid (CSF). The lateral and third ventricles transport CSF to the fourth ventricle, which is situated between the cerebellum and the midbrain. CSF surrounds the entire central nervous system and travels from the

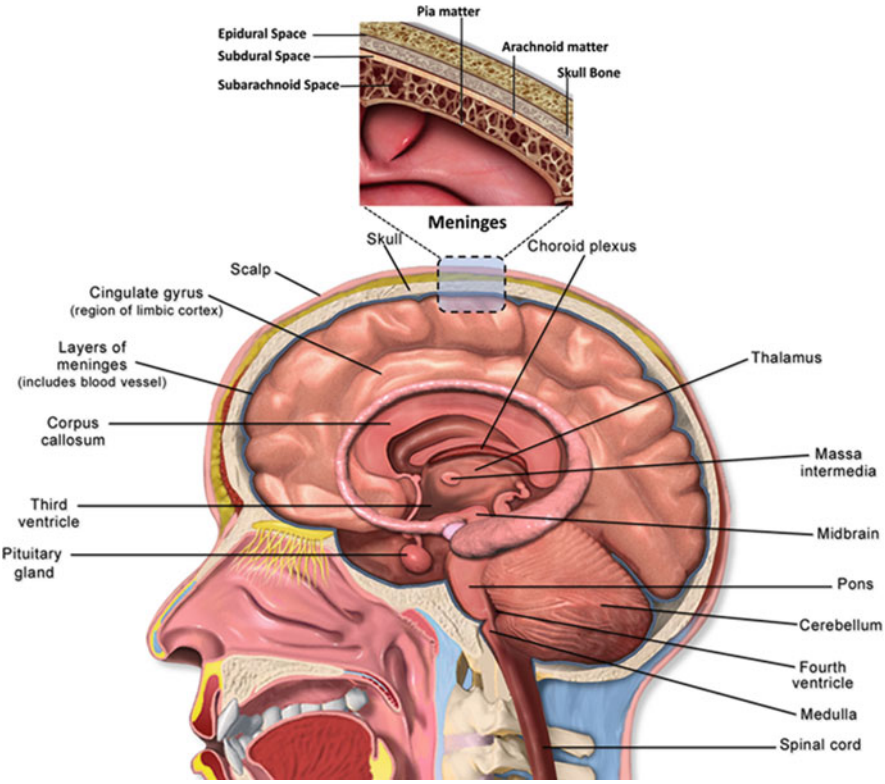

Fig. 2.1 Different layers of meninges

fourth ventricle to the subarachnoid space, arachnoid villi, and the superior sagittal sinus of the dura mater before being reabsorbed into the bloodstream.

Understanding the etiology of CNS infections also requires a solid understanding of the blood supply. The brain and spinal cord have a special capillary supply as the outer layers of endothelial cell layers are merged together. These specialized brain microvascular endothelial cells make up the blood–brain barrier, which isolates the brain and meninges from the circulating blood and prevents the infiltration of microorganisms, toxic agents, and the majority of other compounds while regulating the flow of crucial nutrients and molecules for normal neural function.

As a result, bacteria can infect the central nervous system if they manage to cross the blood–brain barrier. Such breaches can be caused by the organisms themselves, such as *Escherichia coli*, mycobacteria, and spirochetes, or by damage to the blood–brain barrier (such as microhemorrhage or necrosis of the surrounding tissue), the mechanical obstruction of microvessels by parasitized red blood cells, leukocytes, or platelets, excessive production of cytokines that degrade tight junction proteins, or a combination of these factors. The treatment implications are obvious: in order for

antimicrobials administered for CNS infections to be successful, they must be able to cross the blood–brain barrier.

2.2.2 Routes of CNS Infection

Meningitis, encephalitis, and abscesses are the three main types of acute CNS infections, and they are all typically brought on by the transmission of the corresponding microbes through the blood. Bacteremia or viremia can be caused by primary infections at more distant anatomic sites, such as the lungs, heart, skin, gastrointestinal tract, or kidney, as well as locations close to or contiguous to the central nervous system (CNS), such as the mastoid, sinuses, or middle ear. The most frequent predisposing diseases in children are middle ear or sinus infections, which cause temporary bacteremia and hematogenous seeding of the central nervous system (CNS) (Kim 2010; Schuchat et al. 1997). Infections with bacteria in the paranasal and otomastoid sinuses frequently result in phlebothrombosis of the nearby cortical veins that drain into them. It is possible for this thrombotic process to enter nearby dural sinuses. A direct passage from the infected sinus to the nearby extra axial spaces or the brain via cortical venous drainage pathways is provided by the phlebothrombosis turning into thrombophlebitis.

When an organism enters the venous sinuses of a patient with bacteremia or viremia, it may cross the blood–brain barrier, pierce the dura as well as arachnoid, and enter the subarachnoid space, infecting the CSF and spreading the infection further all over this anatomic space. Openings between the CNS and the sinuses, mastoid, middle ear, or nasopharynx can result from fractures near the base of the skull or cribriform plate. All of these locations are close to the upper respiratory system; therefore, if there is a CSF leak at one of these locations, respiratory bacteria may track backward up into the subarachnoid space. Intraoperatively, during neurosurgery procedures, an extrinsic contamination of the CNS can happen. In addition, implants or adjunct hardware (such as shunts, ventriculostomies, or external drainage catheters) can colonize and act as foci of infection. Spina bifida and sinus tracts are two examples of congenital abnormalities that can colonize and serve as sources of infections. Through intraneural routes, viruses including polioviruses, herpes simplex virus (HSV), and rabies can travel to the CNS and cause encephalitis (Archibald and Quisling 2013).

2.2.3 Acute Bacterial Meningitis

An inflammatory reaction following pyogenic bacterial invasion of the pia mater, its arachnoid membranes, and the area surrounding the central nervous system is known as bacterial meningitis. Because the subarachnoid space is continuous, this infection frequently affects the full length of the neuraxis, including the brain itself (cerebrum and cerebellum), the spinal cord, optic nerves, and associated encasing membranes. Non-pyogenic microbes (such as mycobacterium or spirochetes like *Leptospira*

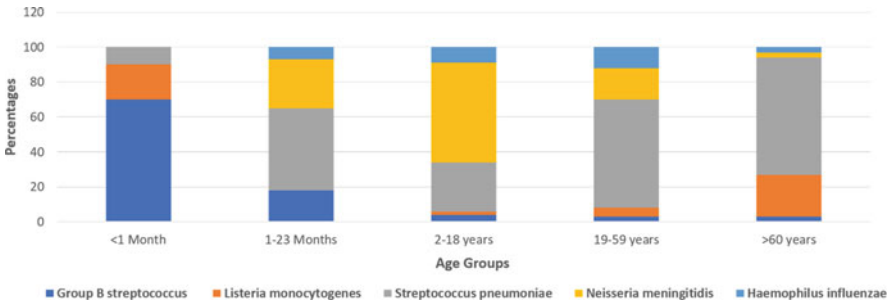

Fig. 2.2 Etiological agents of bacterial meningitis according to different age groups

spp.) are more rarely implicated in pyogenic meningitis and are linked with a prominent, acute inflammatory exudate. Clinically, the illness begins suddenly and progresses over a few hours to a few days to include a fever, headache, irritability, and stiff neck, along with or without specific neurological symptoms (Hsu et al. 2009; Schuchat et al. 1997; Wall et al. 2021).

Streptococcus pneumoniae, Neisseria meningitidis, and *Haemophilus influenzae* type B are the three pathogens most commonly responsible for community-acquired bacterial meningitis. Additionally, specific groups, such as newborns, pregnant women, transplant recipients, and elderly persons, are susceptible to meningitis caused by Gram-negative bacteria like *Escherichia coli* and *Klebsiella pneumoniae* and Group B *Streptococci*, *Listeria monocytogenes*, and *Streptococcus suis* (GBD 2016 Meningitis Collaborators 2018). The age distribution, for the most prevalent agents (Schuchat et al. 1997) in bacterial meningitis, is enumerated in Fig. 2.2.

2.2.4 Tubercular Meningitis

Infection of the meninges with *Mycobacterium tuberculosis* (MTB) bacilli results in tuberculous meningitis (TBM), which presents as extrapulmonary tuberculosis. Droplet inhalation causes the alveolar macrophage to get infected with MTB, which is then transmitted to the host. The lung is where the primary infection first manifests itself, spreading later to the lymph nodes. MTB seeds the meninges in tuberculous meningitis, causing Rich foci, which are sub-ependymal clusters. These foci have the potential to burst into the subarachnoid space, triggering a severe inflammatory reaction that results in meningitis symptoms. This reaction's exudates have the potential to enclose cranial nerves and result in nerve palsies. They can obstruct the flow of cerebral spinal fluid (CSF), which causes hydrocephalus, and entrap blood vessels, resulting in vasculitis. Patients who overcome tuberculous meningitis (TBM) may experience chronic sequelae from these immunological reactions (Slane and Unakal 2023; Thwaites et al. 2000).

Meningitis, tuberculoma, and spinal arachnoiditis are all possible symptoms of Mycobacterium TB infection in the central nervous system (CNS). There are typically three main stages of clinical presentation of TBM (Farinha et al. 2000):

Low-grade fever, malaise, headaches, and a change in behaviors are all signs of the early prodromal phase. Typically, it lasts between 1 and 3 weeks. The meningitic phase then follows, which is distinguished by significant neurologic symptoms, such as persistent headache, urge to vomit, meningismus, fatigue, disorientation, and different presentations of cranial nerve and long-tract indications. In the paralytic phase, confusion is followed by stupor, seizures, coma, and frequently hemiparesis. Untreated sickness frequently ends in death 5–8 weeks after it starts.

2.2.5 Chronic Meningitis

Meningeal inflammation that lasts at least 4 weeks and is accompanied by a CSF pleocytosis is referred to as chronic meningitis (Thakur and Wilson 2018). Atypical bacteria, endemic fungal organisms, and noninfectious etiologies are more frequently responsible for chronic meningitis than community-acquired bacteria and viruses, which are more frequently the causes of acute meningitis. The three most frequent causes of chronic meningitis are neoplasm, TB, and fungal infections.

Chronic meningitis patients with infectious etiology may exhibit symptoms and signs of raised intracranial pressure (ICP), especially when the infection is brought on by *Cryptococcus neoformans* subsp. Fungal meningitis is increasingly recognized in immunocompetent patients as well as those with immunologic diseases taking immunosuppressant drugs or monoclonal antibodies like rituximab. Previously, the disease was thought to only affect those with HIV infection or a hematologic malignancy (Baldwin and Zunt 2014). A list of causes of chronic meningitis (Aksamit 2021; Hildebrand and Aoun 2003; Tan 2003) has been presented in Table 2.1.

2.2.6 Aseptic Meningitis

The phrase “aseptic meningitis” refers to inflammation of the meninges that line the brain caused by a variety of etiologies with sterile cerebrospinal fluid (CSF) culture results. It is determined by CSF pleocytosis of more than 5 cells/mm^3 (Kaur et al. 2023; Tattevin et al. 2019). Although viruses are the most frequent cause of aseptic meningitis, other causes may be categorized as infectious and non-infectious causes.

2.2.7 Meningitis Following Trauma Episodes

Regardless of temporal proximity, post-traumatic meningitis denotes a meningeal infection that is associated with cranio-cerebral trauma. One of the most frequent skull fractures is a basilar skull fracture (BSF) (Das and Pal 2021). Meninges and the

Table 2.1 Causes of chronic meningitis

Infectious causes	Non-infectious	Drugs
Bacterial	Systemic lupus erythematosus (SLE)	NSAIDS
Brucella species	Neoplastic	Intravenous
Francisella tularensis	Sarcoidosis	Immunoglobulins
Actinomyces species	Wegener's Granulomatous Polyangiitis (GPA)	Intrathecal agents
Listeria monocytogenes	Behcet's disease	
Ehrlichia chaffeensis	Central nervous system vasculitis	
Nocardia species	Chemical or drug-induced meningitis	
Tropheryma whipplei (Whipple disease)	Idiopathic	
Spirochetal		
Borrelia burgdorferi		
Treponema pallidum		
Leptospira species		
Mycobacterial		
Mycobacterium tuberculosis		
Fungal		
Cryptococcus neoformans/gattii		
Sporothrix schenckii		
Blastomyces dermatitidis		
Coccidioides immitis		
Others (*scedosporium apiospermum, Paracoccidioides*, dematiaceous molds)		
Parasitic		
Taenia solium		
Angiostrongylus		
Schistosoma		
Toxoplasma gondii		
Acanthamoeba		
Balamuthia mandrillaris		

brain are anatomically close to the inside of the skull; therefore, BSF can cause a dural rupture that causes CSF to leak. BSF frequently involves the frontal and ethmoid bones (Costa et al. 1993). The physical characteristics of the skull bones, especially their thickness and flexibility, play a major role in the degree of deformation and amount of fracture/defect after a skull fracture. The horizontal cribriform plate of the ethmoid bone connects to the frontal bone's ethmoid notch to form a substantial and dense bone complex. However, because of the difference in bone density between these structures, the intersection between the cribriform plate and a comparatively thinner ethmoid labyrinth harboring ethmoidal air cells is especially

susceptible to stress. Additionally, frontal sinus involvement is frequent in BSF and even regarded as high risk due to its relationship with a contusion to the anterior part of the frontal lobe and with dural cuts that may result in CSF leakage.

2.3 Space-Occupying Lesions and Associated Infections

An "Intra-cranial space occupying lesion" (ICSOL) may be defined as a mass lesion in the cranial cavity with diverse etiologies, including inflammatory, neoplasm (benign or malignant), parasitic, hematoma, or AV malformation (Hema et al. 2016). The infectious causes of space-occupying lesions involve pyogenic abscess, tuberculosis (Tuberculoma, TB abscess, TB pachymeninigitis), fungal infections (Aspergilloma, Chromomycosis, Zygomycosis, Cryptococcoma, and Candida), parasitic infections (Cysticercosis, Hydatid cyst, and Toxoplasmosis), and viral infections (progressive multifocal leukoencephalopathy caused by JC virus; Santosh et al. 2010).

2.4 Healthcare-Associated Infections of the CNS

Healthcare-associated meningitis or ventriculitis (HCAVM) is defined as "the presence of a positive CSF culture or at least two symptoms (among fever >38 °C, headache, meningeal or cranial nerve signs), along with at least one additional criterion either of abnormal CSF (increased white cells, elevated protein, and decreased glucose), detection of bacterial growth in CSF on Gram Staining, bacteremia, or diagnostic antibody titers" (Ippolito et al. 2022). Common symptoms include fever, new-onset headache, nausea, convulsions, and changes in mental status. There may also be erythema. Intrathecal infusion pumps may contribute to the development of surgical site drainage and wound infections. It can be challenging to diagnose HCAVM associated with the presence of ventriculoperitoneal, ventriculopleural, or ventriculoatrial shunts because of the presentation, which might include symptoms of peritonitis, abdominal discomfort, pleuritis, glomerulonephritis, or bacteremia. The treating physician should be prompted to include HCAVM in the differential diagnosis if there are no other sources of infection that are suspected. The clinical presentation might not be particularly specific because it may be complicated by the underlying neurological disease (e.g., issues that result in a reduced state of consciousness or coma) or because it may be similar to other concurrent conditions (e.g., septic shock from other sources). Shunt infections typically arise as a result of skin flora colonizing the shunt. This could happen during or afterward surgery because of the disintegration of the surgical wound or surrounding skin. Staphylococci are the most common pathogens in these infections, which happen in the first few weeks following shunt implantation. The most common kind of cerebrospinal fluid shunt infection is an early infection with skin flora; approximately, half of all shunt infections are caused by coagulase-negative staphylococci, and approximately, one-third of cases are caused by *Staphylococcus*

aureus. *Diphtheroids,* like *Corynebacterium jeikeium* and *Cutibacterium* [previously *Propionibacterium*] acnes, may also be pathogenic.

2.5 Viral Encephalitis and Encephalopathies

Encephalopathy is defined as "an altered consciousness persisting for longer than 24 h, including lethargy, irritability or a change in personality or behaviour" (Granerod et al. 2010). Encephalitis is defined as "encephalopathy and evidence of CNS inflammation, demonstrated by at least two of:

- Fever.
- seizures or focal neurological findings attributable to the brain parenchyma,
- CSF pleocytosis (more than 4 white cells per μL).
- EEG findings suggestive of encephalitis neuroimaging findings suggestive of encephalitis"(Granerod et al. 2010).

Various known causes of Encephalitis (Ellul and Solomon 2018), which may be viral etiology, autoimmune etiology, or due to other causes (Table 2.2).

"Inflammation of the brain parenchyma brought on by a virus" is known as viral encephalitis. It coexists commonly with viral meningitis and is the most prevalent kind of encephalitis. Viruses enter the host outside of the central nervous system and then travel retrogradely from nerve terminals or hematogenously to the spinal cord and brain (Said and Kang 2023). Important causes of viral and fungal encephalitis are discussed in later chapters of this book.

Table 2.2 Important causes of encephalitis

Viral
HSV 1 and 2, VZV, Enteroviruses, Adenoviruses, Measles, Parechovirus, HIV, West Nile virus, Japanese Encephalitis, EBV, CMV, HSV-6 and 7, Mumps, Rubella, t. Louis virus, Eastern equine virus, Western equine virus, Dengue virus, and Rabies virus
Autoimmune
NMDAR antibody encephalitis (ovarian teratoma), LGI-1 antibody encephalitis (thymoma), antibodies against intracellular antigens: anti-Hu (small cell lung tumor), anti-Ma (testicular tumors), anti-GAD, acute disseminated encephalomyelitis, and Bickerstaff's encephalitis
Infective
Bacterial meningitis, TB, opportunistic infections in immunocompromised patients (e.g. crytococcus, toxoplasma, and CMV), Systemic sepsis with encephalopathy
Inflammatory
Vasculitis, systemic lupus erythematosus with CNS involvement, Behçet's disease, and neurosarcoidosis
Metabolic
Hypoglycaemia, hyponatremia, hepatic encephalopathy, and toxins (drugs and alcohol)
Neoplastic
Primary brain tumor (mainly low-grade glioma mirroring CNS inflammation), metastases

2.6 Mycotic Neuro-Invasions

A host's immunological wellness plus a fungal pathogen's degree of virulence play major roles in neuro-invasion (Hernández-Chávez et al. 2017). Mycoses result in considerable morbidity in immunosuppressed hosts; in addition, neurological complications may have lethal effects (Table 2.3) (Góralska et al. 2018). Still, several fungi (e.g., Coccidioides, Cryptococcus, Histoplasma, etc.) may also infect patients who have a functioning immune system (Guarner and Brandt 2011).

Cryptococcus neoformans-associated meningoencephalitis is an exceptionally common mycotic neuro-infection infection globally (Maziarz and Perfect 2016). CNS involvement is frequently linked to diffuse mycosis. Patients exhibiting an aggressive cryptococcosis are predicted to experience full-blown neurological involvement in 67–84% of cases. Likewise, 3–64% of invasive *Candida* infections tend to cause secondary neuro-invasion. Some cases of blastomycosis (40%), disseminated coccidioidomycosis (25%), disseminated histoplasmosis (5–20%), mucormycosis (12%), and invasive cases of severe aspergillosis (4–6%) may also bring about neuropathological sequelae (Góralska et al. 2018).

2.6.1 Blood–Brain-Barrier Interactions in Fungal Invasion

Fungal organisms may reach the central nervous system directly or indirectly by penetrating the blood–brain barrier. Direct seeding can occur via iatrogenic means or via an incident/s of trauma. Fungi can penetrate the blood–brain barrier by three main mechanisms (Table 2.4; Fig. 2.3) (Snarr et al. 2020).

Table 2.3 Overview of mycotic neuro-involvements

Fungal pathogen	Remarks
Aspergillus	Brain abscess, skull/base involvements, infarction/stroke, and dissemination
Absidia	Rhino-cerebral syndromes
Blastomyces	Brain abscess
Candida	Brain abscess, dissemination, meningitis, and meningoencephalitis
Coccidioides	Brain abscess, dissemination, meningitis, and meningoencephalitis
Cryptococcus	Dissemination, meningitis, and meningoencephalitis
Exserohilum	Meningitis
Histoplasma	Brain abscess and meningitis
Mucoromycetes	Brain Abscess, dissemination, and infarction/stroke
Rhizomucor	Rhino-cerebral syndromes
Syncephalastrum	Rhino-cerebral syndromes

Table 2.4 Main mechanisms in fugal blood–brain-barrier penetration

	Mechanism	Remarks
1.	Paracellular	Weakened cell-to-cell adhesions
2.	Transcellular	Adherence to endothelial cells
3.	Trojan Horse	Carried over by phagocytes

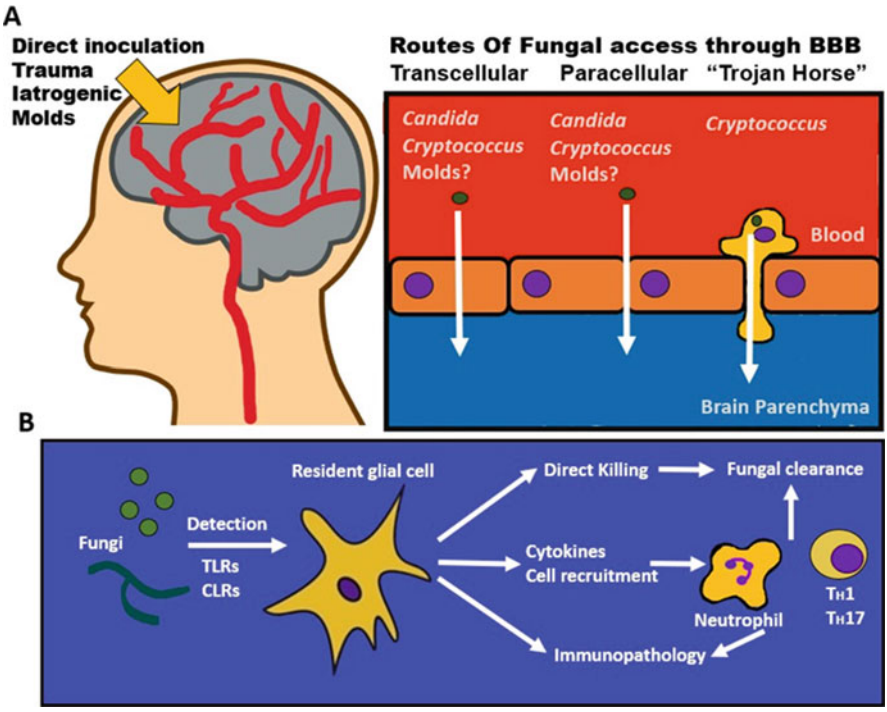

Fig. 2.3 Fugal blood–brain-barrier penetration

The expression of toll-like receptors as well as C-type lectin receptors on astrocytes and microglia enables the detection of invading fungi in the host's CNS (Wu et al. 2023). Subsequently, the glial cells may either actively combat the insult (i.e., fungal clearance from the CNS) or they may bring in particular immune cells by releasing certain chemoattractant peptides and cytokines (Lionakis et al. 2023). It is possible to eradicate the insult with the help of innate (i.e., neutrophils) and adaptive (i.e., T helper 1, 17, etc.) immune system cells. However, resultant severe inflammation plus immunotoxicity may negatively impact the nervous system indefinitely (Bartemes and Kita 2018).

2.6.2 Rhino-Cerebellar Syndromes

A relatively less common condition known as rhino-cerebral mucormycosis, sometimes known as zygomycosis, affects the central nervous system, paranasal sinuses, and the nose (Bhandari et al. 2023). This represents opportunistic fungi that may be isolated among those with compromised immune systems (Hernández-Chávez et al. 2017). A rapid spread of rhino-orbital-cerebral mucormycosis (ROCM) was witnessed in India, among active and post COVID-19 patients (predominantly in diabetic groups) (Dubey et al. 2021).

The filamentous fungi (Table 2.5) spread quickly and vigorously given that they affect people who already have compromised immune systems, leading to a clearly distinguished, fulminant, often fatal condition (Bhandari et al. 2023). In order to reduce associated morbidities and avoid irreversible neurological consequences, timely action is essential (Chikley et al. 2019). The majority of the time, these rhino-cerebral syndromes display acute presentations, but they can also be chronic infections with slower progressions over a period of weeks (Bhandari et al. 2023).

2.6.3 Disseminated Syndromes

Systemic fungal infections and, occasionally, neuro-mycosis may arise from spreading through the bloodstream from distant sites, such as the lungs, gut, or artificial heart valves (Góralska et al. 2018). Therefore, CNS seeding arises via direct propagation from juxta-cranial locations or via hematogenous dissemination (Raman Sharma 2010). Cryptococcosis and coccidioidomycosis are among some of the common disseminated syndromes resulting in CNS fungal infections (Góralska et al. 2018). In addition, meningitis may occur as an unanticipated consequence of disseminated candidiasis (Lionakis et al. 2023). Disseminated blastomycosis, mainly in immunocompromised patients, can present with CNS sequelae, manifesting as meningitis, brain abscess, or epidural abscess (McBride et al. 2017).

2.7 Infections of the Brainstem, Cerebellum, and Spine

Although primary infectious pathologies involving the brainstem are less common, when present, they usually manifest as an abscess or as encephalitis. *Staphylococci*, certain *streptococci*, and *Mycobacterium tuberculosis* are frequent culprits for the development of abscesses in the brainstem (Li et al. 2020). Herpes simplex virus and *Listeria monocytogenes* infection are frequent culprits for brainstem-linked encephalitis (Cunha et al. 2007). During primary brainstem infections, typical brainstem findings occur infrequently and may manifest features of cerebrospinal fluid blockage, as is the case in neurocysticercosis (Archibald and Quisling 2013; Garcia et al. 2014).

Microorganisms, such as John Cunningham virus (JCV), *L. monocytogenes*, and varicella zoster virus (VZV), commonly or primarily attack the cerebellum (Archibald and Quisling 2013; Le Govic et al. 2022). Other such causative viral illnesses include Epstein–Barr virus (EBV), echovirus, and Coxsackievirus infections (Muscat et al. 2017; Muzio 2022). Infections can occasionally produce cerebellar inflammation, which impairs the cerebellum's functional capacity and leads to ataxia. Although bacterial diseases, like Lyme disease, can also produce cerebellar ataxia, viral illnesses like chickenpox are predominantly to blame (Arav-Boger et al. 2002; Betancourt Fursow et al. 2013). This causes an abrupt or rapid bout of ataxia in an individual who was previously well, and it affects youngsters far

Table 2.5 Molds that cause paranasal sinus and orbital infections

Phylum	Zygomycota				Ascomycota	
Class	Zygomycetes				Eurotiomycetes	Dothideomycetes
Order	Mucorales		Eurotiales		Pleosporales	
Family	Mucoraceae	Cunninghamella	Saksenaeaceae	Lichtheimiaceae	Trichocomaceae	Pleosporaceae
Genus/ species	*Apophysomyces elegans*	*Cunninghamella bertholletiae*	*Apophysomyces elegans*	*Lichtheimia corymbifera (also known as Absidia corymbifera)*	*Aspergillus flavus*	Alternaria
	Mucor ramosissimus		*Apophysomyces trapeziformis*		*Aspergillus fumigatus*	Bipolaris
	Rhizomucor pusillus		*Saksenaea vasiformis*			Curvularia
	Rhizopus oryzae					

more frequently than it does adults. Acute post-infectious ataxia or acute cerebellar ataxia are common names for this type of ataxia (Fogel 2012).

Some relevant points regarding spinal infections:

- It is conceivable that a far-off infection source acts as a nidus for the hematogenous propagation of bacteria toward the spinal cord. Typical antecedent locations include the epidermis and the genitourinary system, but other potential foci have also been identified, including sinusitis, pulmonary, gut, oral infections, septic arthritis, and subacute bacterial endocarditis (Tsantes et al. 2020).
- Spinal infections are increasingly being caused by intravenous drug usage. *Staphylococcus aureus* tends to be the microbe that is most probably responsible for infecting the spine, but among intravenous drug abusers, *Pseudomonas* strains are as frequently responsible (Tsantes et al. 2020).
- Yeast, other fungi, parasitic pathogens, and *M. tuberculosis* are all potential causes of non-pyogenic osteomyelitis of the spine (Moritani et al. 2014; Skaf et al. 2010).
- Following spinal operations, surgical-site infections may occur as a negative outcome. The frequency of such infections in spinal surgeries can be decreased by following rigorous aseptic protocols and by timing pre-op antimicrobial prophylaxis effectively (Aleem et al. 2020).
- Mycotic spinal infections are relatively less common, and they typically affect elderly, diabetic, or immune-compromised people. Alcoholics, leukemic patients, people on chemotherapeutic agents, those suffering from lymphomas, and transplant patients are more vulnerable to such fungus infections (Frazier et al. 2001; Kim et al. 2006).
- The region of the lumbar spine has the highest rate of vertebral osteomyelitis due to the great blood supply there (Graeber and Cecava 2023). Intravenous drug addicts are especially prone to getting cervical spine infections, while in tuberculosis, the thoracic spine tends to be the commoner site (Garg and Somvanshi 2011; Singh et al. 2006).
- The most prevalent kind of spinal infection is spondylodiscitis, which is an infection of the intervertebral disc and the nearby vertebral body. More specifically, primary pyogenic (bacterial) spondylodiscitis, in which the pathogen affects the site(s) by hematogenous dissemination, is the most frequent form of spinal infection (Tsantes et al. 2020).

2.7.1 Epidural Abscess of the Spine

A fairly well-demarcated, pus-filled mass can compress the spinal cord or compromise its blood supply (spinal epidural abscess), inflicting spinal cord damage (Gala and Aswani 2016). A purulent growth within the column's epidural space has the potential to press against the cord, resulting in sensory, motor, and paralytic impairments or if left untreated, even death (Ameer et al. 2023). Morbidity and mortality rates tend to be greater for epidural abscesses of the cervical spine than for

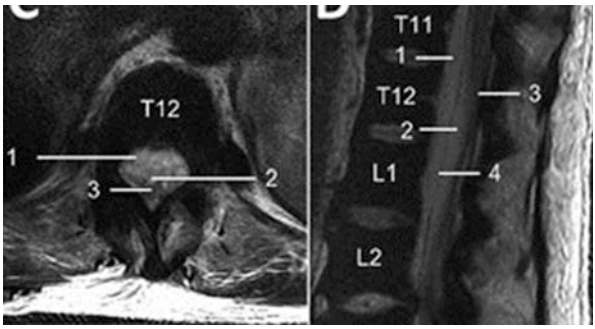

Fig. 2.4 MRI (sagittal and T2-weighted images of thoracic 11 (T11) to Lumbar 2 (L2) vertebra levels) of a patient diagnosed with a methicillin-sensitive *Staphylococcus aureus* infection. There is ventral, 1—epidural and 2—subdural spinal collection with 3—dorsal displacement of conus medullaris. The 4—dura mater can be seen delineating the theca and separating the subdural and epidural spaces. (Image Source—Emerging Infectious Diseases journal—CDC (Jewell et al. 2019)—Copyright Restrictions: NONE; this image is in the public domain and thus free of any copyright restriction)

the more frequently encountered, lumber and thoracic spine abscesses (Sharfman et al. 2020). Although numerous other species, including *Brucella,* Coagulase-negative *Staphylococci, Escherichia coli*, mycobacteria, and *Pseudomonas*, are all documented causes, *Staphylococcus aureus* remains the most reported culprit to date (Fig. 2.4) (Ameer et al. 2023). Methicillin-resistant *S. aureus* (MRSA) is more commonly seen among those who have had spinal procedures, implant insertions, or who have a history of MRSA abscesses (Pi et al. 2023). Individuals who are immunodeficient may present with spinal epidural abscesses linked to unlikely causative microorganisms, including certain fungi (Tsantes et al. 2020).

2.7.2 Neurodegenerative Disorders with Possible Infective Linkages

Neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and Parkinson's disease (PD), are characterized by progressive neuronal degeneration and functional decline (Katsuno et al. 2018). The fundamental molecular mechanisms behind the pathogenesis of these extremely complicated disorders, which are frequently caused by a number of interrelated hereditary and environmental variables, are still poorly understood (Jellinger 2010).

According to several literary works, it is possible that neuro-infections contribute to the development of neurodegenerative illnesses on multiple fronts (De Chiara et al. 2012; Vigasova et al. 2021; Zhou et al. 2013). ALS, which affects motor neurons, may be caused by enteroviruses and human herpesviruses, according to some serological investigations (Cabrera et al. 2020; Xue et al. 2018). Due to the striking resemblance involving the medical manifestations of Japanese encephalitis

virus (JEV) and PD, a JEV-origin for PD has recently been suggested (Ogata et al. 2000; Tadokoro et al. 2018). The flu virus, influenza, has frequently been proposed as a co-factor for PD, dating back to early articles documenting CNS manifestations linked to influenza (Cocoros et al. 2021; Henry et al. 2010; Takahashi and Yamada 2001). A number of research results also suggest that pathogens, mainly herpes simplex virus-1 and *Chlamydia pneumoniae*, play a role in the development of Alzheimer's disease, a complex illness with varying patient-to-patient manifestations (basal cortical neuron, cognition, hippocampus involvement, dementia, etc.) (Breijyeh and Karaman 2020; Harris and Harris 2015; Nicolson and Haier 2009; Wouk et al. 2021). Cytomegalovirus (CMV), EBV, human herpesvirus-6 (HHV-6), HSV, VZV, and now even HHV-7 have been found to be contributors to multiple sclerosis, an inflammatory condition that causes axonal demyelination in the column and brain (Donati and Jacobson 2002).

Transmissible Spongiform Encephalopathies—Prion illnesses, commonly referred to as transmissible spongiform encephalopathies (TSEs), are a collection of deadly CNS illnesses, with the most common theory that they are spread by prions (Moore et al. 2009). Microscopy from affected brain matter reveals numerous cortical holes that resemble a sponge, hence the name. The illness damages CNS function and leads to persistently worsening memory loss, behavioral changes, and difficulties with motion. Human TSEs include Creutzfeldt–Jakob disease (sporadic, familial, iatrogenic, and variant forms), kuru, fatal familial insomnia, and Gerstmann–Sträussler–Scheinker syndrome (Poggiolini et al. 2013). In addition, familial spongiform encephalopathy and variably protease-sensitive prionopathy have also been identified. Having overlapping manifestations, these ailments make up a wide range of disorders (Geschwind 2015; Imran and Mahmood 2011).

2.7.3 Peripheral Nerve Involvement in CNS Infections

Infection may serve as a neglected cause of peripheral nervous system (PNS) disease (Table 2.6) while being very uncommon in comparison to autoimmune, primary inflammatory, or vascular causes. Nevertheless, PNS illness brought on by infection has the potential to result in serious damage to the nervous system, either directly from the microorganism or indirectly via secondary immunological exacerbation. Knowing the variations among multiple illnesses and differentiating between infectious and noninfectious neurological causes may assist in making correct treatment choices and, in certain circumstances, cure or at the very least stop further harm from happening to the patient (Brizzi and Lyons 2014).

2.7.4 Transverse Myelitis, etc.

Transverse myelitis may result from bacterial or viral infections (Table 2.7) that impact the spinal cord. When this inflammatory condition is linked to an infectious etiology, it typically develops following the recovery period (Beh et al. 2013). The

Table 2.6 Microorganisms associated with peripheral nervous system involvement

PNS manifestations	Microorganism	
	Bacteria	Viruses
Acute flaccid paralysis of limb(s)	–	Adenovirus, Enterovirus EV68, Human Immunodeficiency virus (HIV), Poliovirus, Rabies virus, and West Nile virus (WNV)
Acute inflammatory demyelinating polyneuropathy	*Campylobacter jejuni*	Cytomegalovirus (CMV), Epstein-Barr virus (EBV), HIV (early stage), and Varicella zoster virus (VZV)
Axonal sensory polyneuropathy	–	Hepatitis C virus
Compressive radiculopathy	*Mycobacterium tuberculosis*	–
Cranial neuropathy	*Borrelia burgdorferi*, *Brucella* species, *Corynebacterium diphtheriae*, *and Mycobacterium tuberculosis*	HIV (early stage), VZV
Demyelinating polyneuropathy	–	WNV
Distal peripheral neuropathy	–	CMV
Distal sensorimotor polyneuropathy	*Corynebacterium diphtheriae and Mycobacterium tuberculosis*	–
Distal symmetric polyneuropathy	*Mycobacterium leprae*	HIV (late stage)
Encephalomyeloradiculitis	–	CMV
Flaccid paralysis	–	WNV
Mononeuropathy (or mononeuritis) multiplex	*Borrelia burgdorferi and Mycobacterium leprae*	CMV, HIV (early stage)
Motor neuropathy/motor neuron disease	–	Human T-lymphotropic virus (HTLV), VZV
Myasthenia gravis-like syndrome	–	HTLV
Myeloradiculitis/ myeloradiculopathy	–	CMV, EBV, VZV
Peripheral neuropathy	*Brucella* species	–
Polyneuropathies with autonomic dysfunctions	–	HTLV
Polyneuropathy	*Borrelia burgdorferi*	–
Postherpetic neuralgia	–	VZV
Radiculopathy	*Borrelia burgdorferi*, *Brucella* species	–
Sacral radiculitis	–	Herpes simplex virus
Soft palate neuropathy	*Corynebacterium diphtheriae*	–

(continued)

Table 2.6 (continued)

PNS manifestations	Microorganism	
	Bacteria	Viruses
Symmetric descending paralysis	*Clostridium botulinum*	–
Tropical spastic paraparesis	–	HTLV type 1-associated myelopathy

Table 2.7 Microorganisms associated with transverse myelitis

Bacteria	Viruses
Actinomyces species	CMV
Bordetella pertussis	EBV
Borrelia burgdorferi (extremely rare complication)	Echovirus
Clostridium tetani	Enteroviruses (Coxsackievirus, Poliovirus, etc.)
Corynebacterium diphtheriae	Hepatitis B virus
Mycobacterium tuberculosis	Herpes viruses
Treponema pallidum	HIV
Transverse myelitis can also be brought on by bacterial infections of the skin, gastroenteritis, and some strains of pneumonia-causing bacteria.	Influenza virus
	Measles virus
	Mumps virus
	Rubella virus
	WNV
	Zika virus
	Other viruses that do not directly infect the spinal column may nevertheless cause an autoimmune response-associated transverse myelitis.

spinal column can occasionally be affected by parasites and fungi (Beh et al. 2013; Kibiki and Murphy 2006).

Poliomyelitis—The extremely contagious poliomyelitis disease is brought on by the poliovirus, a member of the Picornaviridae family. The main method by which poliovirus spreads from person-to-person is the fecal–oral transmission. For a number of weeks, it can shed in oral secretions, and for a number of months, it can shed in the feces. The virus is capable of destroying the spinal column's anterior horn cells (Mehndiratta et al. 2014).

There are two forms of poliovirus infections: a minor form and a major form (Mehndiratta et al. 2014). The minor-related ailments begin 1–3 days before paralysis presents and are gastrointestinal in nature, including nausea, vomiting, discomfort in the abdomen, cramping, and diarrhea. Additionally, those affected, experience systemic signs, such as headache, fatigue, fever, and sore throat (Wolbert and Higginbotham 2023). The persistence or emergence of any muscular aches and pains indicates that the acute phase has not ended; this phase generally continues for

2–3 weeks but can even last as long as 2 months (Mehndiratta et al. 2014). All poliovirus-related CNS syndromes, such as paralytic poliomyelitis, nonparalytic polio or aseptic meningitis, poliovirus-encephalitis, and bulbar polio, singly or combined, are among the major forms of illness (Mehndiratta et al. 2014).

Countless lives have been affected worldwide by the devastating malformations that have been linked to this illness. The genetic makeup of polioviruses, along with their pathogenicity could only be understood thanks to the persistence and resilience of outstanding scientific researchers during the 1900s (Quarleri 2023). The invention of the oral polio vaccine and the inactivated polio vaccine by Salk and Sabin signaled the beginning of a new era in science. The World Health Organization (WHO) declared the Americas region free from the three forms of wild poliovirus, i.e., types 1, 2, and 3, in 1994. The Western Pacific region followed suit in 2000 and then the European region in June 2002. In 2013, poliovirus was still prevalent in just three nations, namely, Pakistan, Afghanistan, and Nigeria. Polio must be globally eradicated or there will always be a risk of an outbreak (Mehndiratta et al. 2014).

Pott's Spine—Tuberculous spondylitis, referred to as Pott's spine or Pott disease, is a typical extrapulmonary tuberculosis (TB) manifestation. It can cause substantial functional decline and is linked to serious morbidity. Spinal TB is now uncommon in industrialized nations due to the development of anti-tuberculosis medications and better public health practices, yet it remains a serious disease in the developing world (Garg and Somvanshi 2011). Extensive morbidity from spinal involvement of *Mycobacterium tuberculosis*, in the form of serious deformities and lifelong neurological impairment, is conceivable (Rajasekaran et al. 2018). Most people can get their condition under control with therapeutic measures or a combination of therapeutic plus operative regimens (Rasouli et al. 2012).

2.8 Tropical Neuro-Infections

Infections that are common or specific to the subtropics or to the tropics are referred to as tropical diseases (Zumla and Ustianowski 2012). In general, among the more frequent disease, vectors are insects like flies and mosquitoes. The vectors might be carrying a virus, bacteria, or parasite capable of infecting humans as well as animals. The most common way that disease is spread is by the bite of an insect, which transmits the disease-causing agent via subcutaneous blood exchange. Many of these tropical illnesses are not covered by vaccinations, and some may not have efficient treatments (Williams 2023). The presence of extensive wintertime seasons, which drive insects into hibernation, reducing their population, is one reason why these infections are not as common in temperate zones. However, prior to today's knowledge of the causal relationship of different diseases, plenty of these tropical illnesses existed in the Nordic regions and North America around the seventeenth and eighteenth centuries (Rosenau 1925; Zumla and Ustianowski 2012). Expeditions of tropical rainforests by humans, deforestation, increased immigration, global travel, as well as other forms of tropical tourism have all contributed to a spike in the occurrence of such illnesses in non-tropical nations (Lindahl and Grace 2015).

2.8.1 Brain Injury Caused by Neuro-Parasites

Medical manifestations of parasitic CNS infections may vary. It might be challenging to diagnose an illness because its symptoms are frequently modest or ambiguous. It is more probable to identify and treat parasitic neuro-infections when one is acquainted with the fundamental epidemiological traits and distinctive diagnostic imaging results (Carpio et al. 2016) (Table 2.8).

2.8.2 Cerebral Malaria

Cerebral malaria happens to be a particularly serious CNS consequence of *Plasmodium falciparum* disease. It comprises a medical illness marked by coma or other sequelae (Table 2.9); blood films reveal asexual falciparum forms. There is substantial mortality, and those who survive develop sustained brain insult, with lasting cognitive deficits (Idro et al. 2010).

2.8.3 Emerging and Re-emerging Tropical CNS Infections

Globally, as much as 85% of CNS infections are brought about by unidentified causes, with emerging infections (Table 2.10) anticipated to account for a sizable fraction of them. To uncover previously unsuspected infections, clinicians must begin looking beyond the conventional diagnostic algorithms (Ranawaka 2022). Provincial or worldwide outbreaks can be caused by emerging pathogens as they broaden their geographic distribution (such as the Chikungunya virus), often circulating through nonhuman reservoirs (such as the Nipah virus), or developing novel neurovirulence (such as the Chikungunya virus) (Tyler 2009).

2.9 Post-infection Neurological Complications

The relationship between infection and the majority of autoimmune neurological diseases is somewhat complicated. Many individual autoimmune illnesses have been linked to different pathogens, indicating that infections may cause autoimmunity via processes other than just molecular mimicry (Table 2.11) (Blackburn and Wang 2020).

Table 2.8 Overview of CNS lesions caused by parasites (Carpio et al. 2016)

Parasite/disease	CNS lesion(s)	Common medications
Acanthamoeba species, *Balamuthia* species (granulomatous amoebic encephalitis)	Ring-enhancing lesion(s) of gray/white matter, + perilesion edema, mass effect; arterial occlusion and infarction	Fluconazole, flucytosine, pentamidine, sulfadiazine
Echinococcus granulosis (intracranial hydatidosis)	Non-enhancing, thin-walled, globular cysts/small cysts around a bigger cyst, usually in the parietal area	Albendazole
Echinococcus multilocularis (alveolar hydatid disease)	T2WI: contrast-enhanced, globular lesions, ±calcification, +perilesional edema	Albendazole
Naegleria fowlerii, etc. (primary amoebic meningoencephalitis)	T2WI: global edema mostly at the base of the brain, stroke secondary to intracranial tension	Amphotericin B
Paragonimus species (paragonimiasis)	T2WI: 'grape-cluster' ring lesions with perilesion edema at frontal/temporal grey/white matter	Praziquantel
	T1WI: contrast-enhanced lesions with inflammation	
Schistosomiasis (*S. hematobium* favours the spinal column, but other species can infect other parts of the CNS)	T1WI: mass-like lesion with central linear enhancement	Praziquantel
	T2WI: hyperintense lesions, +perilesion edema, mass effect	
	CT: variably enhancing, hyperdense lesion(s), +low-density perilesion edema, mass effect	
Sparganosis	T2WI: edema (increased signal intensities)	Praziquantel
	T1WI/MRI: enhancing/linear mass lesions at frontal/parietal lobes (Rare—cerebellar/brainstem/spinal column involvement)	
Taenia solium (neurocysticercosis)	CT: Solitary lesion/punctate calcification	Albendazole, corticosteroids
	T1WI: 'hole-with-dot' sign, solitary hypointense ring-enhancing lesion (cystic)	
	Intraventricular/subarachnoid/spinal cysts	
Toxoplasma gondii (toxoplasmosis)	Multiple ring-enhancing cerebral lesions, basal ganglia involvement, +cerebral edema	Sulphonamides, pyrimethamine, spiramycin
Trypanosoma brucei (Human African trypanosomiasis)	T1WI: Diffuse grey matter/basal ganglia/internal capsule bilateral hyperintensities	Pentamidine isethionate, corticosteroids, melarsoprol

(continued)

Table 2.8 (continued)

Parasite/disease	CNS lesion(s)	Common medications
Trypanosoma cruzi (Chagas' disease)	T1WI: enhanced, hypointense lesions at frontal/parietal lobes	Benznidazole, corticosteroids
	T2WI: hyperintense perilesion edema, mass effect	

T2WI T2-weighted imaging, *T1WI* T1-weighted imaging, *MRI* magnetic resonance imaging, *CT* computed tomography

Table 2.9 Cerebral malaria's neurocognitive consequences (may be resolving or non-resolving) (Peixoto and Kalei 2013)

Neurocognitive impairments	Attention/executive function/learning/memory abnormalities
Epileptic manifestations	Generalized/tonic clonic seizures
Motor impairments	Spasticity, central hypotonia, cranial nerve palsies, quadriparesis/hemiplegia/quadriplegia
Movement impairments	Ataxia, dystonia, tremors
Neuropsychiatric manifestations	Abnormal behaviors, attention problems, and hyperactive syndromes
Post malaria neurological syndrome	Abnormal behaviors, acute psychosis, catatonia, hallucinations, inappropriate speech, and seizures
Speech abnormalities	Aphasia, language/pragmatic/vocabulary impairments
Vision abnormalities	Mild (resolving) blindness

Table 2.10 Emerging/reemerging tropical pathogens, which may cause CNS involvement

Emerging/reemerging tropical pathogen	Neurological involvements
Burkholderia pseudomallei	Neurological Melioidosis
Chandipura virus	Acute encephalitis
Chikungunya virus	Encephalitis
	Encephalomyelitis
	Encephalopathy
	Guillain-Barré syndrome
	Meningitis
	Myelopathy
	Myopathy
	Peripheral neuropathy
Dengue virus	Acute disseminated encephalomyelitis
	Cerebellitis
	Cranial/peripheral neuropathy
	Dengue-associated muscle dysfunction
	Encephalitis
	Encephalopathy
	Guillain-Barré syndrome
	Optic neuritis and
	Transverse myelitis
Nipah virus	Encephalitis
Ebola virus	Encephalitis
	Encephalopathy
	Frontal lobe dysfunction
	Meningitis
	Seizures

Table 2.11 Post-infection autoimmune CNS complications (Blackburn and Wang 2020)

Infective pathogen	Autoimmune CNS disorder
Coxsackie B virus	Acute disseminated encephalomyelitis
Dengue virus	
HIV	
Legionella	
Measles	
Mumps	
Mycoplasma pneumonia	
Varicella Zoster virus (VZV)	
Herpes simplex virus	Autoimmune encephalitis
Japanese encephalitis virus	
Mycoplasma pneumoniae	
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	
West Nile virus (WNV)	
Campylobacter jejuni	Guillain–Barre syndrome
Chlamydia pneumonia	
Cytomegalovirus	
Epstein Barr virus	
Haemophilus influenzae	
Hepatitis A virus (HAV), HEV	
HIV	
Influenza viruses	
Mycoplasma pneumonia	
SARS-CoV-2	
Zika virus	
WNV	Myasthenia gravis
VZV	Neuromyelitis optica spectrum disorders
WNV	Stiff person syndrome
Group A Streptococcus	Sydenham's chorea

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