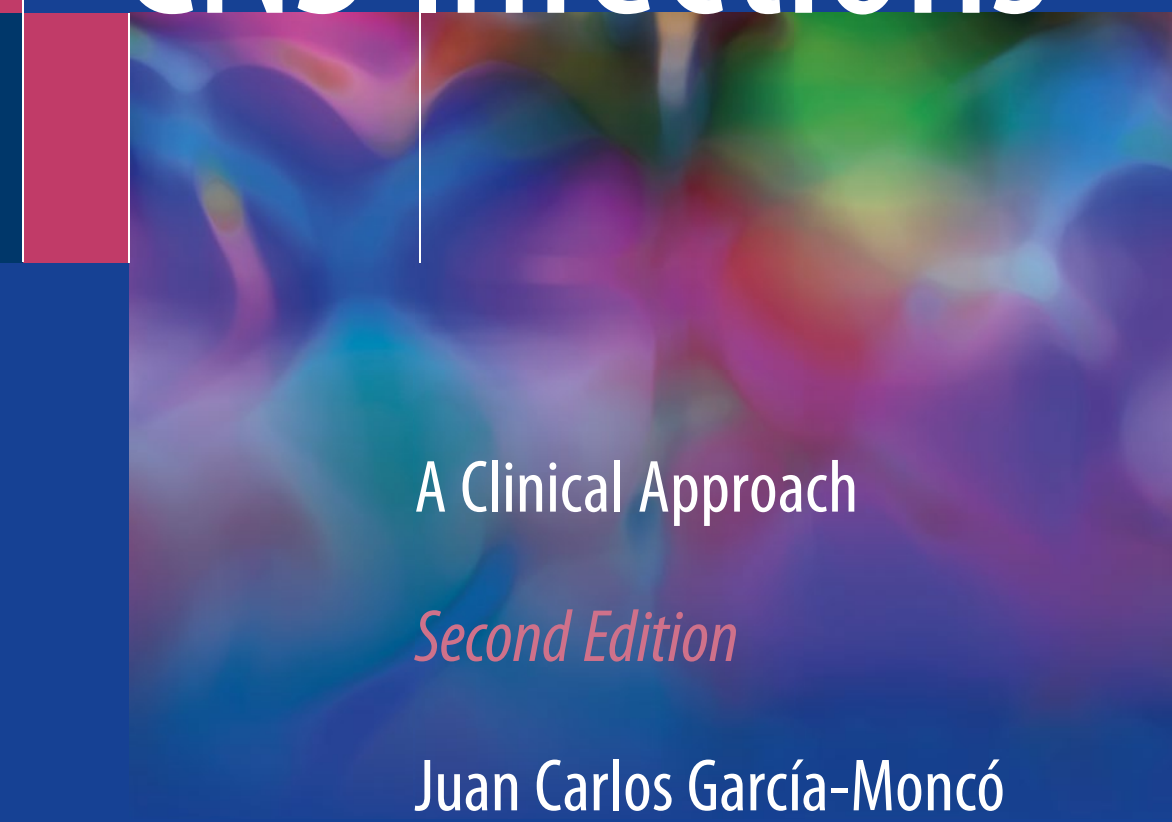
CNS Infections



A Clinical Approach

Second Edition

Juan Carlos García-Moncó
Editor

Springer

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To my wife Beatriz, and to my children Carlos, Pablo, and Sofia, for they all have been taken away many hours during the preparation of this book.

To Jorge Benach, once my mentor then my friend, for his continuous help and support.

To our patients, for they are a continuous source of inspiration.

Preface

The first edition of this book was published in 2014. It was intended to provide the clinician with an easy access, clinically oriented book dealing with the most frequently encountered infectious conditions affecting the nervous system.

The response from the readers indicated that we succeeded in our effort. With this in mind, Springer Nature made a proposal for a second edition of the book which we enthusiastically accepted.

With the help of our many contributors, we have updated the contents of the entire book, again with the goal of providing the reader with current information on the topic that will help them deal with their patients. We have also added a new chapter on infections involving the peripheral nervous system including Zika virus and other infectious neuropathies. The spectrum of encephalitis has expanded over the last few years, particularly those of autoimmune origin, and this has also led to expand the information of the chapters dealing with encephalitis.

Writing book chapters requires much hard work and discipline. Even the updating of a previously written chapter is a time-consuming task. Thus, I want to emphasize that without the enormous effort of our authors this book simply could have not been possible. I sincerely thank them for undertaking the updates of each of the chapters.

I want also to thank Prakash Jagannathan, from Springer Nature, who has coordinated the enormous work that putting together a book represents. Without his help, it would have been impossible to have all the chapters ready on time.

Finally, I want to express my gratitude to the members of Springer for suggesting and supporting this second edition.

Galdacano, Vizcaya, Spain
September, 2017

Juan Carlos García-Moncó, M.D.

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Lumbar Puncture and CSF Analysis and Interpretation

1

Marian Gomez-Beldarrain and Juan Carlos García-Moncó

Abstract

Cerebrospinal fluid (CSF) analysis is essential in the diagnosis of the infectious diseases of the central nervous system. It is also helpful in the differential diagnosis of other conditions that simulate infectious disorders and in monitoring the effects of antibiotic therapy.

The CSF is formed by the choroid plexuses of the ventricles. Its volume in adults is 150 ml. Most of the CSF is reabsorbed by the arachnoid granulations, located along the superior sagittal sinus toward the venous system. The main CSF function is mechanical, protecting the brain from acute or sudden changes in pressure.

The lumbar puncture (LP) to obtain CSF is not without risks, and the complications, such as brain herniation, spinal hematoma, and iatrogenic CNS infection, which, although rare, can be serious. Nevertheless, LP remains the gold standard procedure for the diagnosis of CNS infections. The LP should be performed in aseptic conditions with the patient assuming a lateral recumbent position. Local anesthesia at the needle insertion point makes the procedure easier. Using atraumatic needle is associated with less post-puncture headache, which is the commonest complication.

The normal CSF appears sparkling clear; any change in this characteristic is pathologic. The normal total CSF leukocyte counts are $<5/mm^3$ in adults, the normal glucose level is between 45 and 80 mg/dl, and the normal total protein is between 15 and 50 mg/dl. An increased intrathecal synthesis of immunoglobulins indicates a chronic infection of the CSF. Microbiological analysis of the CSF includes stains; aerobic and anaerobic cultures for bacteria, fungi, virus, and tuberculosis; serologic testing; and viral and bacterial screen by PCR.

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Introduction

The analysis of the cerebrospinal fluid (CSF) is essential in the diagnosis of the infectious diseases of the central nervous system (CNS). To this end, it is necessary to become familiar with the normal composition of the CSF as well as with the different CSF profiles that may indicate not only the location of infection (encephalitis vs. meningitis) but also the organism implicated.

The analysis of the CSF is also helpful in the differential diagnosis of other conditions that simulate an infection, such as inflammatory processes, subarachnoid hemorrhage, or cancer. CSF analysis is irreplaceable in the diagnosis and monitoring of the effects of antibiotic therapy.

The term meningitis refers to an infection limited to the subarachnoid space. When the infection crosses the pial cell lining and spreads through the perivascular spaces of Virchow-Robin to the brain parenchyma, the term meningoencephalitis is used [1, 2].

Anatomy and Physiology of the CSF

The CSF occupies the ventricles and subarachnoid spaces. The subarachnoid space separates the arachnoid membrane from the pia mater, and this space also contains vessels that enter or leave the CNS. The CSF is mainly formed by the choroid plexuses of the lateral, III, and IV ventricles, at a rate of production of 0.35 mL/min or about 500 mL/day. The total volume of the CSF in adults is 150 ml and is renewed four to five times daily. Infants and children have lower amounts, ranging from 30 to 60 ml in the neonate to 100 in adolescents. The CSF also comes from the water produced by oxidative metabolism and from an ultrafiltrate through the blood-brain barrier of the cerebral capillaries [2]. At both sites, the choroid plexuses and cerebral capillaries, the Na+/K + −ATPase pump creates an osmotic gradient that pulls water from the blood. The blood-brain barrier (BBB) includes the apical surface of the choroid plexuses, the cerebral endothelial cells, and the arachnoid. On each side of the BBB, continuous tight junctions seal the paracellular pathway and restrict the transport of substances between the brain and the outer space. Thus, the BBB impedes entry from the blood to brain of virtually all molecules, except those that are small and lipophilic or those that enter the brain through an active transport mechanism, such as essential nutrients, cofactors, or precursors [1]. The failure of some of these mechanisms explains the low glucose level in CSF in bacterial meningitis. Multiple causes of BBB breakdown are operative in CNS infections,

including the release of reactive oxygen species and inflammatory cytokines that increase the BBB permeability and facilitate the entry of toxins and chemokines which contribute to neuronal dysfunction [3].

The CSF circulates downward from the point of production in the lateral ventricles following a descending pressure gradient. It exits the ventricles through the foramina of Monro to the III ventricle and through the median foramen of Magendie and the lateral foramina of Luschka to the IV ventricle, perimedullary space, and ambiens cisterna. After exiting the foramina of the IV ventricle, the CSF enters the subarachnoid space, and from there it flows downward around the spinal cord and to the lateral and superior surface of the brain toward the superior sagittal sinus, where it is reabsorbed.

Some of the CSF is reabsorbed by the ependymal lining the lateral ventricles, but most is reabsorbed by the arachnoid granulations toward the venous system. Granulations are more common on the superior surface of the brain hemispheres, and when large are known as Pacchionian granulations, located along the superior sagittal sinus. They are also present in the basal cisterns and along the spinal roots. At the spinal level, drainage takes place at the root sleeves, where the pia and arachnoid fuse with the connective tissue of the spinal nerves. Arachnoid granulations protrude through the dura into the superior sagittal sinus and act as one-way valves. As CSF pressure increases, more fluid is absorbed. When CSF pressure falls below a threshold value, the absorption of CSF ceases so that CSF pressure remains constant [4].

Cells and CSF are transported across the arachnoid villi within vesicles, which may become obstructed by bacteria during meningitis or by red blood cells during bleeding, thus resulting in hydrocephalus.

The main CSF function is mechanical, protecting the brain from acute or sudden changes in pressure. The CSF provides a flotation layer around the brain and spinal cord that protects them from trauma. Since there is no classical lymphatic drainage system in the CNS, the CSF permits the degradation of cerebral metabolism products such as CO_2, lactate, and hydrogen. However, this long-held belief is now on debate as some authors searching for the mechanisms governing the entrance and exit of immune cells from the CNS in mice discovered functional lymphatic vessels lining the dural sinuses connected to the deep cervical lymph nodes. This discovery may change concepts on the pathogenesis of neuroinflammatory or infectious diseases of the CNS [5]. The CSF aids in regulating the pH and electrolyte balance of the extracellular space of the CNS and permits the circulation of electrolytes, neurotransmitters, hormones, antibodies, etc. [6].

Other CSF functions include getting rid of metabolic by-products linked to the biological activity of the CNS. Recent work demonstrates that sleep contributes to this function, since tracer molecules injected into the CSF of mice are cleared twice as fast when the mice are sleeping or anesthetized as compared to their awakened state [7].

The mechanisms whereby microorganisms cross the blood-brain barrier to gain access to the CNS are incompletely understood but involve the attachment of specific bacterial surface components to endothelial cells.

When an organism invades the CNS, an inflammatory response is initiated in the meninges, and there is a secondary release of cytokines and chemokines. Cytokines,

including tumor necrosis factor-α and interkleukin-6, are elevated in the CSF of patients with bacterial meningitis and contribute to secondary tissue damage. In a similar manner, proteases and free radicals attack brain capillaries, the components of the blood-brain barrier.

In bacterial meningitis, matrix metalloproteinases (MMPs) increase considerably and contribute to the severity of the infection. Steroids and some antibiotics (e.g., doxycycline) suppress the expression of MMPs and have a beneficial effect in reducing inflammation and thus the course of the meningeal infection. Pneumococcal meningitis is associated with significantly higher CSF concentrations of IFN-γ and of MMPs 9 and is associated with a higher case fatality rate than meningitis caused by *N. meningitidis* or *H. influenzae* [8].

Cerebrospinal Fluid Examination: The Lumbar Puncture

The LP to obtain CSF is not without risks and requires knowledge of the indications and contraindications, the pertinent anatomy, and the methods to minimize the risk of complications which, although rare, can be serious [9]. LP remains the gold standard procedure for CNS infections. Other indications are detailed in Table 1.1.

Table 1.1 Indications, contraindications, and complications of lumbar puncture

Indications	Contraindications	Complications	CT scan before LP in suspected meningitis patients
Diagnosis of CNS infection	Lumbar skin infection	Transtentorial brain herniation	>60 years old
Antibiotic therapy monitoring	Severe bleeding disorders	Headache and post-puncture syndrome	Immunocompromised
Subarachnoid bleeding diagnosis	Posterior fossa or cervical cord mass	Back pain	Known CNS lesion
Diagnosis of neoplastic CNS invasion	Increased intracranial pressure other than pseudotumor cerebri: Midline shift, loss of cerebellar, suprachiasmatic, or quadrigeminal plate cisterns	Spinal bleeding	Abnormal level of consciousness
Pseudotumor cerebri diagnosis (pressure measurement)		Cranial nerve palsies	Focal findings on exam
Inflammatory or demyelinating CNS diseases (protein evaluation)		Iatrogenic infection	Seizure within 1 week of presentation
Intrathecal chemotherapy administration or anesthesia			
Obtain biomarkers that correlate with neurodegenerative diseases			

Lumbar Puncture Technique

A video describing the procedure is available in reference [9].

It should be performed in aseptic conditions to avoid iatrogenic infection of the subarachnoid space from the patient's skin flora or from the operator's oropharynx flora. Wearing sterile gloves is required, and wearing a chirurgical mask is optimal.

The patient should assume a lateral recumbent position, with the head, spine, and extremities flexed, adopting a fetal position, so that the distance between the dorsal processes and lamina of adjacent vertebrae increases, making it easier to insert the needle. The recumbent position allows proper CSF opening pressure evaluation, unlike the sitting position that makes pressure measurement unreliable, although allows a better identification of the spinous processes (Fig. 1.1). The lumbar spine should be perpendicular to the table with the patient in the sitting position and parallel to the table with the patient in the lateral recumbent position.

The lower lumbar area should be cleaned with povidone-iodine, chlorhexidine, or 70% alcohol applied in widening concentric circles, and a sterile drape should be

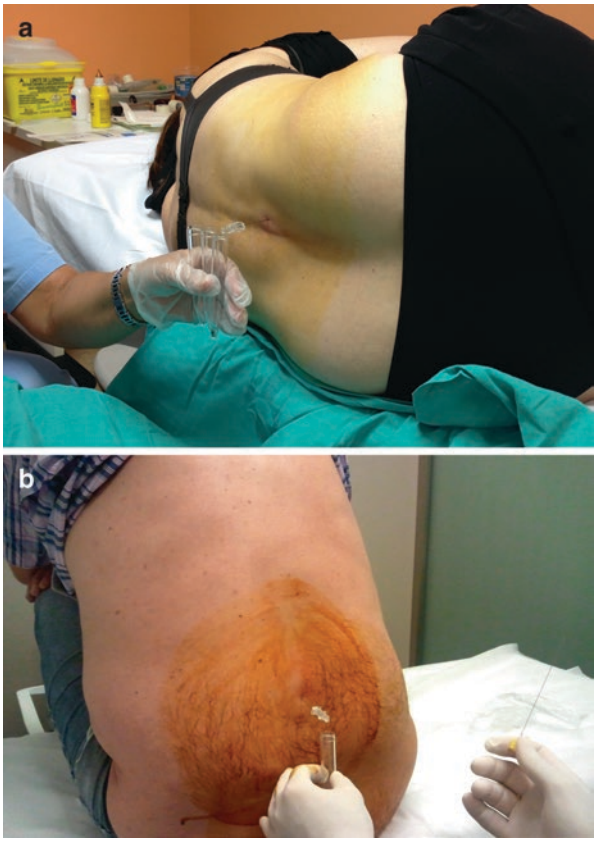

Fig. 1.1 Lateral recumbent (**a**) and sitting positioning (**b**) for lumbar puncture

applied. Local anesthesia with 1% lidocaine at the insertion point facilitates the patient's relaxation and makes the procedure easier and painless.

The needle should be in the vertebral interspace between L3 and L4 or L4 and L5, because these points are below the termination of the spinal cord (usually at L2 level in adults, lower in children). As a reference, the line between the superior aspects of the iliac crests intersects the midline at the L4 spinous process.

Small caliber (20 or 22 gauge) needles are preferred, since they are associated with less post-puncture headache. For the same reason, the American Academy of Neurology endorses the use of atraumatic needles (22-G Sprotte) instead of the more commonly used cutting needle (20-G Quincke) [10].

The needle should be inserted with the bevel parallel to the long axis of the spine, thus separating the fibers of the dura without transecting them and reducing the leakage of the CSF. The needle should be directed cephalad to parallel the slant of the dorsal spine of the vertebrae. When the needle enters the subarachnoid space from the dura, a slight "pop" is felt. Sometimes the needle comes up against the bone (usually spinous processes or lamina of the vertebrae); in that case, it should be retired and reintroduced following a nearby trajectory. To arrive into the subarachnoid space, the needle goes through the skin, subcutaneous fat, supraspinosus ligament, interspinosus ligament, yellow ligament, epidural fat, dura mater, and finally the arachnoid. Occasionally, the CSF flow stops due to (a) displacement of the tip of the needle or incomplete penetration, (b) a nerve root has fallen over the level of the needle, and (c) a blood clot is deposited in the needle lumen [11].

For diagnostic purposes, approximately 10–15 ml of CSF should be withdrawn from adults and 3–5 ml in neonates or children. For the diagnosis of a CNS infection, it is recommended to obtain three or four tubes to be sent for biochemical, microbiological, and pathologic examination.

The first obtained tube should contain at least 2 ml (40 drops) and should be sent to the biochemical laboratory. Simultaneous blood glucose levels should be measured. The second tube should be sent to the microbiological laboratory; if an uncommon infection is suspected, this tube should contain a great volume of CSF (10 ml) and often will require additional samples in different days. The last tube should go to the pathology laboratory for cellular analysis and must be processed straightaway as cells are degraded quickly after the LP.

Currently, the development of a checklist for LP to avoid unnecessary risks and make the technique safer is being validated [12].

Lumbar Puncture Contraindications (Table 1.1)

LP should be avoided in patients with evidence of brain herniation or increased intracranial pressure, with progressive headache, or with suspicion of a mass lesion of the CNS. In those cases, CSF removal may result in pressure changes that will displace downward the cerebellar amygdala with the ensuing brain herniation, coma, and death. Although brain herniation as a consequence of LP is a greatly feared event, its occurrence, even in patients with papilledema and intracranial

hypertension, is quite low. The quoted incidence of herniation in patients with acute bacterial meningitis is 5% [13]. Neuroimaging before LP is commonly recommended in patients with papilledema, suspected intracranial hypertension, and depressed level of consciousness [14]. See Table 1.1. It should be remembered that LP should never delay potentially lifesaving interventions, such as the administration of antimicrobial therapy if CNS infection is suspected.

Coagulopathies represent a relative contraindication for an LP and can be complicated by spinal bleeding (subarachnoid, subdural, or epidural) at the point of insertion. When platelet count is <50,000/μl, many experts recommend platelet transfusion.

Anticoagulation should be reversed before LP, and administration of anticoagulants should be delayed by at least 1 h after LP. With heparin therapy protamine should be administrated, and if the patient is on warfarin, frozen plasma and vitamin K should be injected before the LP to minimize the bleeding risk [15].

Relative contraindications are also the presence of a cervical cord lesion, where CSF removal could result in cord shifting against the lesion with quadriplegia, and skin infection of the lumbar area.

Lumbar Puncture Complications

The most frequent complications after an LP are post-LP headache and post-LP low CSF volume syndrome, bleeding on the point of puncture, cranial nerve palsies (the commonest is the cranial nerve VI), and back and radicular pain. Other, less frequent complications are the transtentorial or transforaminal herniation of the brain and iatrogenic infection. Factors that acutely lower CSF pressure, e.g., seated positioning or extracting very high volumes of CSF, may be associated with post-LP headache, although collection of up to 30 mL of CSF appears to be well tolerated and safe [16]. It is important to explain the procedures, benefits, risks, complications, and alternative options to the patient and obtain a signed informed consent prior to the LP.

Post-LP Headache

It occurs in one-fourth of patients, lasts between 2 and 8 days, and is likely due to a persistent CSF leakage through the dural puncture site that exceeds the rate of CSF production and leads to CSF hypotension. This causes the brain to sink down with traction on pain-sensitive structures such as the dura, cranial and upper cervical nerves, and bridging veins [17].

The incidence of post-LP headache seems higher in women; in patients with low body mass indices; in young adults, particularly those between 18 and 30 years; and in individuals with chronic or recurrent headache. While the reasons are unclear, it seems that the increased incidence in young adults may relate to a more elastic dura that prevents the hole from sealing quickly. Patients with purulent meningitis are at less risk of developing a post-LP headache, probably because the inflammatory

reaction seals the dura mater hole, thus preventing the leaking of CSF. Headaches are typically bilateral and their cardinal feature is that they are positional: they occur in the upright position and are relieved by recumbence. They are generally severe enough to incapacitate the patient, often throbbing, worsened by coughing, and associated with nausea and tinnitus [18].

The incidence of post-LP headache is decreased by using small-bore needles (20 or 22 gauge), performing only one puncture, and by placing the bevel of the needle parallel to the long axis of the spine [19].

Most headaches resolve spontaneously in 1 week. Bed rest, forced hydration, caffeine, and nonsteroidal anti-inflammatory agents are used but are of questionable benefit [20]. When all these measures fail, a blood patch may be in order. It consists of an epidural injection of 15–20 mL of autologous blood at the puncture site. Presumably this maneuver produces an inflammatory reaction that seals the dural wound [21].

In some cases in addition to the post-LP headache, a low CSF volume syndrome is present; patients experience vertigo, tinnitus, nausea, and vomiting. The symptoms occur because of a loss of flotation, allowing the cerebrum to descend onto the brain stem. Traction on the cortical veins occurs, and rupture of stretched bridging veins can lead to a subdural hematoma or subarachnoid hemorrhage [22]. An MRI or CT scan would be necessary to diagnose this complication and occasionally surgery is required.

Brain MRI often reveals meningeal enhancement in these patients. The reason for this is unclear [23].

Infection After Lumbar Puncture

Streptococcus viridans are the most common cause of LP-related meningitis, particularly *S. salivarius*. Less common organisms include *Staphylococcus* species, *Pseudomonas* species, and *E. coli* [17]. Meningitis after a diagnostic LP is very rare, with an estimated frequency of 1/20,000 after spinal anesthesia [24]. The possible causes of post-LP bacterial meningitis include contamination of the instruments or the field by the oropharyngeal flora of the operator (clusters of meningitis have been associated with the same operator) [25], incomplete disinfection of the skin, contaminated instruments, or contamination of injected material in the case of spinal anesthesia. The latter possibility seems less likely in current medical practice with the use of commercially prepared trays and single-use vials; nevertheless, an outbreak of neutrophilic fungal meningitis has been reported recently after injection of intra-articular contaminated methylprednisolone [26].

Cranial Nerve Palsies

They occur as a consequence of low CSF pressure and traction on the cranial nerves. Diplopia due to sixth nerve palsy, decreased hearing, tinnitus, and a plugged or blocked sensation in the ears are the most frequent complaints [27].

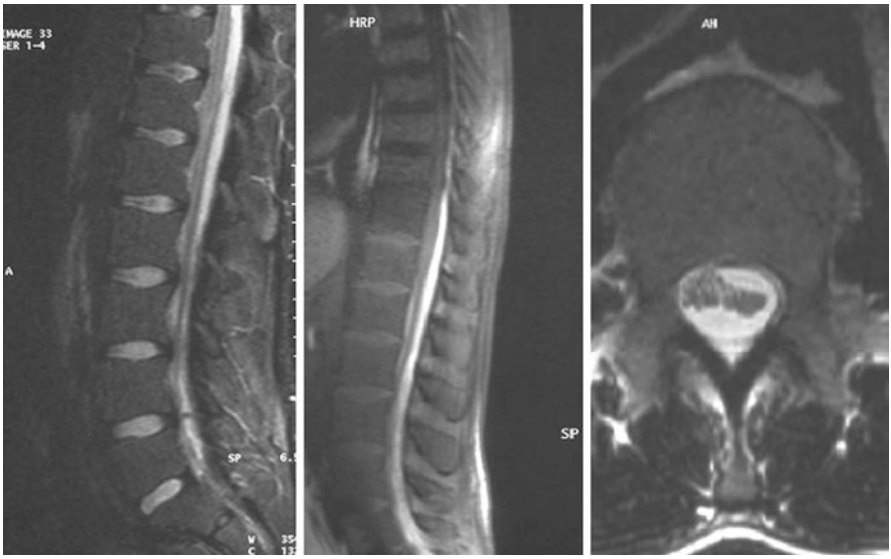

Fig. 1.2 Sagittal T1- (*left panel*) and T2-weighted MRI (*middle panel*) showing a hematoma extending from T10 to S2 vertebral bodies, most prominent at L1–L3 level, and displacing laterally the lumbosacral roots and the conus medullaris (*right panel*, axial view)

Local Bleeding

After a so-called bloody tap, epidural, subdural, or subarachnoid bleeding at the point of puncture may occur [28]. A spinal hematoma may produce progressive radicular pain and represent a neurosurgical emergency. Figure 1.2 shows a patient without coagulation disorders or any other predisposing factors that developed a spinal cord hematoma following a diagnostic LP.

Back Pain

Back pain is due to local trauma and occurs in up to 35% of patients. Rarely, the needle is inserted too far anteriorly and punctures the annulus fibrosis, resulting in disk herniation.

Spinal Epidural CSF Collection

Extensive dissection of CSF in the epidural space can occur after puncture of the dura from extravasation from the thecal sac and may spontaneously resolve in a few days [29].

Characteristic and Composition of the CSF

Pressure

CSF pressure is measured in recumbent position by attaching a manometer to the needle inserted into the subarachnoid space. The normal CSF pressure in adults is 80–180 mm of water and up to 250 mm of water for obese individuals. If the patient is seated, the pressure may increase to 300 mm of water. Children's normal pressure is 10–100 mm of water.

Disposable manometers measuring the CSF pressure in cm of water are available. Normal values in adult are between 7 and 20 cm.

With the needle properly placed in the subarachnoid space, the CSF pressure fluctuates with breath and pulse. Applying pressure on the cervical veins should increase the CSF pressure up to 200 mm of water (Queckenstedt's maneuver). A lack of pressure increase indicates a block in the CSF circulation. Low CSF pressure may occur with dehydration or in the presence of a CSF fistula [1].

Components of the CSF

The CSF contains ions, oxygen, sugars (glucose, fructose), lactate, proteins (albumin and globulins), amino acids, urea, ammonia, creatinine, lipids, neurotransmitters and its metabolites, hormones (insulin, gastrin), and vitamins. The regulation of these components is not known, but some of these substances are transported into the CSF by active diffusion and by a proteolytic transporter [4].

Macroscopic Appearance of the CSF

The normal CSF appears sparkling clear; any change in this characteristic is pathologic. The color may vary from red (erythrochromia) when there are >1000 red blood cells per mm^3 to yellow (xanthochromia) if there is >150 mg/100 ml of proteins and to cloudy if there is an increased number of white blood cells, usually >300 polynuclear cells per mm^3, or >500 lymphocytes per mm^3. Some drugs such as rifampin may produce a reddish coloration of the CSF [30].

A traumatic tap is frequent and misleads the results of CSF analysis and is difficult to distinguish from a true hemorrhage. Comparing the redness of three subsequent CSF tubes (the three-tube test) may be helpful, since blood from a traumatic tap tends to clear in successive tubes. In contrast, in hemorrhages prior to the tap, blood mixes freely with the CSF and all the tubes display the same color.

When white blood cells (WBC) are present in the CSF of a traumatic tap, it must be decided whether these cells were introduced in the subarachnoid space by the spinal tap or they represent a real pleocytosis in a patient with meningitis. In an individual with a normal blood formula, 1 WBC per mm^3 for every 700 red blood cell (RBC) per mm^3 is subtracted. As an example, having 20 leukocytes with 14,000 RBCs in the CSF is considered normal and not an indication of meningitis.

Microbiological analysis of a bloody tap is unreliable, and therefore it is advisable to repeat the LP at a superior vertebral interspace or 48 h later. If the patient has significant anemia or leukocytosis, the following formula should be employed to accurately determine the true number of leukocytes in the CSF: CSF WBC = blood WBC × CSF RBC/blood RBC. To complicate the clinical decision, the presence of blood in the subarachnoid space produces a secondary inflammatory response that leads to a disproportionate increase in the number of WBCs, particularly 48 h after onset [15].

Microscopic Composition of the CSF

Cells

The normal total CSF leukocyte counts are <20/mm^3 for preterm infants, <15/mm^3 at 4–8 weeks, and no more than 5/mm^3 in older infants and adults. While cells in the CSF of adults are monocytic, polynuclears predominate (60%) in newborns.

Normal CSF does not contain polynuclears, eosinophils, plasma cells, or red blood cells but may contain ependymal cells [6].

The normal total protein level of CSF ranges between 15 and 50 mg/dl.

Protein values are lower in the ventricles and cisterns than in the lumbar space.

Proteins

An elevated protein level is a nonspecific finding reflecting a pathologic increase in blood-brain barrier permeability, which occurs in many inflammatory, infectious, or neoplastic diseases, or with CSF blocks.

In acute bacterial meningitis, there is a brisk inflammatory response with protein level increasing up to 100–500 mg/dl. Proteins are moderately elevated in viral meningitis, usually <100 mg/dl (Table 1.2). To correct the CSF protein value in the presence of blood (bloody tap), subtract 1 mg for every 1000 RBC; thus, if the red cell count on a CSF sample is 20.000 per mm^3 and the total protein is 120 mg/dl, the corrected protein level would be 100 mg per dl.

Although many proteins could be measured in the CSF, only an increase in immunoglobulins bears diagnostic importance. Such an increase is indicative of an

Table 1.2 Normal CSF values and tests for diagnosis

Test	Normal value
Cells	0–5 cells/μl (lymphocytes)
Glucose	40 mg/dl
	60% of serum glucose
Proteins	
Lumbar	15–45 mg/dl
Cisternal	10–25 mg/dl
Ventricular	6–15 mg/dl
Gamma globulins	6–13% of total CSF proteins
IgG	<8.4 mg/dl
IgM	37–374 ng/ml
IgG index	<0.77
Oligoclonal bands	0–1

infectious or inflammatory CNS disorder. Most CSF immunoglobulins are derived from plasma, and only a small fraction is synthesized intrathecally. Their CSF concentration is <40 mg/L.

Immunoglobulin increase in CSF may be due to an increase in plasma, a blood-brain barrier impairment, or because an increase in intrathecal synthesis, which is the case of a chronic infection of the CNS. The integrity of the blood-brain barrier permeability is confirmed by a normal albumin index.

To verify if high immunoglobulin values correspond to intrathecal synthesis or they correspond to a blood-brain barrier leakage, the CSF IgG index is calculated. The normal CSF IgG index value is 0.65 and is calculated by the formula IgG (CSF) × albumin (serum)/IgG (serum) × albumin (CSF).

Isoelectric focusing allows the detection of CSF oligoclonal bands. The presence of ≥2 oligoclonal bands in the CSF that are absent in serum suggests intrathecal IgG synthesis. They are present in inflammatory CNS disorders, i.e., multiple sclerosis, and in chronic infections.

Glucose

Glucose CSF concentration depends on serum glucose level, the carrier system that transfers glucose between blood and CSF, and the rate of glucose metabolism by various cellular elements of the CSF. Normal CSF concentration is between 45 and 80 mg/dl, approximately 60% of the serum glucose level [31]. Values <40 mg/dl are always pathological, regardless of serum values. Hypoglycorrhachia may be caused by bacterial, fungal, or tuberculous meningitis and less often by viral infections, particularly mumps [32], and is the result of glycolysis of the CSF white cells and the pathogen and impaired glucose transport. Noninfectious conditions, such as carcinomatous meningitis, subarachnoid hemorrhage, and hypoglycemia, also result in low glucose levels.

An isolated low glucose level in the CSF (i.e., normal cell count, proteins, and lactate) is highly suggestive of a genetic metabolic disorder known as a glucose transporter type 1 deficiency syndrome (GLUT1DS), in which glucose transport into the brain is disturbed [33]. It can be associated with epilepsy and movement disorders and requires specific diets.

A serum glucose determination should be obtained at the time of LP. Normal CSF values are summarized in Table 1.2.

Identification of Infectious Agents in the Cerebrospinal Fluid (Table 1.3)

Microbiological CSF analysis includes stains, aerobic and anaerobic cultures, serologic testing, nucleic acid amplification by polymerase chain reaction (PCR), bacterial antigen detection, and cryptococcal surface antigen detection [6, 11].

Table 1.3 CSF findings in meningitis

	Pressure	Leukocytes (per µl)	Proteins (mg/dl)	Glucose (mg/dl)
Acute bacterial	Increased	>100 (mostly PMNs)	Increased (100–500)	Decreased (<40 or <60% of serum value)
Viral	Normal to moderately increased	Five to few hundreds (lymphocytes; PMNs may predominate initially)	Mild increase (<100)	Normal Reduced in 25% of cases of mumps and herpes simplex virus infection
Fungal	Increased (particularly with *Cryptococcus*)	0–800; mostly lymphocytes, rarely PMNs	Increased (20–500)	Decreased in most cases
Parasitic	Usually elevated. Low if dynamic block[a]	Increased mononuclear and PMNs with eosinophilia in 50% of cases	Increased (50–200)	Decreased in 20% of cases
Tumor	Normal or elevated	None to hundreds of mononuclear and malignant cells	Increased	Decreased in 75% cases of carcinomatous meningitis
Tuberculous	Usually elevated may be low if dynamic block of CSF[a]	Rarely >500, mostly lymphocytes but PMNs the first days	Increased, 100–200 much higher if dynamic block of CSF	Decreased in 75% of cases

PMNs polymorphonuclear cells
[a]Block: Due to inflammatory response in basal meninges, the CSF does not circulate properly and the pressure at lumbar levels is low

The use of PCR has revolutionized the diagnosis of CNS infection and allows for a demonstration of certain organisms regardless of prior antibiotic therapy.

PCR amplifies by at least one millionfold the abundance of defined microorganism nucleic acid present in the specimen. Its sensitivity and specificity for a specific organism are critical in correctly integrating the results. Negative results do not fully exclude infection and often depend on the timing of the spinal tap, as well as on the presence of bloody CSF [34].

Flow cytometry examination of the CSF represents a quantitative assay that identifies small cell populations with aberrant phenotypes and separates a few neoplastic cells within a population of normal lymphocytes. This technique may be useful for distinguishing between neoplastic and infectious meningitis [35].

CSF Profile in the Commonest Meningitis (Table 1.3)

Bacterial Meningitis

Classical CSF abnormalities include an increased opening pressure, the presence of polymorphonuclear pleocytosis (>100–500 WBCs/mm^3 in 90% of patients), decreased glucose (<40 mg/dl), and increased proteins (>45 mg/dl in 90% of patients).

Prior therapy with oral antibiotics will not alter the cell count or glucose concentration but will decrease the likelihood of identifying the organism. Gram staining identifies the pathogen in 60–90% of patients and relies on the CSF concentration of bacteria.

The commonest organisms of community-acquired meningitis may be detected by latex particle agglutination in the CSF, and their availability should be consulted with the laboratory. If the infecting organism is sensitive to the antibiotic prescribed, Gram and cultures should be negative in 24 h. CSF glucose concentration returns to normal in 3 days [11].

Viral Meningitis

With viral infections opening pressure is usually normal, and there is a lymphocytic pleocytosis with normal glucose concentration and normal to moderately increased proteins.

Enteroviruses (coxsackieviruses, echoviruses, and enteroviruses 68–71) are the most common, followed by herpesviruses, human immunodeficiency virus, and arthropod-borne viruses.

Distinguishing between bacterial and viral meningitis may be difficult, particularly in patients with CSF abnormalities classic for bacterial meningitis but in whom the CSF Gram stain and culture are negative.

CSF lactate levels are nonspecific and can be elevated in both conditions. Increased serum procalcitonin levels is more consistent with bacterial meningitis but has not been universally adopted.

Fungal Meningitis

Fungal infections usually show normal or slightly elevated opening pressure (cryptococcal meningitis is notorious for significant pressure increase), lymphocytic pleocytosis (20–500 cells/mm^3), decreased glucose concentration, and elevated protein concentration. Aspergillus and related fungi result in neutrophilic meningitis. CSF should be sent for India ink and specific fungal culture. The cryptococcal antigen test is quite sensitive (90%) and specific. When fungal meningitis is suspected, large volumes of CSF are needed to increase the yield.

Tuberculous Meningitis

The CSF shows an increased opening pressure, lymphocytic pleocytosis (10–500 cells/mm^3), decreased glucose concentration, and elevated protein concentrations (100–500 mg/dl). Adenosine deaminase levels, an enzyme associated with disorders that induce cell-mediated responses, are increased in the CSF although false positives and negatives do occur in other infectious and neoplastic CNS disorders [36, 37].

The combination of chronic CSF lymphocytic (more than 4 weeks) pleocytosis or a persistent CSF neutrophilic pleocytosis with decreased glucose levels should raise the suspicion of TB meningitis.

Once specific therapy has begun, a so-called therapeutic paradox may occur and is characterized by clinical worsening and by a shift of the CSF lymphocytic pleocytosis into a polymorphonuclear response. It must not be interpreted as a failure in treatment [38]. CSF cultures are positive in 50–75% but require 3–6 weeks. PCR is available but, at present, has insufficient sensitivity [39] and has not been properly standardized among different laboratories.

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Acute Community-Acquired Bacterial Meningitis

2

Adarsh Bhimraj

Abstract

Community-acquired bacterial meningitis is a significant cause of morbidity and mortality. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causative organisms. The incidence of *Listeria monocytogenes* infection increases over age 50 years and in those with compromised cell-mediated immunity. Symptoms and signs are not sensitive or specific enough to diagnose community-acquired bacterial meningitis. A lumbar puncture for cerebrospinal fluid is needed to reach the diagnosis, to identify the organism, and to determine antimicrobial susceptibilities. Computed tomography of the head is not necessary in all patients prior to a lumbar puncture, only in immunocompromised patients and in those who have features suggestive of or who are at risk of increased intracranial pressure. Appropriate empiric antimicrobials should be started as soon as possible.

Keywords

Meningitis • Acute meningitis • Community-acquired bacterial meningitis Central nervous system infection • *Streptococcus pneumoniae* • *Neisseria meningitidis* • *Listeria monocytogenes* • Kernig's sign • Brudzinski's sign • Jolt accentuation • Neck stiffness • CSF pleocytosis

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Introduction and Epidemiology

Rapid diagnosis and management of acute community-acquired bacterial meningitis (ACBM) is important as delayed treatment has a poor prognosis. Meningitis is inflammation of the pia and arachnoid (the inner two layers of the meninges). Acute community-acquired meningitis can develop within hours to days and is usually viral or bacterial. Viral meningitis usually has a good prognosis, whereas bacterial meningitis is associated with significant rates of morbidity and death, so it is critical to recognize and differentiate them promptly. Meningitis from fungi and mycobacteria, especially tuberculosis, can rarely present acutely, but generally tend to be subacute to chronic (weeks to months), and occurs in patients with specific risk factors for those diseases. Fungal and mycobacterial meningitis should be considered under those circumstances, but their discussion is beyond the scope of this chapter.

The incidence, mortality, and morbidity, from ACBM, have decreased significantly, especially in high-income countries, probably as a result of vaccination and better antimicrobial and adjuvant therapy, but the disease still has a high toll. Still, in the United States, mortality remains at 10–20% [1, 2]. In the developing world, the mortality rates are as high as 50% [2]. In the United States, meningitis from all causes accounts for about 72,000 hospitalizations and up to $1.2 billion in hospital costs annually [3]. However, the incidence of bacterial meningitis has declined from 3 to 5 per 100,000 per year a few decades ago to 1.3–2 per 100,000 per year [1]. In the early 1900s in the United States, the death rate from bacterial meningitis was 80–100%. The use of intrathecal equine meningococcal antiserum during the first decades of the 1900s dramatically reduced the rate of death from meningococcal meningitis. With the advent of antimicrobial drugs in the 1930s and 1940s, the death rate from bacterial meningitis further declined [1].

The organisms that cause community-acquired bacterial meningitis differ somewhat by geographic region and by age. Surveillance data in the United States, from 1998 to 2007, show that the most common cause among adults is *Streptococcus pneumoniae*. Among young adults, *Neisseria meningitidis* is nearly as common as *S. pneumoniae*. The incidence of *Listeria* infections increases with age in adults [1]. The relative incidence of these organisms is similar in Europe and in most high-income countries [4].

The epidemiology of the disease also has changed in the last few decades due to the introduction of the conjugated vaccines against *H. influenzae* type b, *N. meningitidis* serogroup C, and 7-, 10- and 13-valent pneumococcal conjugate vaccines [5]. The most dramatic effect was after the introduction of the vaccines against *H. influenzae.* In 1986, about half the cases of acute bacterial meningitis were caused by *H. influenzae*, but a decade later, the incidence was reduced by 94% [3].

Pathogenesis

Most cases of CABM begin with colonization of the mucosal surface of the upper respiratory tract. In certain individuals, this leads to mucosal invasion and bacteremia. Not all organisms that cause bacteremia are capable of breaching the

blood-cerebrospinal fluid barrier to enter the subarachnoid space to cause meningitis. Very few organisms have this capacity, but *Haemophilus influenzae*, *N. meningitidis*, and *S. pneumoniae*, especially those strains that have a capsule, do [6]. Some patients are at higher risk of meningitis because of an abnormal communication between the nasopharynx and the subarachnoid space due to either trauma or a congenital anatomic abnormality. The organisms in these instances can directly spread from the nasopharynx to the meninges. Patients without a spleen or with an immunoglobulin deficiency are also more prone to infections from encapsulated organisms such as pneumococci and meningococci. The opsonizing immunoglobulins coat the capsule, helping phagocytes in the spleen to remove them from the bloodstream. A patient presenting with multiple episodes of bacterial meningitis merits evaluation for these conditions. In contrast, *Listeria* spp. and, rarely, Gram-negative bacteria enter the bloodstream through the gastrointestinal tract and then spread to the meninges.

Once in the subarachnoid space, bacteria elicit a profuse inflammatory response, which can be damaging [6]. The inflammation in the subarachnoid space can extend along the Virchow-Robin spaces surrounding the blood vessels deep into the brain parenchyma. This perivascular inflammation can cause thrombosis in both the arterial and venous circulations. This inflammation can lead to intracranial complications such as hydrocephalous from blocking the arachnoid villi, cerebral edema, and strokes from thrombosis or vasculopathy involving the arterial or venous circulations [6, 7].

Organisms and Organism-Specific Risk Factors

Streptococcus pneumoniae is the most common cause of ACBM [1, 8, 9]. It can also cause a concomitant upper respiratory tract infection, pneumonia, and rarely endocarditis. Though it can affect any immunocompetent adult, those who are at a higher risk of infection are people without a spleen or/and with a primary or secondary immunoglobulin deficiency, including patients with multiple myeloma or human immunodeficiency virus infection.

Neisseria meningitidis is more common in children and young adults [6, 10]. It is easily transmitted and is associated with crowding, as in school dormitories and military barracks. People with congenital deficiencies of components of complement are at greater risk for both meningococcal and gonococcal infections. Patients with recurrent episodes of *Neisseria* infection should be evaluated for complement deficiency. Meningococcal infection is more commonly associated with a rash. The most common rash of meningococcal meningitis is a very transient, maculopapular rash that appears early in the course of the disease. More pathognomonic is a petechial rash due to thrombocytopenia, which can very rapidly progress to purpura, ecchymosis, and disseminated intravascular coagulation. The petechial rash is evident in 60% of adults and up to 90% of children [11], and it is most likely to appear in dependent areas (such as the back of a patient lying down) and in areas of pressure, such as under the elastic band of underwear or stockings.

Listeria monocytogenes infection is usually acquired through contaminated food such as raw vegetables, unpasteurized milk, cheese, and deli meats. It spreads from the gastrointestinal tract to the bloodstream and then to the meninges. It is an intracellular pathogen; thus, people at greater risk are those with poor cell-mediated immunity due to immunosuppressant medications such as steroids or tumor necrosis factor inhibitors. The rate of *Listeria* meningitis starts to increase with age, especially after age 50, probably due to immune senescence or decreased immunity with age.

Aerobic Gram-negative enteric bacilli like *Escherichia coli* usually cause meningitis after head trauma or neurosurgery and are uncommon causes of community-acquired meningitis. Disseminated strongyloidiasis should be suspected in any patient with community-acquired meningitis caused by enteric Gram-negative bacilli. *Strongyloides stercoralis* is a parasitic intestinal roundworm that is found in the tropics, in the subtropics, and in certain parts of the United States and Europe. The adult worm lives in the intestines where it lays eggs; the larvae are excreted in the stool. A small percentage of larvae penetrate the perianal skin and gut mucosa to cause an autoinfection. People may asymptomatically harbor the parasite for decades and then develop hyperinfection syndrome with dissemination to various organs when treated with immunosuppressive drugs such as steroids. In this syndrome, a significant proportion of the larvae penetrate the gut mucosa to enter the bloodstream and travel throughout the body, including the brain, carrying Gram-negative bacteria with them. The mortality rate of untreated hyperinfection syndrome can be greater than 70% [12]; thus, it is important to identify and treat it in the context of Gram-negative bacillary meningitis.

Clinical Signs and Symptoms

The classic triad of acute meningitis is fever, neck stiffness, and altered mental status. Other symptoms that have been described are photophobia, headache, presence of a rash, nausea, and vomiting [13, 14]. Signs that have been described are Kernig's sign (inability to allow full knee extension when the hip is flexed to a 90° angle), Brudzinski's sign (spontaneous flexion of the hips during attempted passive flexion of the neck), and jolt accentuation test (performed by asking a patient with a headache to quickly move his or her head twice horizontally; the result is positive if the headache worsens). The pathophysiologic rationale for the symptoms and signs is pia-arachnoid inflammation, raised intracranial tension, and irritation of cranial and spinal nerves from the inflammation.

Only a few studies of the diagnostic accuracy of signs and symptoms of acute meningitis have been done. Fourteen retrospective studies examined this issue, but they were heterogeneous with respect to patient age, immunosuppression status, and clinical presentation, as well as to how meningitis was diagnosed (via culture or cerebrospinal fluid analysis), making the results difficult to interpret and reach a consensus [15]. Retrospective studies are more prone to bias, as they lack a control group, and examiner bias is more likely. Based on retrospective data, the combination of fever, neck stiffness, and altered mental status has a sensitivity of only 0.46 [15].

Four prospective studies examined symptoms and signs. Thomas et al. [16] evaluated 297 patients with clinically suspected meningitis. In a study by Uchihara and Tsukagoshi [17], a single examiner was used to evaluate patients presenting with fever and headache, with only 54 patients in this series. Waghdhare et al.'s study included 190 patients with suspected meningitis, where the examiners were blinded to the CSF analysis results [18]. Nakao et al.'s study was a prospective study in 230 patients presenting to two inner city ERs with suspected meningitis [19].

A symptom, sign, or a test's diagnostic accuracy can be assessed with sensitivity, specificity, and positive and negative likelihood ratios. A test with a low value for negative likelihood ration (preferably less than 0.1) is good for ruling out a disease and that with a high positive likelihood ratio (greater than 10) is good for inclusion of a disease. For the prospective studies that evaluated symptoms, the 95% confidence intervals (CIs) of the positive and negative likelihood ratios include the value 1 (a simple interpretation of that would be that the likelihood of finding these features is the same in patients with meningitis when compared with those without meningitis). Based on these prospective studies, the presence of nausea and vomiting, headache, or neck pain does not reliably rule in meningitis. Similarly, the absence of these does not rule it out.

The CIs of the positive and negative likelihood ratios for signs like those of the symptoms included the value 1 (see Table 2.1 for the exact values). Jolt accentuation looked promising in Uchihara and Tsukagoshi's study as a sensitive sign, but it did not perform that well in subsequent studies (see Table 2.1). In the physical

Table 2.1 Diagnostic accuracy of signs in acute meningitis

	Sensitivity (%)	Specificity (%)	Positive likelihood ratio (+LR)	Negative likelihood ratio (−LR)
Neck stiffness				
Thomas et al. [16]	30	68	0.94	1.02
Uchihara and Tsukagoshi [17]	14.7	100	6.6	0.83
Waghdhare et al. [18]	39.5	70.3	1.33	0.86
Nakao et al. [19]	13	80	0.6	1.1
Kernig's sign				
Thomas et al. [16]	5	95	0.97	1
Uchihara and Tsukagoshi [17]	8.8	100	4.2	0.92
Waghdhare et al. [18]	14.1	92.3	1.84	0.93
Nakao et al. [19]	2	97	0.8	1
Brudzinski's sign				
Thomas et al. [16]	5	95	0.97	1
Waghdhare et al. [18]	11.1	93.4	1.69	0.95
Nakao et al. [19]	2	98	1	1
Jolt accentuation				
Uchihara and Tsukagoshi [17]	97.1	60	2.4	0.05
Waghdhare et al. [18]	6.06	98.9	5.52	0.95
Nakao et al. [19]	21	82	1.2	1

examination, the presence or absence of fever, neck stiffness, Kernig's sign, Brudzinski's sign, or jolt accentuation could not reliably rule in or rule out acute meningitis. In summary, the history and physical examination are not sufficient to determine whether a patient has meningitis. If a patient is suspected of having meningitis, a lumbar puncture is needed.

Diagnostic Tests

Blood and CSF Cultures

Blood for cultures should be drawn before antimicrobial treatment is started [20–22]. Although they are positive only 19–70% of the time, they can help identify the pathogen and antimicrobial susceptibilities, especially when CSF cultures are negative [23–25]. Lumbar puncture for CSF studies is essential to make the diagnosis, to identify the organism and its susceptibility to various antibiotics. If lumbar puncture can be performed immediately, it should be done before starting antibiotics, to maximize the yield of cultures. Pediatric studies show that after starting antibiotics, complete sterilization of the cerebrospinal fluid can occur within 2 h for *N. meningitides* and within 4 h for *S. pneumoniae* [22]. However, starting antimicrobials should not be delayed if a lumbar puncture cannot be done expeditiously as such a delay can adversely affect the prognosis [26, 27].

CSF Molecular Diagnostics

Molecular diagnostic tests have the potential for rapid results, and there is now an FDA-approved commercially available test. The FilmArray Meningitis/Encephalitis (ME) Panel is a multiplexed in vitro diagnostic test for the simultaneous, rapid (~1-h) detection of 14 pathogens directly from CSF specimen including bacteria (*Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae)* [28]. However, there is limited published data on the diagnostic performance (sensitivity and specificity) for pathogens in adult bacterial meningitis.

Imaging

A computerized tomography of the brain is considered in the workup of acute meningitis as there are other mimicking conditions or complications of meningitis that can cause increased intracranial pressure and the possibility of brain herniation complicating a lumbar puncture. For ethical and practical reasons, it would be difficult to evaluate the need for a CT brain prior to LP in a randomized clinical trial. Hasbun et al. [29] performed a study to evaluate if any features on clinical

presentation can predict abnormal findings on CT of the head suggestive of elevated intracranial pressure and thus the risk of herniation. The study included 301 adults with suspected meningitis. It found that abnormal findings on CT were unlikely if all of the following features were absent at baseline:

- Immunocompromised state
- History of central nervous system disease (mass lesion, stroke, or a focal infection)
- New onset of seizure (≤1 week from presentation)
- Specific abnormal neurologic findings (e.g., an abnormal level of consciousness, inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, abnormal language)

The absence of these baseline features made it unlikely that CT brain would be abnormal (negative likelihood ratio 0.1, 95% CI 0.03–0.31) [29].

According to the guidelines from the Infectious Diseases Society of America (IDSA) [30], if none of those features is present, blood cultures and a lumbar puncture can be done immediately without performing a CT brain, followed by empiric antimicrobial therapy. If any of the features is present, blood cultures should be obtained first, and then empiric antimicrobial therapy started, followed by CT of the brain to look for contraindications to a lumbar puncture (Fig. 2.1 – modified from IDSA guidelines 1).

Lumber Puncture, CSF Cell Counts, Chemistry, and Gram Stain

These studies should be done stat, as they help determine whether bacterial meningitis is present and, if so, whether the cause is likely bacterial or viral. *The opening pressure* is elevated (usually > 180 mm H_2O) in acute bacterial meningitis. The diagnostic accuracies (likelihood ratios) of the CSF tests were analyzed in a systematic review by Straus et al. using a positive CSF culture as a reference standard [31].

CSF white blood cell count is raised and is predominantly neutrophilic, in acute bacterial meningitis. A CSF WBC count of 500/μL or higher increased the likelihood of meningitis (+ LR of 15; 95% CI, 10–22), and a count of less than 500/μL lowered the likelihood (−LR 0.3, 95% CI, 0.2–0.4) [31, 32].

CSF glucose level is lower in bacterial meningitis than in viral meningitis. Because the glucose levels in the CSF and the blood equilibrate, *the ratio of CSF glucose to serum glucose* has better diagnostic accuracy than the CSF glucose level alone. The equilibration takes place within a few hours, so the serum glucose level should be ordered at the same time lumbar puncture is done. The CSF/blood glucose ratio would be the preferred form which is a better predictor of bacterial meningitis than the CSF white blood cell count. Bacterial meningitis is likely if the ratio is

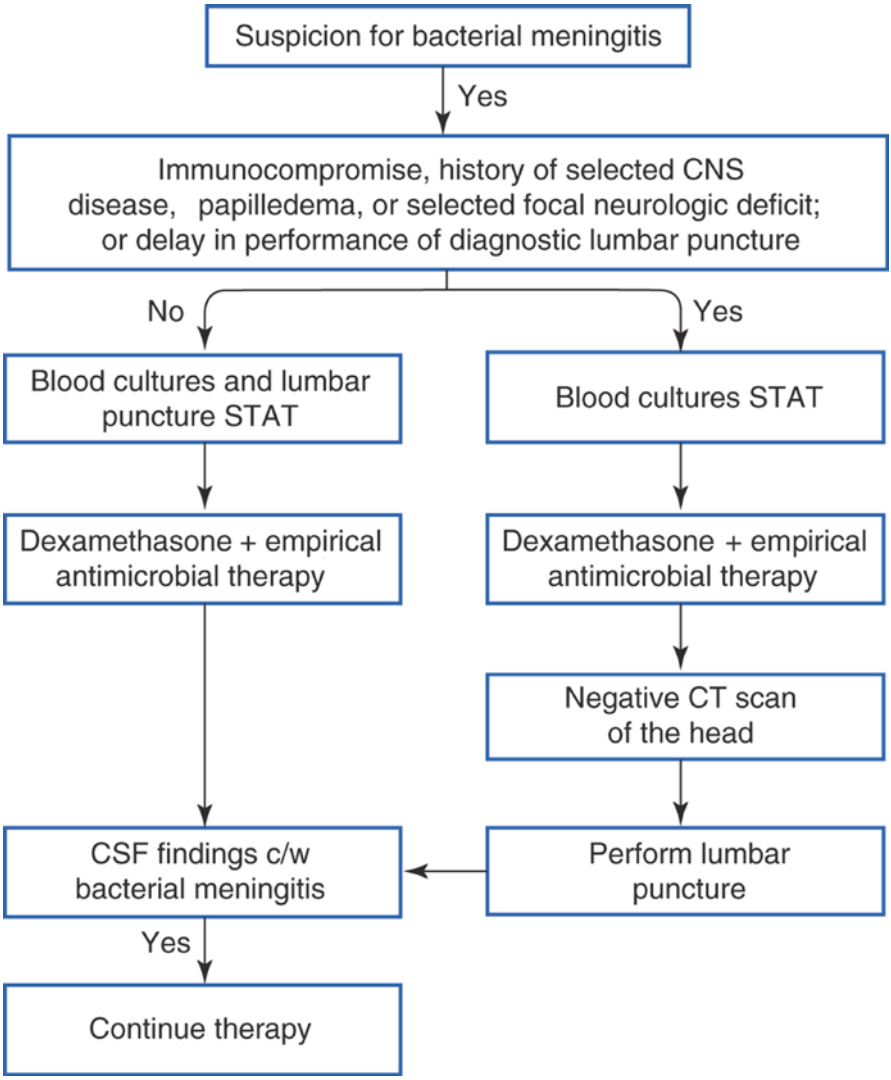

Fig. 2.1 Management algorithm for suspected bacterial meningitis (Adapted from Tunkel et al. [30])

lower than 0.4. A CSF/blood glucose ratio of 0.4 or less increased the likelihood of bacterial meningitis (+LR 18; CI, 12–27), but a normal value lowered the likelihood (−LR 0.31; 95% CI, 0.21–0.45) [31].

CSF lactate level is a good diagnostic test for evaluation of CABM. A CSF lactate level greater than 31.5 mg/dL (3.5 mmol/L) is predictive of meningitis (+LR 21; 95% CI, 14–32), and a value lower than that makes the diagnosis unlikely (−LR, 0.12; 95% CI, 0.07–0.23) [31].

CSF protein shows a mild to marked elevation in bacterial meningitis but is normal to elevated in viral meningitis and in a lot of other CNS diseases, so is of limited diagnostic value.

Gram stain of the cerebrospinal fluid can be done quickly. *S. pneumoniae* is a Gram-positive diplococcus, and *N. meningitidis* is a Gram-negative diplococcic. *Listeria* is a Gram-positive rod and *E. coli* is a Gram-negative rod. If no bacteria are seen, the information is not helpful in ruling out bacterial meningitis (−LR 0.14; 95% CI, 0.08–0.27). If it is positive, it is almost 100% specific for bacterial meningitis due to the organism seen (+LR 735; 95% CI, 230–2295) and so can identify the pathogen days before the culture results [31].

Management

Antimicrobial Therapy

Empiric antimicrobial therapy must be started as soon as feasible. Most studies of the timing of antimicrobial drugs are retrospective and even when prospective included a very heterogeneous population [26, 27, 33]. Proulx et al. [27] in a retrospective study found that if antibiotics were given within 6 h of the time the patient presented to the emergency department, the case fatality rate was only 5–6%. If treatment started 6–8 h after presentation, the death rate was 45%, and if it started from 8 to 10 h after presentation, the death rate was 75%. In a prospective, multicenter, observational study of 156 consecutive adults hospitalized for pneumococcal meningitis, an interval of greater than 3 h between hospital admission and administration of antibiotics was associated with an increase in 3-month mortality (odds ratio 14.12; 95% CI, 3.93–50.9) [26]. Most experts would agree that starting antimicrobials early would be beneficial in an emergency like acute bacterial meningitis.

CSF concentrations of most antimicrobial drugs are considerably less than in the serum due to poor penetration of the blood-CSF barrier. Thus, the dose for treating meningitis is usually higher than the regular dose. For example, for the treatment of pneumococcal pneumonia, ceftriaxone is used at a dose of 1 g every 24 h, but for pneumococcal meningitis, the dose is 2 g every 12 h.

Empiric treatment of community-acquired bacterial meningitis in immunocompetent adults up to 50 years of age consists of a third-generation cephalosporin such as cefotaxime 2 g intravenously every 4 h or ceftriaxone 2 g intravenously every 12 h, which covers most *S. pneumoniae* and *N. meningitides* strains [30]. The IDSA guidelines recommend adding vancomycin empirically in suspected *S. pneumoniae* meningitis when there are concerns about drug-resistant pneumococcal strains [30]. For vancomycin, 45–60 mg/kg intravenously per day divided into every-6-h or every-8-h doses would achieve better CSF concentrations [34]. In patients over age 50 or those with a cell-mediated immunodeficiency, empiric therapy should also include ampicillin 2 g intravenously every 4 h to cover *Listeria*. It is important to tailor therapy to the results of Gram stain, culture, and susceptibility as they become available.

Role of Corticosteroids

Glucocorticoids, especially dexamethasone, have been well studied as adjunctive therapies in bacterial meningitis. The rationale behind their use is that the profuse inflammatory response to the bacterial components in the CSF by itself has deleterious effects and steroids can reduce that.

In 2004, a Cochrane meta-analysis [35] of five randomized clinical trials, including 623 adults with bacterial meningitis, found a significant reduction in the death rate for patients who received steroids: the death rate was 12% in patients who received steroids versus 22% in those who did not (odds ratio 0.6; 95% CI 0.40–0.81). This led to an IDSA practice guideline recommendation that in adults with suspected or proven pneumococcal meningitis, dexamethasone would be beneficial [30]. But since then, many more studies have emerged from Europe, South America, Malawi, and Vietnam. Cochrane meta analyses [36, 37] including these studies with 4121 participants was published recently. In this analysis, corticosteroids were associated with a nonsignificant reduction in mortality (17.8% versus 19.9%; risk ratio (RR) 0.90, 95% CI 0.80–1.01). They also had lower rates of severe hearing loss (RR 0.67, 95% CI 0.51–0.88), any hearing loss (RR 0.74, 95% CI 0.63–0.87), and neurologic sequelae (RR 0.83, 95% CI 0.69–1.00). In subgroup analyses, steroids reduced mortality in *S. pneumonia* meningitis, but not in *N. meningitides* and *H. influenza* meningitis. The beneficial effects on morbidity were seen in high-income countries, but not in low-income countries. Based on these findings, the authors recommended the use of steroids in high-income countries, though the strength of the evidence was not optimal.

The recommended steroid is dexamethasone 0.15 mg/kg intravenously and should be preferably started with or before the first dose of antimicrobials and administered every 6 h for 4 days [30]. Steroids should be given closer to antimicrobial administration to prevent inflammation secondary to antimicrobial-induced bacteriolysis. Though there is no strong data, the ESCMID guideline consensus recommendation is to start steroids up to 4 hours after starting antimicrobials [4].

Other Treatments

Therapeutic hypothermia has been shown to be neuroprotective in postanoxic encephalopathy and neurotrauma, but has been shown not to be helpful and might even be harmful in bacterial meningitis. A randomized controlled trial done was stopped early due to increased mortality in the intervention arm. More patients died in the hypothermia group (25 of 49 patients [51%]) compared to the control group (15 of 49 patients [31%]; relative risk [RR], 1.99; 95% CI, 1.05–3.77; P = 0.04) [38]. Osmotic agents like glycerol, which are used to reduce intracranial pressure, were not shown to be beneficial. Other therapies like antiepileptics and hypertonic saline have not been well studied [4].

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Healthcare-Acquired Meningitis and Ventriculitis

3

Adarsh Bhimraj

Abstract

Healthcare-associated meningitis or cerebral ventriculitis are infections complicating neurosurgeries, CSF shunt, and CSF drain surgeries. It is different in clinical presentation, pathogenesis, and management from community-acquired meningitis. Gram-positive cocci like *Staphylococcus epidermidis* and *S. aureus* are the most common pathogens, followed by Gram-negative rods and anaerobes like *P. acnes*. The diagnosis can be difficult as other noninfectious neurologic conditions and neurosurgeries can cause similar clinical and CSF findings. The management of these infections often requires surgical interventions and may need intraventricular or intrathecal administration of antimicrobials, as the organisms can be refractory to IV antimicrobials alone. Periprocedural antimicrobials and antimicrobial impregnated CSF catheters have been shown to reduce infection rates.

Keywords

Meningitis • Ventriculitis • VP shunt infections • External ventricular drain (EVD) infections • Ventriculostomy-related infections (VRI) • Craniotomy-related infections • Neurosurgical infections • Intraventricular antibiotics • Intrathecal antibiotics • Central nervous system (CNS) infections • Antimicrobial-impregnated catheters

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Introduction

Healthcare-associated cerebral ventriculitis or meningitis is a distinct entity, which differs considerably from community-acquired meningitis in epidemiology, pathogenesis, microbiology, and clinical features. They usually occur after surgeries like craniotomies, spine, and otorhinologic surgeries where there is dural breach, cerebrospinal fluid (CSF) shunts (ventriculoperitoneal, lumboperitoneal, and ventriculoatrial shunts), or CSF drain (external ventricular drains and lumbar drains) surgeries. They can also occur after head trauma and rarely after lumbar punctures.

CSF shunts are permanent catheters, used for CSF diversion, with the proximal end in the cerebral ventricle or the lumbar subarachnoid space and the distal end in the peritoneal cavity, pleural cavity, or right atrium of the heart. The most common type of CSF shunt is the ventriculoperitoneal (VP) shunt. CSF drains are temporary catheters that divert the fluid externally. The proximal end is either in the cerebral ventricle (ventricular drain) or in the lumbar subarachnoid space (lumbar drain). The distal end of the catheter is connected to a collecting system, which has a drip chamber, sampling and injection ports, and a collection bag. Ventricular drains are mostly used for the temporary management of patients with elevated intracranial pressure (ICP) secondary to acute hydrocephalus caused by intracranial hemorrhage, neoplasms obstructing the CSF circulation, or trauma. Lumbar drains are mostly used in patients with CSF leaks after neurosurgery or for NPH (normal pressure hydrocephalous) trials to see if their symptoms respond to CSF drainage.

Often with CSF catheters whose proximal tips are in the cerebral ventricles, the resulting infection is only ventriculitis without meningitis. This has implications on clinical presentation and the site of CSF sampling for diagnostic testing. They may lack meningeal signs, and the best site for CSF studies would be ventricular CSF and not subarachnoid CSF (Fig. 3.1).

Epidemiology, Pathogenesis, and Microbiology

The incidence of CSF shunt infections reported in the literature has a wide range but in most studies rates around 10% [1, 2]. Reported ventricular drain infection rates were also around 10% [3]. In a large meta-analysis of 35 studies which yielded 752 infections from 66,706 catheter-days of observation, the overall pooled incidence of external ventricular drain-related CSF infection was 11.4 per 1000 catheter-days (95% CI 9.3–13.5); for high-quality studies, the incidence was 10.6 per 1000 catheter-days (95% CI 8.3–13) [4]. Infection rates due to lumbar drains are 4.2% [5].

The organisms that cause ventriculitis and meningitis, after neurosurgeries, CSF shunt, and CSF drain surgeries are the same. During these surgeries, the skull and meninges, which act as natural barriers to pathogens, are breached, making it

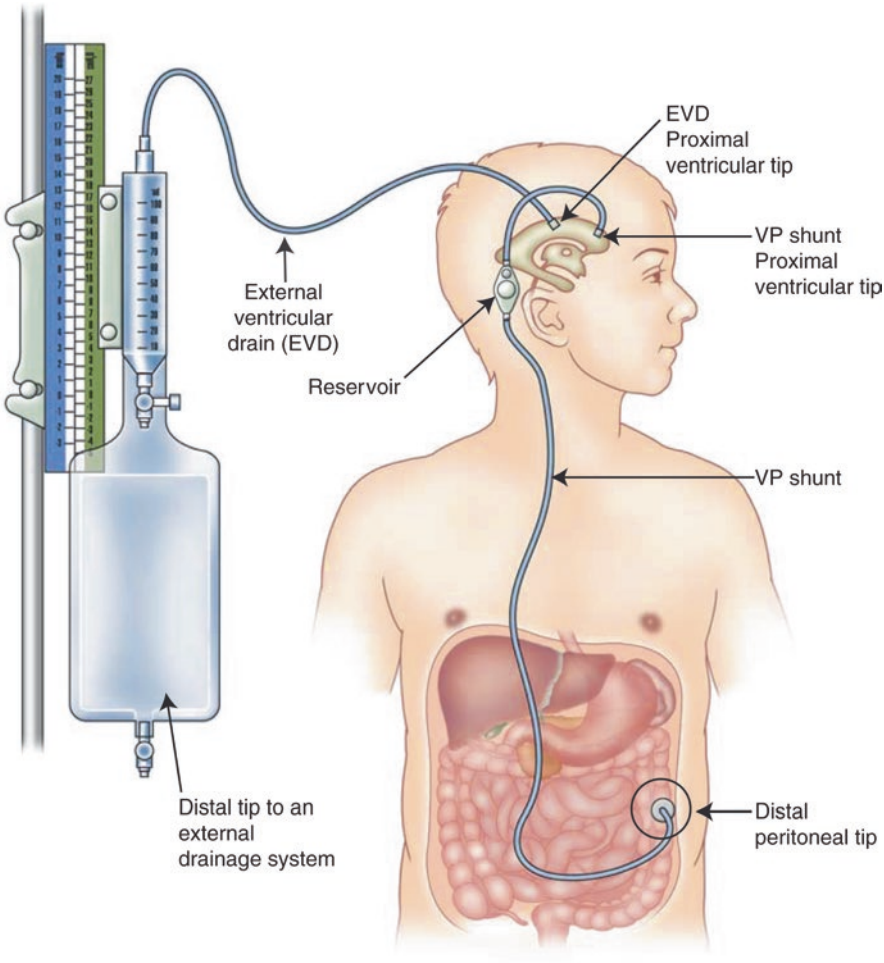

Fig. 3.1 CSF diversion catheters: ventriculoperitoneal shunt and external ventricular drain

possible for microorganisms that colonize the scalp and skin of the back, or those that live in the healthcare environment, to enter the subarachnoid space or cerebral ventricles and cause an infection. In patients with ventriculoperitoneal shunts, another less common route by which organisms enter the ventricles is spreading up along the catheter after a peritonitis. On the surface of catheters, these organisms can form biofilms, which are thick sticky polysaccharide layers making them resistant to antimicrobial action [6, 7]. The organisms that usually colonize the skin, especially the scalp, are coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Propionibacterium acnes*. The organisms that can be present in the healthcare environment are *Staphylococcus aureus* (both methicillin-resistant and

methicillin-susceptible strains) and Gram-negative bacteria like *Escherichia coli*, *Klebsiella*, *Pseudomonas*, and *Acinetobacter* species (some of the strains can be multidrug resistant).

Staphylococcal species are the most common organisms causing infections, with *Staphylococcus epidermidis* (47–64% of infections) being more common than *Staphylococcus aureus* (12–29% of infections) [1, 3, 8]. Gram-negative bacteria account for 6–20% of the infections [1, 3, 8, 9]. Diphtheroids (including *Propionibacterium acnes*) account for 1–14% of the infection, but the reason for the low reported rates of *P acnes* infection in some studies is probably an inadequate culture technique. Anaerobic cultures with prolonged incubation are needed to detect *P. acnes*, but most microbiology labs only perform aerobic cultures and hold CSF cultures for 2–3 days [1–3, 10–12]. Fungi like *Candida*, though reported in the literature, are usually rare [13].

Clinical Symptoms and Signs

The clinical presentation of healthcare-associated ventriculitis can vary from being acute and severe, if caused by virulent organisms like *Staphylococcus aureus* or Gram-negative bacteria, to more subtle and chronic, if due to less virulent organisms. Unlike the organisms that cause community-acquired bacterial meningitis, those causing CSF catheter-associated ventriculitis, like coagulase-negative staphylococci and *P. acnes*, are indolent, evoke minimal inflammation, and are usually more virulent in the presence of prosthetic material [6, 7]. Often there may be ventriculitis without meningeal involvement or only mechanical blockage as a result of biofilm formation in or on the catheter, without significant inflammation [14]. In CSF shunt infections, fever can be present only in about half the time (52%) [15]. Headaches (31%) and changes in mental status (29%) can be present less than half the time [15]. Meningismus is rarely found (4%) [15] in these patients, and this is probably because this is mostly a ventriculitis than a meningitis.

Clinical signs and symptoms are even less reliable in ventricular and lumbar drain-related ventriculitis as symptoms like change in mental status, fever, or meningismus could be a manifestation of other neurologic diseases like intracranial hemorrhage or hydrocephalus from other causes. Fever in the neurocritical care unit can be due to intracranial hemorrhage, central fever, thrombotic episodes, and drug fevers [16] in addition to non-CNS infections like bloodstream infections, hospital-acquired pneumonias, and urinary tract infections.

WBC Count, CRP, and Procalcitonin

There are several studies that evaluated blood or serum markers like procalcitonin, C-reactive protein (CRP), and peripheral white blood cell counts in patients with healthcare-associated ventriculitis. In one open prospective study which recruited consecutive patients with ventricular drains, those with proven bacterial

ventriculitis had significantly higher procalcitonin levels (4.7 ± 1.0 vs. 0.2 ± 0.01 ng/mL, $p < 0.0001$), CRP levels (134 ± 29 vs. 51 ± 4 mg/L, $p = 0.0005$), and peripheral white blood cell counts (16.1 ± 1.3 vs. 10.7 ± 0.3 10^9/L, $p = 0.0008$) [17]. In Martinez et al.'s study, a procalcitonin cutoff value of 1.0 ng/mL or more showed a specificity of 77% and a sensitivity of only 68% for ventriculitis, though it had better diagnostic accuracy in community-acquired bacterial meningitis [18]. In another study in children with suspected CSF shunt infections, the values for serum CRP in infected individuals were higher than in noninfected ones (91.8 ± 70.2 mg/L compared with 16.1 ± 28.3 mg/L, $p < 0.0001$) [19]. Despite the statistically significant p values in some studies, the confidence intervals for calculated sensitivities, based on traditional cutoffs, are wide. Though these markers are easy to obtain and are often presumed to be sensitive indicators of infections, we need further well-designed prospective studies to recommend their routine use in ruling out healthcare-associated ventriculitis, especially in infections with indolent organisms which cause minimal inflammation.

CSF Cell Count and Chemistry (Glucose, Protein, Lactate, and Procalcitonin)

The diagnostic accuracy of CSF markers in healthcare-associated ventriculitis has been evaluated in several studies. Like the blood marker studies, they have design and methodological limitations. One of the major limitations in interpreting these studies is the heterogenous definition of the reference (gold) standard for the diagnosis of healthcare-associated ventriculitis. To evaluate the diagnostic utility of CSF parameters or any other test, an independent comparison to an acceptable reference standard is required. Often CSF cultures are used as a reference standard in many studies, but diagnosing ventriculitis by a single positive CSF culture will run the risk of a false-positive diagnosis due to colonization or contamination. More specific diagnostic criteria like the presence of multiple CSF cultures with CSF pleocytosis or hypoglycorrhachia with attributable clinical signs and symptoms (fever, headache, photophobia, neck stiffness, decreased level of consciousness) would be clinically meaningful, but using that as a reference standard to calculate diagnostic accuracy like sensitivity and specificity would be erroneous as they are part of the definition of the reference standard and are not statistically independent. There are studies that applied the existing heterogenous definitions and criteria for ventricular drain-related meningitis and ventriculitis to the same cohort of patients. One of the studies found 16 unique definitions in the published literature. When the definitions were applied to the test cohort, the frequency of infection ranged from 22 to 94% (median 61% with interquartile range (IQR) 56–74%) [20].

In CSF drain-related ventriculitis, the diagnostic utility of CSF leukocyte count, glucose, and protein is limited, as noninfectious entities like intracranial hemorrhage and neurosurgical procedures can also cause abnormalities in these parameters. Schade et al. [21] performed a prospective study in a cohort of 230 consecutive

patients with ventricular drains. Results from analyses of 1516 CSF samples showed no significant differences between the patients with EVD-related ventriculitis and a control group without EVD-related meningitis, with regard to CSF leukocyte count, protein concentration, glucose concentration, and CSF/blood glucose ratio. They evaluated the predictive and diagnostic value of the CSF parameters. For none of the routine CSF parameters could they establish a cutoff value with a sensitivity and specificity of at least 60%. Pfisterer et al. [22] conducted a 3-year prospective study in patients with ventricular drains. Standard laboratory parameters, such as peripheral leukocyte count, CSF glucose, and CSF protein, were not reliable predictors for incipient ventricular catheter infection. The only parameter that significantly correlated with the occurrence of a positive CSF culture was an elevated CSF leukocyte count (unpaired *t* test, $p < 0.05$). In a prospective study, Pfausler et al. [23] looked at the utility of cell index (CI), which is the ratio of leukocytes to erythrocytes in CSF and leukocytes to erythrocytes in peripheral blood, in predicting ventriculitis. The study was done in patients with intraventricular hemorrhage who had external ventricular drains. Diagnosis of bacterial ventriculitis by CI was possible up to 3 days prior to "conventional diagnosis" which was described as rise of CSF cell count, reduction of CSF/serum glucose, or a positive CSF culture.There are few studies that evaluated the diagnostic utility of CSF lactate in CSF drain-related ventriculitis. In a prospective study of ventricular drain-related ventriculitis, a CSF lactate cutoff value of 4 mmol/L had a sensitivity of 86%, specificity of 86%, positive likehood ratio of 6.1, and a negative likehood ratio of 0.16 [24].

There are few studies evaluating the diagnostic accuracy of CSF parameters in CSF shunt infections. In a retrospective study which compared children with VP shunt infection ($n = 10$) to controls ($n = 129$), a CSF leukocyte count over 100/mm^3 had a 96% specificity and 60% sensitivity. The CSF glucose of <40 mg/dL had a 93% specificity and 60% sensitivity. The reference standard (shunt infection) in this study was defined as "clinical signs and symptoms with a positive CSF culture" [25]. Often, less virulent organisms like *Staphylococcus epidermidis* and *P. acnes* might not cause significant inflammation, so a lower cutoff for CSF leukocyte count would have probably increased the sensitivity but that was not addressed in this study. However, CSF shunt infections can present with no CSF pleocytosis at times. In a retrospective analysis of CSF shunt infections in adults, the CSF white blood cell counts and lactate concentrations were normal in approximately 20% of episodes [14]. The CSF parameter values might significantly differ depending on the site from which the CSF is obtained. In one study the leukocyte counts were significantly higher in CSF obtained by the use of lumbar puncture (median leukocyte count, 573 × 10(6) cells/L; $p = 0.001$) and valve puncture (median leukocyte count, 484 × 10 (6) cells/L; $p = 0.016$) than in ventricular CSF (median leukocyte count, 8.5 × 10(6) cells/L) [14]. The site of sampling should be considered when interpreting the values as the CSF pleocytosis from ventricular fluid might not be very high even in patients with CSF shunt-related ventriculitis.

There are few studies on the diagnostic accuracy of CSF parameters in post-neurosurgical meningitis and ventriculitis. Often the surgery itself can cause

"chemical meningitis" or postoperative meningitis, particularly posterior fossa surgeries. The CSF leukocyte and CSF glucose values can look very similar to infectious meningitis, making it hard to distinguish these entities based on these parameters. In one study only extreme values of CSF leukocyte count >7500/μL (7500 × 10(6)/L) and a glucose level of <10 mg/dL were able to distinguish post-neurosurgical chemical meningitis from bacterial meningitis [26]. Another caveat in post-neurosurgical patients is that the CSF pleocytosis and low CSF glucose might be a result of a bone flap infection, a subgaleal infection, or a deeper infection in the surgical bed-like cerebritis or brain abscess. CSF lactates have shown to perform better in post-neurosurgical meningitis, and CSF procalcitonins have not been well studied. A recent meta-analysis of five studies evaluating CSF lactate in post-neurosurgical menigits, with a total of 404 patients, showed a pooled sensitivity of 0.92 (95% CI 0.85–0.96) and a pooled specificity of 0.88 (95% CI 0.84–0.92 with significant heterogeneity [27]. In another retrospective study, patients with post-neurosurgical meningitis showed significantly elevated levels of CSF procalcitonin and CSF lactate compared with the non-meningitis group ($p < 0.001$ for both). For CSF procalcitonin, a cutoff value of 0.075 ng/Ml had a sensitivity of 68% and specificity of 73%. For CSF lactate a cutoff value of 3.45 mmol/L had a sensitivity of 90% and specificity of 85% [28].

CSF Microbiology Studies

CSF cultures are traditionally considered the reference standard for the diagnosis of meningitis and ventriculitis. In the context of community-acquired bacterial meningitis, positive CSF cultures for pathogenic organisms like pneumococcus or meningococcus are highly suggestive of meningitis. In the context of healthcare-associated meningitis, the common pathogenic organisms like *Staphylococcus epidermidis* and *P. acnes* are skin colonizers, and the possibility of contamination during specimen collection should be considered. Unlike organisms that cause acute community-acquired meningitis, those causing healthcare-associated meningitis are slow to grow on cultures and require anaerobic media. In a study on healthcare-associated ventriculomeningitis, a substantial number of positive CSF specimens grew bacteria after >3 days, with some requiring as long as 10 days [29].

The site of specimen collection for microbiology studies is also important, particularly for CSF shunt infections. The site of CSF collection for ventricular catheter infection is generally ventricular fluid, for LP shunts is lumbar subarachnoid fluid, and for post-craniotomy infections is either lumbar subarachnoid fluid or intraoperative ventricular fluid and tissue cultures. For VP shunt infections, the options are CSF by a lumbar puncture, from a "shunt tap" (percutaneous accessing of the shunt reservoir underneath the scalp), or rarely intraoperatively during shunt surgery. In VP shunt infection studies, direct aspiration of the shunt yielded a positive culture in 91–92%, whereas a lumbar puncture CSF culture was positive in only around 45–67% [14, 30]. There is a fear of causing a shunt infection by tapping it, but in a pediatric study with 266 children who underwent 542 shunt taps,

there was no evidence of shunt infections. One patient developed an infection after a tap, but there was redness over the shunt tract at the time of the tap, so was not sterile [31].

CSF polymerase chain reaction (PCR) can prove useful to detect organisms that are difficult or slow to grow by culture. In a study that used PCR to detect Gram-positive bacteria in 86 specimens, 42 were culture negative but PCR positive [32]. There were no positive culture results in patients with a negative CSF PCR, suggesting that a negative PCR result is predictive of the absence of infection. More studies are needed, however, before routine use of PCR can be recommended in this setting.

Diagnostic Approach

Given the limitations of symptoms, signs, and lab and CSF tests and the lack of a clear reference (gold) standard for healthcare-associated ventriculitis, it is often a difficult diagnosis to make. The diagnostic criteria and cutoffs for CSF parameters suggested here are based on clinical experience.

CSF Drain-Related Ventriculitis

Lozier et al. [33] proposed a classification system for ventriculitis with a hierarchy based on suspected probability of infection. The diagnostic classification proposed here is a modification of that. In addition to being clinically helpful for deciding when to use antimicrobials, such classification would hopefully establish standard criteria for future research and epidemiological purposes. We have used CSF parameter criteria (the rate of rise or degree of abnormality of inflammatory markers) PLUS microbilogic criteria for the following classification:

- *Contamination*: An *isolated* positive CSF culture or Gram stain, with expected CSF cell count and glucose with *no attributable symptoms or signs*
- *Colonization*: *Multiple* positive CSF cultures or Gram stain, with expected CSF cell count and glucose with *no attributable symptoms or signs*
- *Possible ventriculitis*: Progressive rise in cell index or progressive decrease in CSF/blood glucose ratio or an extreme value for CSF WBC count (>1000/μL) or CSF/blood glucose ratio (<0.2), with attributable symptoms or signs, but *negative* Gram stain and cultures
- *Probable ventriculitis*: CSF WBC count or CSF/blood glucose ratio *more* abnormal than expected, but *not* an extreme value (CSF WBC count >1000/μLor CSF/blood glucose ratio < 0.2) and *stable* (not progressively worsening) with attributable symptoms or signs and *positive* Gram stain and cultures
- *Definitive ventriculitis*: Progressive rise in cell index or progressive decrease in CSF/blood glucose ratio or an extreme value for CSF WBC count (>1000/μL) or CSF/blood glucose ratio (<0.2), with attributable symptoms or signs and a *positive* Gram stain and cultures

Contamination and colonization with skin colonizers generally do not need treatment. Antimicrobial treatment of contamination or colonization with virulent organisms is more controversial, but many clinicians might opt to treat positive CSF cultures for *Staphylococcus aureus* or Gram-negative rods. Antimicrobial treatment of a possible ventriculitis should also be individualized depending on the circumstances, as at times chemical meningitis from subarachnoid hemorrhage or neurosurgery could cause extreme CSF pleocytosis or hypoglycorrhachia, which a clinician might prefer not to treat. On the other instance, it might be classified as a possible ventriculitis if the CSF cultures are negative due to prior antimicrobial use or if the organism is slow to grow, when one might chose to treat with antimicrobials. Probable and definitive ventriculitis would be treated with antimicrobials by most clinicians (Fig. 3.2).

Post-Neurosurgical Meningitis

Post-craniotomy meningitis can also be classified as possible, probable, and definitive meningitis using the above criteria as the confounding comorbidities and organism causing meningitis are similar to CSF drain infections.

CSF Shunt-Related Ventriculitis

A diagnosis of CSF shunt-related ventriculitis should be considered when the WBC count (from a shunt tap) is greater than 10/μL OR CSF/serum glucose ratio < 0.4 with a positive CSF culture and attributable symptoms. The reason for using such a low cutoff for WBC count is because most often indolent organisms cause minimal inflammation, but the decision to treat based on this should be individualized.

Another instance would be when the WBC count and glucose values are normal, but there are multiple positive CSF cultures (from multiple shunt tap or explanted proximal shunt components) and attributable symptoms. CSF shunt infections can present as shunt blockage due to biofilms formed by organism without significant inflammation.

Principles of Management

Treatment of healthcare-associated ventriculitis is challenging for the following reasons:

1. It is difficult to achieve high CSF antimicrobial levels with intravenous antimicrobials because of the blood-CSF barrier.
2. Organisms like *Staphylococcus* spp. and Gram-negative rods tend to have higher MICs (minimum inhibitory concentrations) for antimicrobials than community-acquired organisms, making it harder to achieve therapeutically effective levels in the CSF.
3. Organisms often form biofilms on the catheters, which are mucoid layers into which antimicrobials do not penetrate well. This is especially an issue if the infected catheters are not removed.

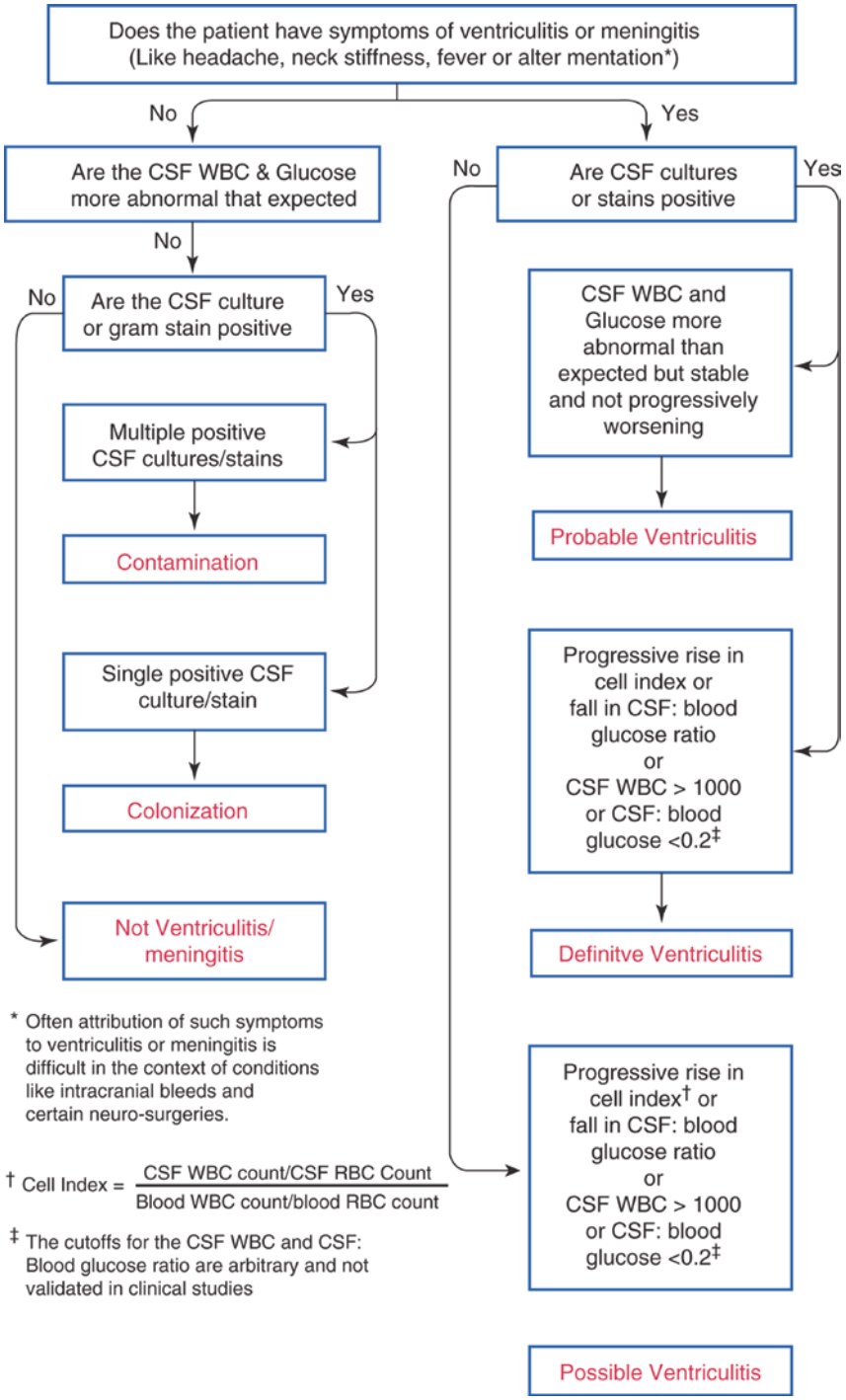

Fig. 3.2 Algorithmic approach to the diagnosis of CSF drain ventriculitis

Intravenous Antimicrobials

The recommendations for intravenous antimicrobials in patients with a normal renal clearance would be as follows:

Empiric Intravenous Antimicrobial Therapy

If ventriculitis is suspected, first, obtain CSF cultures and then start empiric treatment with vancomycin (for Gram-positive bacteria) as a continuous infusion or divided doses (2–3) of 60 mg/kg/day after a loading dose of 15 mg/kg with intravenous ceftazidime 2 g/8 h or cefepime 2 g/8 h (for Gram-negative bacteria).

In a penicillin-allergic patient, start empiric coverage with intravenous vancomycin (same dose as above) and aztreonam 2 g/6 h.

Organism-Specific Intravenous Antimicrobial Therapy

The following antibiotics can be started for specific organisms pending on antimicrobial susceptibilities, but knowledge of the local antibiogram and susceptibilities at each institution should direct therapy.

MRSA (methicillin-resistant *Staphylococcus aureus*) and MRSE (methicillin-resistant *Staphylococcus epidermidis*) with a vancomycin MIC $\leq$ 1 μg/Ml can be treated with vancomycin (same dose as above). If the catheter is retained, rifampin 300 mg IV q 12 h should be added.

MRSA and MRSE with a vancomycin MIC > 1 μg/mL or for patient with vancomycin allergy can be treated with linezolid 600 mg IV or PO q 12 h.

Specific treatment for MSSA (methicillin-susceptible *Staphylococcus aureus*) and MSSE (methicillin-susceptible *Staphylococcus epidermidis*) is nafcillin or oxacillin 2 g IV q 4 h.

Specific treatment for *Propionibacterium acnes* is penicillin G 2 MU IV q 4 h.

Specific treatment for *Pseudomonas* spp. is ceftazidime 2 g IV q 8 h or cefepime 2 g IV q 8 h or meropenem 2 g IV q 8 h.

Specific treatment for *E. coli* is ceftriaxone 2 g IV q 12 h or meropenem 2 g IV q 8 h use meropenem if there are epidemiological risk factors for prior colonization or infection with ESBL (extended-spectrum beta-lactamase) producers.

Specific treatment for *Enterobacter* spp. or *Citrobacter* spp. is cefepime 2 g IV q 8 h or meropenem 2 g IV q 8 h.

Intraventricular Antimicrobials

Intraventricular or lumbar intrathecal administration of antimicrobials might be needed when patients do not respond satisfactorily to intravenous treatment or when organisms have high MICs to antimicrobials that do not penetrate the CSF well. This route of administration bypasses the blood-CSF barrier, with controlled delivery directly to the site of infection. CSF pharmacokinetic modeling studies [34–37] show that for most Gram-negative bacteria if the MIC for some cephalosporins is

greater than 0.5 μg/mL or for meropenem is greater than 0.25 μg/mL and for Gram-positive bacteria if the MIC for vancomycin is greater than 1 μg/mL, the target pharmacokinetic-pharmacodynamic (PK-PD) parameters in the CSF with intravenous antimicrobials may not be achieved.

Although no antimicrobial agent has been approved by the US Food and Drug Administration for intraventricular and intrathecal use, there have been several studies on their pharmacokinetics, safety, and efficacy, especially in adults [38–44]. CSF sterility and normalization of CSF parameters were achieved sooner with intraventricular and intravenous use when compared to intravenous use alone. However, the use of intraventricular antimicrobial agents was not recommended in infants based on data in a recent Cochrane review [45]. A clinical trial found a three times higher relative risk of mortality when infants with Gram-negative meningitis were treated with intraventricular gentamicin and intravenous antimicrobials, when compared to intravenous therapy alone, although one half of the infants in the intraventricular gentamicin group had received only one dose, raising doubts about the exact cause of death.

Antimicrobial agents administered by the intraventricular or intrathecal route should be preservative-free and should be prepared and given using strict sterile precautions. To avoid increasing the intracranial pressure prior to instilling the drug, a volume of CSF equal to the volume of drug diluent and saline flush should be aspirated and discarded. After administering the drug via a CSF drain, a saline flush can be used to minimize the amount of drug remaining in the draining catheter. When administered through a CSF drain, the drain should be clamped for 15–60 min to allow the antimicrobial solution to equilibrate in the CSF before opening the drain [46]. During and after the procedure, the patient's level of consciousness and ICP should be closely monitored. In treating CSF shunt ventriculitis, administration of the antimicrobials through the shunt reservoir may result in the agent draining distally into the peritoneal cavity; to avoid this issue, antimicrobials can be administered into the cerebral ventricles by placing a ventricular access device separate from the shunt reservoir [47].

Determining the correct dosing regimen is challenging as the CSF concentrations obtained for the same intraventricular dose in pharmacokinetic studies have been highly variable, probably due to the differences among patients in either the volume of distribution depending upon ventricular size or variable CSF clearance as a result of CSF drainage [38–43, 45]. A consensus guideline by the British Society for Antimicrobial Chemotherapy Working Party on Infections in Neurosurgery has recommended that the initial dose of an intraventricular antimicrobial be based on ventricular volume [48]. In adults, the recommended dose of vancomycin is 5 mg in patients with slit ventricles, 10 mg in patients with normal-sized ventricles, and 15–20 mg in patients with enlarged ventricles. Using the same rationale, the initial dosing of an aminoglycoside can also be tailored to ventricular size. The same Working Party recommended that the frequency of dosing be based on the daily volume of CSF drainage: once daily dosing if CSF drainage is >100 mL/day, every other day if the drainage is 50–100 mL/day, and every third day if drainage is

<50 mL/day. The ranges of intraventricular or intrathecal dose/day for other antimicrobials are as follows:

Gentamicin, 4–8 mg.
Tobramycin, 5–20 mg.
Amikacin, 5–30 mg.
Colistimethate sodium, 10 mg, which is 125,000 IU or 3.75 mg CBA (colistin base activity).
Daptomycin, 2–5 mg.

Another approach, when drug levels can be monitored, is to base dosing on CSF drug concentrations, after the initial intraventricular dose. However, there are very few studies that have evaluated CSF therapeutic drug monitoring and given the variable CSF clearance of an antimicrobial agent; it is difficult to determine when to obtain CSF to measure peak and trough drug concentrations. A CSF drug concentration can be obtained 24 h after administration of the first dose, which can be presumed to be the trough CSF concentration. The trough CSF concentration divided by the minimal inhibitory concentration of the agent for the isolated organism is termed the *inhibitory quotient*, which should exceed 10–20 for consistent CSF sterilization [49, 50]. Although not standardized, this approach is reasonable to ensure that adequate CSF concentrations of the antimicrobial are obtained.

Operative Management

There is a wide range of management approaches to CSF shunt ventriculitis, in the published literature, ranging from conservative treatment with antimicrobials alone to removal of the entire shunt and later reimplanting a shunt after resolution of the ventriculitis [51, 52] There has only been one prospective, randomized trial that evaluated three different approaches to management of infected CSF shunts in 30 children (10 per each arm of the study) [53]. In the study, the arm that received antimicrobial therapy alone with no shunt removal had a 30% cure rate, the arm with the one-stage shunt replacement (removal of the infected CSF shunt with replacement of a new shunt in the same surgery) had a 90% cure rate, and the arm with the two-stage shunt replacement (removal of the infected CSF shunt with replacement of a new shunt in a second surgery after the ventriculitis cleared) had a 100% cure rate. In a decision analysis [51] and a systematic review [52] which synthesized results from many studies, the outcomes were similar to that of the aforementioned trial. They showed that cure rates were better with a two-stage procedure (88–96%) compared to a one-stage procedure (65%), which were better than when treated with antimicrobials alone without removing the infected shunt (34–36%) [51, 52]. In the two-stage approach, there might be a need for a temporary CSF drain, to treat raised ICP or hydrocephalus, while waiting for CSF cultures to clear before reimplanting a new CSF shunt. The optimal timing of shunt reimplantation has not been studied.

Early placement may increase the risk of relapse, but a delay in reimplantation may increase the risk of secondary infection of the external ventricular drain. The timing of reimplantation should be individualized based on the isolated organism, severity of ventriculitis, and improvement of CSF parameters and CSF sterilization in response to antimicrobial therapy. Most experts in the field would wait for at least 7–10 days after the CSF cultures become sterile to reimplant a new shunt.

Conservative management without explanting infected prosthetic devices usually has lower cure rates as the organisms adhere to prostheses and form biofilms making them resistant to antimicrobial therapy. However, in one observational study of treatment with systemic and intraventricular antimicrobial agents (instilled via a separate ventricular access device), 84% of 43 patients were cured, with a 92% success rate for infections caused by bacteria other than *S. aureus* [47] suggesting that conservative management may be appropriate for selected patients with CSF shunt infections caused by less virulent microorganisms such as coagulase-negative staphylococci and *P. acnes*. In the treatment of CSF drain infections, removal of the infected drain would be a prudent approach.

Infection Prevention

Systemic Antimicrobial Prophylaxis

In addition to sterile technique and aseptic precautions during neurosurgeries such as craniotomies, the use of periprocedural systemic antimicrobial prophylaxis has been shown to decrease infection rates in most studies [54]. However, there are some studies that show that it does not prevent meningitis [55]. Systemic antimicrobial prophylaxis has also been shown to be effective in reducing CSF shunt infections. In a meta-analysis, the infection rates were found to be decreased with the use of antibiotic prophylaxis for CSF shunt surgery (odds ratio 0.51; 95% confidence interval 0.36–0.73) [56]. The antimicrobials that are generally used are first- or second-generation cephalosporins or vancomycin. Although periprocedural systemic prophylactic antimicrobials are used for CSF drains, the use of prolonged prophylactic systemic antimicrobials for the entire duration of external CSF drainage is more controversial. One study noted that the infection rate was 3.8% in those who received prophylactic antibiotics for the duration of placement of the CSF drain and 4.0% in those who received only periprocedural antibiotics [57], suggesting that prophylactic antibiotics throughout drainage did not significantly decrease the rate of ventriculitis. In contrast, another study demonstrated a lower infection rate with prophylactic antibiotics (2.6% CSF infection rate vs. 10.6% in those who only received periprocedural antibiotics; $P = 0.001$) [58], although the infections in those receiving prophylactic antimicrobials were caused by more drug-resistant, virulent pathogens and had a higher mortality rate (66% vs. 41%). In a systematic review [59] which pooled data from two randomized controlled trials and four observational studies, there was a relative risk reduction of 0.45 with the use of prophylactic prolonged systemic antimicrobials, although there were significant methodological limitations and heterogeneity in the pooled studies, the definitions of ventriculitis were variable,

the type and dose of antimicrobials were different, adverse effects were not well studied, and most of the studies were retrospective and prone to bias. Given the availability of a safer efficacious alternative (i.e., antimicrobial-impregnated catheters; see below), it would be prudent to avoid the use of prophylactic prolonged systemic antimicrobials for the prevention of CSF drain infections.

Antimicrobial-Impregnated Catheters

The currently available antimicrobial-impregnated CSF drains and CSF shunts are typically impregnated with either minocycline or clindamycin, combined with rifampin. In a meta-analysis of 12 studies comparing antimicrobial-impregnated to non-antimicrobial-impregnated VP shunts, there was a statistically significant decrease in infections in patients who had received antimicrobial-impregnated shunts (RR 0.37; $P < 0.0001$) [60]. A similar reduction in infection rates has also been shown with the use of antimicrobial-impregnated external ventricular drains. A meta-analysis of five studies showed a statistically significant reduction in infections with antimicrobial-impregnated external ventricular drains (RR of 0.31; $P = 0.009$) [60]. The studies show that antimicrobial-impregnated CSF shunts and CSF drains are effective in preventing infections though larger prospective studies are needed to confirm this.

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Acute Viral Meningitis

4

Virginia Pomar and Pere Domingo

Abstract

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving.

Although acute viral meningitis has usually a benign course, it requires hospitalization in some patients. The development of the polymerase chain reaction (PCR) has allowed the detection of viral genomes, facilitated a rapid diagnosis, and enabled the use of antiviral treatment in selected cases. Common etiologies include enteroviruses, followed by arboviruses and herpesviruses. Clinical presentation is not specific and includes fever, headache, and variable evidence of meningeal irritation. Prognosis overall is favorable.

Keywords

Meningitis • Encephalitis • Aseptic meningitis • Cerebrospinal fluid • Central nervous system disease • Antiviral therapy

Meningitis is an inflammation of the meninges, the thin membranes (especially the leptomeninges, i.e., pia mater and arachnoid) that surround the brain and spinal cord, most often caused by a bacterial or viral infection. The subarachnoid space lying between both meningeal layers contains the cerebrospinal fluid (CSF) and is

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also affected by inflammation. Since the subarachnoid space surrounds the brain and spinal cord, meningitis is by definition cerebrospinal.

Acute meningitis is defined as a syndrome characterized by the onset of meningeal symptoms over a period of hours to several days. Among them, headache is a prominent early symptom, often followed by a state of abnormal consciousness or coma, usually accompanied by signs of meningeal irritation.

Encephalitis is distinguished from meningitis, on a clinical basis, by the presence of an early abnormal level of consciousness with minimal meningeal signs [1]. On a pathological basis, in encephalitis the inflammatory process predominantly affects the brain parenchyma. However, secondary meningeal affection is usually present, and hence the term meningoencephalitis is applied.

Definition

Viral meningitis is an infection of the meninges and subarachnoid space (the covering of the brain and spinal cord) caused by a virus. The term is used interchangeably with aseptic meningitis, which refers to meningitis with negative cultures and clear CSF. Aseptic meningitis, however, may also be caused by drugs and systemic disorders, among others.

Epidemiology

The exact incidence of viral meningitis is difficult to determine since most cases go unreported to public health authorities. The etiological panorama varies in different parts of the world as well as over time and must be adapted to the individual history of each patient, including recent travels [2]. In temperate climates, there is a substantial increase in cases during the summer and early autumn, reflecting the seasonal predominance of enteroviruses and arthropod-borne encephalitis virus (arboviruses) infections. In contrast, herpes simplex virus (HSV) and human immunodeficiency virus (HIV) have no seasonal predilection.

Clinical Manifestations

Viral meningitis presents with fever, headache, and signs of meningeal irritation and may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Mild lethargy and drowsiness are not uncommon. Headache associated with viral meningitis is usually frontal or retro-orbital and often associated with photophobia and pain on moving the eyes.

The presence of more profound alterations in consciousness, such as stupor, coma, or marked confusion, should prompt the consideration of alternative diagnoses. Similarly, seizures or other focal neurological signs or symptoms suggesting involvement of the brain parenchyma do not usually occur in uncomplicated viral meningitis.

Table 4.1 Viruses causing acute meningitis.

Common	Less common	Rare
Enteroviruses	HSV-1	Adenoviruses
Arboviruses	LCMV	CMV
HIV	VZV	EBV
HSV-2		Influenza A and B, parainfluenza, mumps, rubella

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *LCMV* lymphocytic choriomeningitis virus, *VZV* varicella-zoster virus

Nuchal rigidity (or neck stiffness) is present in most cases but may be mild and present only near the limit of the neck anteflexion. Other meningeal signs such as Kernig's and Brudzinski's signs are generally absent [3].

Etiology

The development of modern molecular techniques has greatly improved the diagnostic yield and is now widely applied to CSF samples [2, 4].

Using a variety of diagnostic techniques including CSF real-time polymerase chain reaction (PCR) tests, culture, and serology, a specific viral etiology can be found in 75–90% of cases of viral meningitis [3]. Enteroviruses account for 85–90% of aseptic meningitis cases in most series (see Table 4.1) [4].

Diagnosis

Cerebrospinal Fluid Examination

The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical CSF profile shows a lymphocytic pleocytosis (25–500 cells/mm^3), although neutrophils may predominate in the first 48 h of illness (they shift to lymphocytes in 24–48 h); mildly increased CSF proteins and normal or mildly decreased CSF glucose concentrations can also be found. Viral organisms are not seen on Gram's or acid-fast stain smears or India ink preparations (see Table 4.2).

Amplification of viral-specific DNA or RNA using real-time PCR has become the single most important method for diagnosing central nervous system viral infections. It allows a rapid and accurate diagnosis for enterovirus, herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) infections and assists in clinical decision-making, particularly regarding the potential use of antiviral therapy [5].

The overall results of viral CSF cultures for the diagnosis of viral infection are disappointing, presumably because of the generally low concentration of infectious virus present and the need to customize isolation procedures for individual viruses

Table 4.2 Cerebrospinal fluid (CSF) cyto-biochemical parameters associated with acute meningitis

	Normal CSF	Viral meningitis	Bacterial meningitis
White cells	<10/μl	100–500/μl	>1000/μl
Neutrophils	–	<50%	>50%
Protein (mg/dl)	<30–40	<100	>100
Glucose (mg/dl)	>50	>50	<40
Gram's stain	Negative	Negative	Positive (60%)

[3]. A delay in transporting or processing the sample further decreases the minimum number of viable viruses necessary to replicate in cell lines. However, the combination of both methods (PCR amplification and culture) remains useful [6].

Other Sources for Viral Isolation

Viruses may also be isolated from sites and body fluids other than the CSF, including the throat, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and lymphocytic choriomeningitis viruses (LCMVs) in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. Nevertheless, the presence of enteroviruses in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection [3].

Serologic Studies

Serology is the method of reference for meningitis caused by West Nile virus and LCMV, which are quite uncommon. Serum serologic studies are less useful for other viruses such as HSV, VZV, CMV, and EBV, for which the prevalence of antibody seropositivity among the general population is high. The demonstration of specific serum IgM to VZV, IgG seroconversion between serum of acute disease and the convalescent phase, or intrathecal production of specific antibodies can be useful for VZV meningitis (see Table 4.3) [6, 7].

Brain CT

Upon presentation, patients who are immunocompromised and have a prior history of central nervous system disease, papilledema, or focal neurological deficits should have a brain CT performed prior to lumbar puncture. However, the need for a brain CT should not mean delaying specific antimicrobial therapy if deemed necessary. This is especially important when bacterial etiologies are considered. The same is applicable in presumed cases of HSV encephalitis.

Table 4.3 Performance of the main methods for microbiological diagnosis of viral meningitis [6]

	CSF			Other sources		
Microorganisms	PCR	Culture	Serology	PCR	Culture	Serology
Enteroviruses	+++	++	–	+++ (throat, feces)	+++ (throat, feces)	+
Herpesviridae						
HSV	+++	–	+	–	–	–
VZV	+++	+/–	++	++ (vesicle)	++ (vesicle)	++
Mumps	+++	++	++	++ (urine, saliva)	++ (urine, saliva)	++
Arbovirus						
TOSV	+++	++	+	–	–	+++
WNV	++	+	++	++ (serum)	–	+++
LCMV	++	++	++	–	–	+++

CSF, cerebrospinal fluid; *PCR*, polymerase chain reaction; *HSV*, herpes simplex virus; *VZV*, varicella-zoster virus; *TOSV*, Toscana virus; *WNV*, West Nile virus; *LCMV*, lymphocytic choriomeningitis virus.
+++, high performance; ++, moderate; +, low; –, not recommended.

Differential Diagnosis

The most important issue in the differential diagnosis is the exclusion of nonviral causes that may mimic viral meningitis. The major categories of disease that should always be considered are [2, 5]:

- Bacterial meningitis and other infectious meningitides (*Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Brucella*, *Cryptococcus*, *Coxiella*, and *Rickettsia*). However, in these cases, presentation is not acute, there are predisposing factors, or meningitis represents a complication of a preexisting infection.
- Parameningeal infections or partially treated bacterial meningitis.
- Carcinomatous meningitis.
- Meningitis secondary to noninfectious, inflammatory diseases such as sarcoidosis, Behçet's disease, and the uveomeningitic syndrome.
- Vascular and metabolic diseases.
- Some medications or drug toxicity (i.e., NSAIDs).

Specific Viral Etiologies

Enteroviruses

They are the most common cause of viral meningitis (accounting for more than 85% of all cases). They belong to one of the three types of the viral family *Picornaviridae* that cause disease in humans. Nearly 70 serotypes exist, and they are divided into three subgroups: echoviruses, coxsackieviruses A and B, and polioviruses [8].

They are highly contagious and most often spread from person to person through fecal contamination but may also be spread through respiratory secretions (saliva, sputum, or nasal mucus) of an infected person. Waterborne infection has also been documented [2]. Cases appear most often during the summer and autumn in temperate climates. However, sporadic cases are seen all year-round.

Patients typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting are also common. Other clues to the presence of enteroviral disease include the presence of exanthemas, myopericarditis, conjunctivitis, pleurodynia, herpangina, and hand-foot-and-mouth disease [1, 3, 9].

Molecular diagnostics using PCR for detection of enteroviruses RNA is the method of choice for central nervous system (CNS) infections.

Herpes Simplex Virus (HSV)

Two distinct epidemiologic and antigenic types of HSV exist: HSV type 1 and HSV type. 2. HSV has worldwide distribution, and direct contact with infected secretions is the principal mode of spread.

In some series, HSV-2 has been the most important cause of aseptic meningitis in adults, especially women, and overall, it is probably second only to enteroviruses as a cause of viral meningitis.

HSV-1 usually establishes latency in the trigeminal ganglion, and CNS infection typically results in an encephalitic illness, whereas HSV-2 establishes latency in the sacral sensory ganglia and typically causes meningitis [5]. Neurological disease after primary HSV-2 is seen most often in neonates.

Meningitis (usually by HSV-2) is usually characterized by a stiff neck and an acute onset of headache, fever, and photophobia; about 50% of patients have transient neurological manifestations including seizures, hallucinations, diplopia, cranial nerve palsies, or altered consciousness. Sometimes it is associated with urinary retention, constipation, dysesthesia radiating pain, or weakness in the lumbosacral area and lower limbs, indicating sacral myeloradiculitis [2].

Meningitis appears in 36% of women and 13% of men at the time of an initial (primary) episode of genital herpes [1]. Herpetic mucocutaneous lesions may precede the meningitis by about 2–14 days, but sometimes it can appear after the onset of meningitis, and the two manifestations may occur independently. However, more than 50% of patients with HSV do not report any herpetic blisters [2].

Of these patients, 20% will develop a few or up to ten episodes of meningitis lasting 2–5 days followed by spontaneous recovery [10]. Almost all cases of recurrent HSV meningitis are due to HSV-2. Genital lesions may not be present, and most patients report no history of genital herpes.

Although HSV can be cultured from CSF during a first episode of meningitis, cultures are invariably negative during recurrences [11]. The diagnosis is verified in the acute stage by detection of HSV-1 or HSV-2 DNA in the CSF by

PCR. False-negative results appear very early, 1–3 days from the onset of neurological symptoms [2].

Varicella-Zoster Virus (VZV)

Primary VZV infection, chicken pox (varicella), usually occurs during childhood as a mild-to-moderate disease. Latent VZV infection may occur in the cranial nerve ganglia, any dorsal root ganglia, and autonomic ganglia along the entire neuraxis. Years later, usually in association with a decline in cell-mediated immunity in elderly and immunocompromised individuals, VZV reactivates and causes a wide range of neurological disease; in fact, in recent years, VZV has been implicated with increasing frequency as a meningitis-producing agent and especially meningoencephalitis with or without rash [12].

The sensitivity and specificity of PCR in the CFS have not been studied systematically, but a high viral load is usually seen in meningitis [2]. Serological analyses have been hampered by cross-reactivity between HSV and VZV.

Epstein-Barr Virus (*EBV*), *Cytomegalovirus* (*CMV*), *and Human Herpesvirus 6* (HHV-6)

EBV, CMV, and HHV-6 are all members of the HHV family and therefore share some characteristics. Primary infection often occurs early in life and is usually asymptomatic, but all of these viruses can cause aseptic meningitis, particularly in immunocompromised hosts but also in immunocompetent adults [2]. EBV and CMV are almost never cultured from CSF, but DNA can be amplified in some patients [13]. Finding DNA from CMV in CSF is strongly indicative of CMV-related disease. However, EBV- and HHV-6-positive DNA findings must be interpreted with caution [2].

Human Immunodeficiency Virus (HIV)

It has been estimated that HIV infection is the cause of 5% of cases of aseptic meningitis. Aseptic meningitis may occur as part of the primary exposure to HIV (in up to 24% of cases during or after the mononucleosis-like syndrome) or may be detected in an already infected patient (more commonly in patients with 200–500 CD4/mm^3 than in earlier stages) and can assume the form of chronic meningitis [14–16].

HIV meningoencephalitis may be the presenting form of HIV primary infection in around 8% of patients. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections.

This syndrome usually resolves spontaneously within 2–4 weeks. The diagnosis of HIV meningoencephalitis is an accepted indication for starting antiretroviral therapy during primary HIV infection.

Mumps

Parotiditis (mumps) is asymptomatic in nearly 30% of children. Mumps meningitis has been reported in 1–10% of persons with mumps and usually follows the onset of parotiditis, when present, by about 5 days. The most frequent clinical presentation is the triad of fever, vomiting, and severe headache, but only half of patients will have the salivary glands enlarged [2]. Most patients have signs of meningitis but no evidence of cortical dysfunction. Mumps meningitis is usually self-limited, although cranial nerve palsies have occasionally led to permanent sequelae, particularly deafness [1, 17]. Hydrocephalus is frequent, particularly in children, and CSF analysis shows lymphocytic pleocytosis and increased proteins; in one-fourth of patients, glucose levels are decreased [18].

Recently, concern has been raised about vaccine failure and infection resurgence, with important outbreaks in the UK in 2005 and in the USA in 2006 [1, 3]. Prior to widespread vaccination, mumps was the main cause of aseptic meningitis. The vaccine with live attenuated virus is protective but imperfect, and outbreaks still occur even among vaccinated individuals [19].

Mumps meningitis should be considered during late winter or early spring, especially in males. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis.

Diagnosis is typically made by isolation of virus from the CSF and/or demonstration of seroconversion between acute phase and convalescent sera [2, 3].

Lymphocytic Choriomeningitis Virus (LCMV)

LCMV was one of the earliest and seemingly most significant viruses to be associated with human aseptic meningitis.

It is transmitted to humans by contact with rodents (rats, mice, hamsters, etc.) or their excreta; the greatest risk of infection is in laboratory workers, pet owners, and persons living in impoverished and unhygienic situations. Presumed routes of transmission are ingestion of food contaminated with animal urine and exposure of open wounds to dirt [1]. Person-to-person transmission has occurred only through maternal-fetal transmission (associated with congenital hydrocephalus, chorioretinitis, and mental retardation) and solid organ or hematopoietic transplantation [21–23].

Human cases are most common in autumn due to the result of seasonal population densities of rodents and the movement of mice into homes and barns during cold weather. Most LCMV infections occur among young adults, although persons of all ages have been affected [1].

LCMV illness occurs in most infected individuals usually 8–13 days after being exposed to the virus, and it is usually nonspecific or influenza-like. Thirty-five percent of infected persons exhibit clinical evidence of CNS infection in the second phase (following a few days of recovery). There is an especially severe form of the disease in immunosuppressed patients because of solid organ or hematopoietic stem cell transplantation, in which LCMV may result in serious systemic infections and death [20]. The overall case fatality rate is less than 1%, and people with complications including meningitis almost always recover completely. A more severe disease is likely to occur in people who are immunosuppressed. Mortality in these patients may be as high as 75% [20–23].

Arbovirus Infections

The term arboviruses refer to viruses that have an arthropod vector, such as mosquitoes or ticks. These viruses are members of togavirus (Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis, etc.), flavivirus (St. Louis encephalitis, West Nile viruses, Japanese encephalitis, Murray Valley encephalitis, dengue and yellow fever viruses), and bunyavirus families (California encephalitis virus group, hantaviruses, Toscana virus).

For some arboviruses, distribution is universal, while for others, it is geographically restricted since it is determined in large part by the range of their arthropod vectors. These infections appear most often during the summer and early autumn in temperate climates.

Most infections are asymptomatic, and the clinical picture, when it occurs, can range from a self-limited febrile syndrome to severe symptoms (meningitis or meningoencephalitis).

For the diagnosis, it is especially relevant to collect data about recent travel or insect bites; in the laboratory, the use of direct detection techniques such as CSF culture and/or PCR usually warrants etiologic diagnosis [24–26].

Treatment

Patients with a clinical picture suggestive of meningitis should be investigated for the possibility of bacterial and viral causes for the purpose of establishing the diagnosis and potential avoidance of unnecessary hospitalization and/or antibiotic treatment.

In the usual case of viral meningitis, treatment is symptomatic and hospitalization is not required.

Intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or HSV-2 (10 mg/kg per day in three divided doses for 14–21 days) and VZV (10–15 mg/kg per day in three divided doses for 10–14 days). VZV is less sensitive to acyclovir than HSV, and a higher dose may be used in younger patients without renal impairment [2]. Oral acyclovir (800 mg, five times a day), famciclovir

(500 mg, twice a day), or valacyclovir (1000 mg, twice a day) for the last week of the treatment may be used, although data on efficacy are lacking [2].

There are no controlled trials of antiviral treatment of CNS infection caused by CMV, EBV, or HHV-6, and most of the results described are in immunocompromised patients. Ganciclovir and foscarnet are sometimes recommended in CMV [2]. Ganciclovir is ten times more potent in vitro against CMV and EBV than acyclovir and is equally effective against HSV-1, HSV-2, and VZV [2].

Antiviral therapy of enteroviral meningitis is limited. Pleconaril prevents viral replication by inhibiting viral uncoating and blocking viral attachment to host cell receptors. Pleconaril was tested in two placebo-controlled clinical trials and in both shortened the course of illness compared to placebo recipients, especially when given early in the course of the disease. However, the benefits were only modestly achieved in the subgroup of patients with more severe disease after adjusting for confounding variables [2, 8]. Pleconaril has not achieved approval by the US Food and Drug Administration (FDA) because it induces CYP3A enzyme activity and has the potential for drug interactions. Ribavirin appears to be effective in animal models, but clinical experience is lacking. Treatment with intravenous immunoglobulin and milrinone has been used in patients with severe neurological complications. A recent prospective, open-label, randomized controlled study has demonstrated that both can reduce morbidity and mortality [2, 27].

Antiretroviral therapy should be started without delay for HIV meningoencephalitis [14, 16].

Corticosteroids are often administered in the acute phase of HSV encephalitis, in patients with clinical signs of increased intracranial pressure, but this situation is not frequent in the meningitis. The pathogenesis in VZV meningitis has not been elucidated, and the value of additional corticoids has not been studied. A short duration, such as 3–5 days, is generally recommended to avoid adverse effects [2].

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Acute Viral Encephalitis: Herpesviruses and Enteroviruses

5

José Luis Sánchez-Menoyo and Jone Bocos Portillo

Abstract

Acute encephalitis is a syndrome of diverse etiology, mostly viral, which varies according to the time of the year and the geographic location. Etiology remains unidentified in up to one-third of cases. The current outcome of viral encephalitis remains unsatisfactory with high mortality and morbidity rates in adults and children. Worldwide, herpes simplex type 1 encephalitis is the most common cause of sporadic encephalitis. Viral encephalitis represents a medical emergency that requires prompt diagnosis and therapy and a high index of suspicion. Early initiation of antiviral therapy is crucial, while diagnostic test is being performed. Supportive care should be directed at the prevention and treatment of secondary complications, including cerebral edema and epilepsy.

Keywords

Encephalitis • Herpesvirus • Herpes simplex • Herpes zoster • Cytomegalovirus Enterovirus

Acute encephalitis is a syndrome of diverse etiology, mostly viral, which varies according to the time of the year and the geographic location (Table 5.1). In many instances, however, the etiology remains unidentified (up to 30% in some series) [1]. A prospective Finnish study on encephalitis identified an etiologic agent in 36% of the patients. The most common were herpes simplex type 1, varicella zoster, and arboviruses [2]. In 2006, the California Encephalitis Project evaluated 1570 patients with encephalitis and identified an infectious causative agent in one-third of them [3].

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Table 5.1 Commonest agents of acute encephalitis

Etiologic agent	Comments
Herpesviruses	Throughout the year
Enteroviruses	Summer and fall
Arboviruses	Summer and fall
	Mosquito- or tick-borne

In this chapter, the most common causes of viral sporadic encephalitis will be reviewed, with particular focus on the most frequent and severe herpes simplex encephalitis. Other herpesviruses, as well as enteroviruses and a type of arboviruses, tick-borne encephalitis, will be also discussed. Other arboviral infections are covered in Chap. 6.

Herpes Simplex Virus Encephalitis

Herpes simplex encephalitis (HSE) is caused by herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2), two DNA closely related, worldwide human pathogens that belong to the *Herpesviridae* family. They produce a wide variety of diseases, including mucocutaneous infections, central nervous system (CNS) infection, and infections of visceral organs. There are no animal vectors for HSV, and humans are the only natural reservoir. Infection with HSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. Antibodies to HSV-2 appear during puberty and correlate with initiation of sexual activity. Whereas HSV-1 typically causes encephalitis, HSV-2 is more often associated with aseptic meningitis and accounts for most cases of recurrent Mollaret's syndrome.

Epidemiology

HSE is the most common sporadic viral encephalitis worldwide, with an annual incidence of 1 in 250,000–500,000 [4]. In the United States, HSE accounts for approximately 10–20% of the 20,000 annual viral encephalitis cases, with an incidence of approximately 2.3 cases per million [5]. In a nationwide study of HSV-1 encephalitis in Sweden over a 12-year period, the annual incidence of confirmed cases was 2.2 per million [6]. HSV is also the most commonly identified pathogen among hospitalized patients diagnosed with encephalitis in Australia [7, 8]. Cases are distributed throughout the year, and the age-specific incidence is bimodal, with peaks in the young (one-third of all cases occur in children and adolescents [9]) and in the elderly. Most HSE cases are due to HSV-1, but about 5–10% are caused by HSV-2, particularly in immunocompromised individuals and neonates [10].

Pathogenesis

HSV often causes a mild disease restricted to the skin and mucosa and much less commonly a severe encephalitis. While HSV-1 is typically transmitted via the orolabial route, HSV-2 is the cause of most cases of genital herpes [11]. Primary infections, acquired through close contact from an infected individual, are mostly asymptomatic in adults but result in gingivostomatitis in 10% of infected children. They occur during the first three decades of life, while reactivation occurs at any time. After initial replication in the skin and mucosa, the virus infects the sensory nerve endings innervating the infected territory and migrates by retrograde axonal flow toward the neuronal nuclei of the trigeminal ganglia where it remains latent. Latency is defined by the presence of the viral genome in the host tissue without the production of infective particles [12].

Reactivation gives rise to mucocutaneous recurrence confined to the anatomic distribution of a single dorsal root ganglion and is not accompanied by permanent sensory deficit, a marker of neuronal death. Reactivations can be symptomatic (recrudescence) or, more frequently, asymptomatic with inadvertent transmission.

The mechanisms whereby HSV-1 penetrates the nervous system, evades the immune response, and causes encephalitis are incompletely understood. HSV can enter into the brain by reactivation of the viral genome in the trigeminal ganglion with axonal spread via the trigeminal nerve into the frontal and temporal lobes [13]; an olfactory pathway has also been postulated [14]. Herpes simplex encephalitis. Immunohistological demonstration of spread of virus via olfactory and trigeminal pathways after infection of facial skin in mice. Also, in situ reactivation of the latent virus from the central nervous system (CNS) tissue can occur [15], as well as primary CNS infection. These options are not mutually exclusive. HSV encephalitis occasionally occurs after neurosurgery (the vast majority of infectious complications of neurosurgical procedures are of bacterial origin), in which case prognosis is somber [16].

HSE may occur either during primary HSV infection, a situation more common in children and adolescents, or during reactivation in HSV-seropositive adult patients. Only 10% of patients present symptoms of cutaneous or mucous HSV infection at the time of encephalitis. However, a study showed that the viral strain recovered from the brain differed from the strain recovered from the lip or pharynx in three out of eight HSE cases, suggesting that encephalitis can occur after reinfection as well as after primary infection or reactivation [17].

Several studies implicate the immune response to HSV-1 in causing widespread CNS disease, but the exact cause of the extensive destruction of the CNS is unknown. Multiple cell populations, including natural killer cells, macrophages, T lymphocytes, and lymphokines, play a role in host defense against HSV infection [18]. T cells play a major role in viral containment and prevention of lethal disseminated disease, although antibodies also help reduce viral titer in the neural tissue [19]. Widespread local extension and dissemination occur in patients with inadequate cell-mediated immunity, including infants, organ transplant recipients, and

HIV-infected persons [18]. Defects in the innate immune response have been associated with severe viral infections in humans as in animal models [20], suggesting that the outcome of viral infection depends on a balance between the host immune response and counteracting viral factors [21]. Genetic defects impairing recognition of pathogens by the innate immune system have been identified. Deficiency of an intracellular protein, UNC-93B, causing impaired cellular interferon α/β and λ antiviral responses, was associated with HSE [22].

Neonatal infection acquired through the mother's genital tract during delivery implicates both HSV-2 and HSV-1. In the newborn, encephalitis may be caused by hematogenous spread with multiorgan involvement and diffuse brain necrosis. It occurs during the first week of life and is the only manifestation of 25% of neonatal HSV infections. Most often, encephalitis develops after the second week of life and presents a focal cerebral involvement resembling the transneuronal spread of older patients [23].

The highest risk to the neonate (30–50% risk of transmission) is a primary maternal infection close to delivery [24] leading to a high viral load in the absence of HSV antibodies passed to the neonate. The risk of transmission from mothers with recurrent infection on delivery is much lower (<3%). Primary and recurrent infections are often asymptomatic in pregnant women. Neonatal HSV-1 infections may also be acquired through postnatal contact with people with orolabial HSV-1 infection. Thus, nursery personnel and other adults with HSV external lesions should avoid intimate contact with the newborn. Neonates (infants younger than 6 weeks) have the highest frequency of visceral and CNS infection of any HSV-infected population. Congenitally infected infants have been reported, but they were almost invariably born to mothers with primary HSV-1 or HSV-2 infection during pregnancy [25]. Clinical features included microcephaly, hydrocephalus, and chorioretinitis.

Clinical Features

Symptoms and signs of HSE include headache, fever, nausea and vomiting, and sometimes neck stiffness associated with signs of brain dysfunction such as abnormal consciousness, behavioral changes (hypomania, hallucinations, agitation), focal neurological signs (dysphasia, hemiparesis, hemianopia), cognitive disturbances (memory, speech, and orientation disturbances), and seizures. However, there are no pathognomonic clinical features that reliably distinguish HSE from other neurologic infections. There may be prodromal symptoms of upper respiratory tract infection and neurological dysfunction of the frontotemporal lobes, sometimes mimicking acute psychiatric conditions.

Behavior disorders may also include excessive animation, decreased need for sleep, inflated self-esteem, and hypersexuality [26]. There are atypical cases with milder and less severe forms of encephalitis without the classical frontotemporal syndrome [27]. These include low-grade fever, speech disturbances (dysphasia and aphasia), and behavioral changes, which can be mistaken for psychiatric illness or

the consequences of drugs or alcohol [28]. A rather unique presentation of HSE has been reported, in which a bilingual patient developed aphasia only for his most recently learned language [29].

Disease presentation is acute, usually less than a week. Fever and headache are present in the vast majority (up to 90%) at the time of presentation, and their absence should cast doubts upon the diagnosis.

In the clinical series of the pre-PCR era, personality changes, confusion, and disorientation were present in about three-quarters of the patients, seizures in half, and focal neurological signs in one-third of all patients [30].

In AIDS and others immunocompromised patients, the presentation of HSE might vary and become a clinical challenge. Patients may present with behavioral abnormalities without prodromal symptoms, fever, or even headache or focal neurological deficits [31, 32].

Immunosuppressed patients present with less prodromal symptoms and focal deficits and more extensive CNS involvement, including the brainstem and cerebellum, sometimes in the absence of temporal lobe involvement. Normal CSF cell counts are not unusual, and their morbidity and mortality are substantially higher [32].

Neurological examination shows findings related to the presence of meningeal irritation and brain dysfunction. Signs of autonomic and hypothalamic disturbances may be present (diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion).

Only 10% of patients present symptoms of cutaneous or mucous HSV infection at the time of encephalitis [21]. The finding of labial herpes has no diagnostic specificity for HSV encephalitis and may be merely a marker of critical illness [28]. The very young and the very old display the most extensive and serious signs of encephalitis [33].

Neonatal HSV infection occurs in approximately 1 in 3200 deliveries [24] and may present with a combination of (a) involvement of the skin, eyes, mouth, or a combination, (b) neurological infection, and (c) disseminated infection [23, 34]. Neonates have the highest frequency of CNS infection of any HSV-infected population. If untreated, neonatal herpes undergoes dissemination or develops into CNS infection in more than 70% of cases with an overall rate of death of 65%; less than 20% of survivors with CNS infection develop normally. Skin lesions may be absent in infants until well into the course of disease [35]. In the pediatric population, HSE most commonly occurs under the age of 3, particularly in children aged 3–12 months [36, 37].

The classical clinical presentation of HSE in children consists of fever (>38.5 °C), altered level of consciousness, and focal seizures. Focal febrile seizures in the context of a nonspecific febrile disease and soon turning into status epilepticus are the first neurological symptoms in most children under the age of 3 [21]. Subacute or milder forms of HSE are common in children.

The acute opercular syndrome, characterized by a disturbance of voluntary control of the facio-linguo-glosso-pharyngeal muscles leading to orofacial palsy, dysarthria, and dysphagia, may be the initial neurological manifestation of HSE in

children [38, 39]. Its occurrence in children is probably due to the high frequency of extra-temporal brain lesions occurring in this patient group [40].

Diagnosis

HSE is a medical emergency that requires prompt diagnosis and therapy; yet, both are often delayed for several reasons. First, clinical presentation is nonspecific and may be mistaken for stroke, epilepsy, delirium, or a primary psychiatric disorder. Most patients have serological evidence of prior infection with HSV-1, consistent with reactivation disease. Furthermore, CSF cell count is normal in 5–10% of patients, particularly in children, and neuroimaging may be normal and DNA detection negative early in the infection [41]. A high index of suspicion is therefore required, particularly in immunocompromised patients with febrile encephalopathy.

We will review the diagnostic aids for HSE.

Electroencephalography (EEG)

The EEG shows background slowing and frequent periodic lateralized epileptiform discharges (PLEDs) over the temporal lobe (Fig. 5.1). PLEDs are not specific for HSE and are present from day 2 to day 14 after disease onset [42]. The severity of EEG abnormalities correlates with prognosis. EEG is also useful to identify nonconvulsive seizures, which occur in both HSE and other encephalopathies [43]. EEG has a high sensitivity (84%) but low specificity (32%) for the diagnosis of herpes simplex encephalitis [44].

Neuroimaging

Initial computed tomography (CT) scan of the brain shows changes consistent with HSE in 25–80% of patients, mostly over the temporal and frontal lobes (Fig. 5.2a). They include contrast-enhancing, hypodense lesions with mass effect, scattered hemorrhages. Follow-up scans demonstrate more widespread abnormalities with contralateral temporal lobe, insulae, and cingulate gyrus involvement [33, 45]. Early CT scan also helps in detecting mass lesions that could represent a risk for lumbar puncture and in indicating an alternative diagnosis. One study showed that 2 of 21 patients (10%) with suspected encephalitis had a cerebrovascular event detected by CT scan [46].

Magnetic resonance imaging (MRI) is more sensitive and specific than CT and is the choice in patients with suspected HSE [47] (Fig. 5.2b). Ninety percent of patients with PCR-proven HSE have MRI abnormalities [45].

Early findings include gyral edema (T1-weighted sequences) and high signal intensities over the medial temporal lobe and cingulate gyrus (T2, FLAIR, and diffusion-weighted (DWI) sequences), often with foci of hemorrhage. Bilateral,

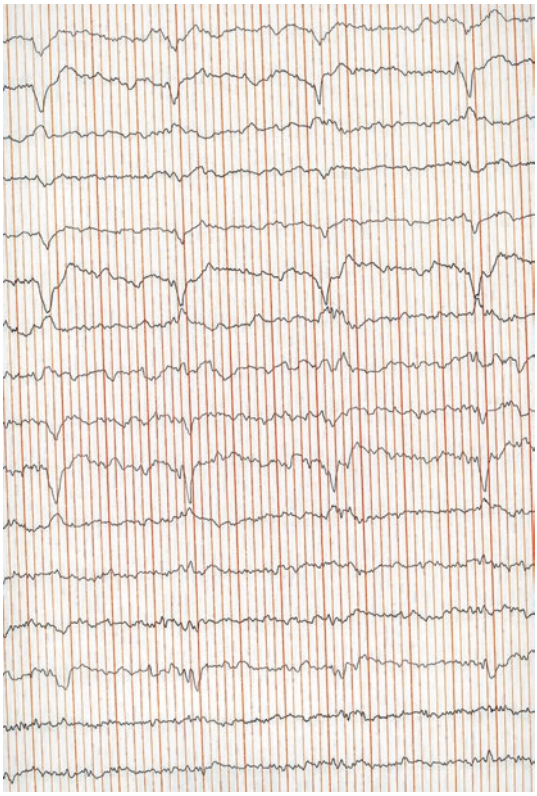

Fig. 5.1 EEG of a patient with herpes simplex type 1 encephalitis. Note the presence of slow right temporal lobe discharges over a moderately slow background activity. The same patient as in Fig. 5.2

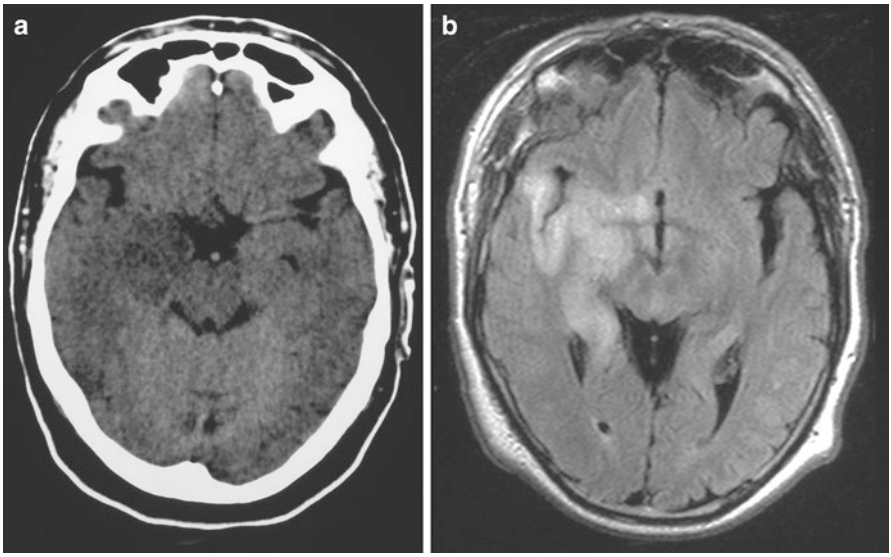

Fig. 5.2 Neuroimaging of a patient with herpes simplex type 1 encephalitis. Note the hyperintense lesion involving the right temporal lobe. Brain CT scan (*left panel* **a**) and brain MRI (FLAIR sequence, *right panel* **b**).

asymmetrical temporal lobe and cingulate gyrus involvement is nearly pathognomonic of HSE but is a late development [47]. DWI sequences are very sensitive to early changes [48, 49].

Neonatal HSV-2 encephalitis causes more widespread abnormalities than HSV-1 encephalitis, with periventricular white matter involvement and sparing of the medial temporal and inferior frontal lobes [50].

Cerebrospinal Fluid (CSF)

CSF analysis is essential in diagnosing encephalitis, and lumbar puncture can only be delayed in the presence of formal contraindications, in which case antiviral therapy should be empirically started.

In adults with HSE, the CSF opening pressure is moderately elevated, and there is a lymphocytic CSF pleocytosis (10–500 cells per mm^3, average 100 cells per mm^3), mildly increased proteins, and normal glucose [45]. Occasionally, polynuclear cells predominate, particularly in immunocompromised and children. Pleocytosis is absent in 5–10% of adults with proven HSE [33, 45], particularly early in the illness, in infants, in immunocompromised, and in patients taking tumor necrosis factor (TNF-alpha) inhibitors [51]. When the initial CSF is normal, a subsequent sample 24–48 h later is likely to be abnormal [33, 45]. Red blood cells are present in the CSF of 50% of patients reflecting the hemorrhagic nature of HSE. Low glucose is uncommon and may suggest an alternative diagnosis [52].

Virological Diagnosis

The gold standard for diagnosis is the detection of herpes simplex virus DNA in the CSF by polymerase chain reaction (PCR). CSF PCR for HSV between days 2 and 10 of illness has an overall sensitivity and specificity >95% in immunocompetent adults [53]. Although HSV PCR may be negative in the first few days of illness, a second CSF taken 3–7 days later will often be positive, even with acyclovir treatment [54], and remains detectable for at least 2–4 weeks. The use of PCR has allowed the identification of atypical forms of HSE, including brainstem encephalitis, myelitis, and diffuse encephalitis without temporal lobe involvement [53]. Negative PCR results have been associated with CSF containing <10 cells/mm^3 and low protein levels, a situation more frequent in the pediatric population [36], where PCR sensitivity is 75–100%.

Quantification of viral load in the CSF has been estimated between 10^2 and 10^7 HSV genomes/ml, with no apparent correlation between initial load and prognosis [55], though a lack of decline in the viral load after treatment correlates with a poor outcome [6].

Intrathecal synthesis of anti-HSV IgG also has diagnostic value [11], particularly in patients in whom an earlier CSF was not taken or was not tested for HSV by PCR and in atypical forms of the disease. Intrathecal synthesis of HSV-specific IgG

antibodies is detected after 10–14 days of illness, peaks after 1 month, and persists for years. Although titers of CSF and serum antibodies to HSV increase in most cases of HSE, they rarely do before 10 days of illness and thus are not helpful in early diagnosis [56]. Intrathecal immune responses may be abrogated by early antiviral therapy.

Viral culture of CSF is rarely positive in patients with brain biopsy-proven HSV encephalitis and is not a useful diagnostic tool.

Brain Biopsy

Prior to the availability of PCR testing, brain biopsy was the only accurate diagnostic test, but nowadays, it is rarely performed. It may be useful in patients with suspected HSE who are PCR negative and in those who deteriorate despite acyclovir. In dubious cases, it can identify potentially treatable mimickers of encephalitis. In one series, brain biopsy revealed an alternative diagnosis (treatable in 50% of cases) in one-fifth of patients with suspected HSE [57].

The histopathological basis of HSE is the association of damage to the parenchyma, reactive gliosis, and inflammatory cellular infiltration. Macroscopically, the brain shows necrotic bilateral, asymmetrical lesions of the temporal and orbital cortices. Microscopically, necrosis is associated with diffuse inflammation and perivascular lymphocytic infiltration [58]. Viral intranuclear inclusions are inconstant, and viral antigens are detectable only at early stages [59]. Later, gliosis and microglial proliferation develop. Viral DNA is detectable in the brain tissue [60].

Differential Diagnosis

Many infectious and noninfectious conditions can mimic HSE. In a retrospective study of 432 patients who underwent brain biopsy for a presumed diagnosis of HSE, 45% had a final diagnosis of HSE, 22% had other identifiable causes of their symptoms, and 33% remained undiagnosed [57]. Infectious encephalitis cannot be separated on clinical grounds. Among cases with biopsy-proven HSE, there are no distinguishing clinical characteristics with other encephalitis.

HSV-1, varicella zoster virus, Epstein–Barr virus, mumps virus, measles virus, and enteroviruses are responsible for most cases of sporadic viral encephalitis in immunocompetent individuals [2]. This also depends on geographic and environmental factors: West Nile virus has become an important cause of viral encephalitis in the United States. Nonviral infectious causes of encephalitis include tuberculosis, rickettsial disease, and trypanosomiasis. Involvement of the CNS has also been reported recently in a 81-year-old male affected by meningoencephalitis in the context of an infection with the Zika virus [61].

Epidemiological and demographic features, such as prevalent or emergent infections in the community, occupation, a history of travel, and animal contacts, may provide helpful clues.

There are postinfectious and noninfectious encephalitis that occur without direct brain infection. Acute disseminated encephalomyelitis is an example of postinfectious encephalitis, more frequent in the young. Noninfectious causes include antibody-associated encephalitis, often paraneoplastic [44].

Encephalitis should be differentiated from encephalopathy, the latter defined as a diffuse disruption of brain function without a direct structural or inflammatory process. It can be caused by drug intoxication, systemic organ dysfunction (e.g., liver, kidney, pancreas), or systemic infection. In contrast to encephalitis, CSF values are usually normal, and there is no parenchyma inflammation on neuroimaging.

Treatment

Acyclovir remains the therapy of choice for HSE since two randomized trials in the 1980s showed that it reduced the mortality to <20–30%, while vidarabine had a mortality rate in excess of 70%. The functional status was significantly better in the acyclovir-treated patients [62, 63].

Acyclovir is an acyclic nucleoside analog that is a substrate for HSV-specified thymidine kinase and is selectively phosphorylated by HSV-infected cells to acyclovir monophosphate and then by cellular enzymes to acyclovir triphosphate, a competitive inhibitor of viral DNA polymerase. Acyclovir triphosphate is incorporated into the growing DNA chain of the virus causing chain termination. Acyclovir has potent in vitro activity against both HSV-1 and HSV-2. Because acyclovir is only effective in stopping viral replication, it should be given early to prevent extensive replication and CNS damage. Patients with advanced age, a reduced Glasgow coma score, or delay of >48 h between admission and treatment [45] have the worst outcome.

Acyclovir dosing in the randomized trials was 10 mg/kg/8 h a day for 10 days. However, relapses after 10 days of treatment may occur [64], likely due to immune-mediated, inflammatory reaction to the infection (read below) [62, 64, 65]. The presence of choreoathetoid movements during relapses conveys a poor prognosis and might also be due to an immune-mediated process [66].

Nonetheless, there is evidence for continuing viral replication in some cases, including the appearance of new lesions distant from the initial site of HSE and positive CSF PCR [21, 45, 65]. Thus, most clinicians extend its use to 14–21 days in confirmed cases, and some advocate repeating a CSF examination at 14–21 days and continuing treatment until the CSF PCR becomes negative [28]. The duration of therapy for immunosuppressed patients is 21 days [33]. Dosing for neonatal HSE is 60 mg/kg/day. Pediatric HSE suffers clinical relapses in 30% of cases.

Later relapses appearing several weeks after HSE occasionally occur [45]. They can represent a true relapse of HSE or, more likely, an immune-mediated disorder triggered by HSV and mediated by antibodies against cerebral NMDA receptors (the GluN1 subunit). The patient develops neurological or psychiatric symptoms resistant to acyclovir therapy without evidence of new brain lesions on MRI; herpes

virus PCR in the CSF at that point is negative, indicating the absence of active viral infection [67]. A retrospective analysis of CSF samples from 44 patients with PCR-proven HSE showed the presence of NMDA receptor antibodies in 13 of them (30%) [68]. Anti-NMDA receptor encephalitis in adults evolves into stages, with an initial prodromal phase with fever, malaise, and myalgias followed within a few weeks by psychiatric or behavioral problems, including anxiety, seizures, choreoathetoid movements, and autonomic instability, among others. Chorea relapses are more common in children and are associated not only with autoantibodies to NMDA receptor but also with antibodies to dopamine-2 receptor [69, 70]. Symptoms in children are often underrecognized. Autoantibodies may persist in serum for long periods of time.

Regarding acyclovir dosage, it should be considered that CSF levels of acyclovir average only 30–50% of plasma levels, the reason why the dose used for treatment of CNS infection (30 mg/kg/day) is double than that used for the treatment of mucocutaneous or visceral disease (15 mg/kg/day). Given orally, acyclovir does not achieve adequate CSF levels; however, its valine ester, valacyclovir, has good oral bioavailability and is converted to acyclovir after absorption [71]. Valacyclovir may have a role in patients with HSV detectable in the CSF after 2–3 weeks [10]. Whether prolonged oral valacyclovir therapy improves long-term outcomes is not clear. In one study an additional 3-month course of oral valacyclovir did not provide additional benefit as evidenced by neuropsychological testing [72].

Acyclovir should be empirically started upon suspicion of HSE and continued until a definite alternative diagnosis is established. Otherwise, it may be continued for 10 days, even if PCR is negative. One case of HSE with normal cerebral MRI scan has been reported, where the diagnosis of HSE was made by PCR from a CSF sample obtained on the day of admission that became negative after 8 days of acyclovir therapy [73].

Acyclovir is excreted unchanged in the urine, so renal impairment can precipitate acyclovir toxicity, and in turn high-dose acyclovir may result in renal failure. Transient renal insufficiency is the main side effect, usually caused by crystallization of the compound in the renal parenchyma. It manifests after 4 days of intravenous therapy and occurs in 20% of patients [74]. Slow drug administration (>1 h) and good hydration can partly avoid it.

Occasionally, acyclovir induces a toxic encephalopathy that causes confusion with the encephalitis itself. Concomitant renal dysfunction may point to this side effect. Other rare adverse events include hepatitis and bone marrow failure.

Acyclovir resistance occurs in the immunosuppressed, organ transplant recipients, and HIV patients. It affects 5–25% of immunocompromised patients receiving long-term prophylactic treatment with acyclovir [75]. Foscarnet, an inhibitor of viral DNA polymerases by binding to the pyrophosphate-binding site, is recommended in acyclovir-resistant HSE (60 mg/kg intravenously infused over 1 h every 8 h for 3 weeks). Foscarnet can cause a dose-related, reversible renal impairment, electrolyte wasting, nausea, paresthesias, and seizures. Cidofovir, a nucleoside analog that is phosphorylated to its active compound by cellular enzymes [76], is the second-line alternative. Cidofovir can be administered once weekly, is nephrotoxic,

and should be administered with probenecid to decrease nephrotoxicity. However, acyclovir-resistant HSE has not been reported in immunocompetent patients, and second-line drugs should be used only in patients with clinically suspected HSE who continue to deteriorate despite acyclovir therapy with a reactive CSF in whom alternative possibilities have been excluded [33].

Corticosteroids are often used, especially in patients with marked cerebral edema, brain shift, or raised intracranial pressure, but their role remains controversial because of their potential to facilitate viral replication. A retrospective analysis of 45 patients with HSE showed that older age, lower Glasgow coma score on admission, and lack of administration of corticosteroids were significant independent predictors of a poor outcome [77].

Surgical decompression for HSE may be indicated in selected cases for impending herniation or increased intracranial pressure refractory to medical management, improving the outcome in individual cases [78]. Intracerebral hematoma as a complication of HSE is rare, with less than 25 cases reported in the literature. Early surgical decompression can lead to a good neurological outcome [79, 80].

Supportive therapy is also essential in the management of HSE patients, who should have access to intensive care unit equipped with mechanical ventilators. Careful attention must be paid to seizure control, respiratory function, cardiac rhythm, fluid balance, prevention of deep vein thrombosis and aspiration pneumonia, and medical management of raised intracranial pressure and secondary bacterial infections.

Prognosis

Despite acyclovir therapy, the current outcome of HSE remains unsatisfactory with high mortality and morbidity rates in adults and children [6, 37, 81]. Almost half of HSE survivors are left with serious disability [82]. HSV-2 produces a more diffuse encephalitis with significant neurologic impairment. In a series of 24 infants with HSV encephalitis, only 4 of 14 (28%) survivors with HSV-2 encephalitis were neurologically normal, as compared with nine of nine infants with HSV-1 [83]. Early treatment, immunocompetent state, young age, and normal level of consciousness associate with improved outcome [32].

HSE sequelae include epileptic seizures, neuropsychiatric deficits, mood and behavioral disorders, developmental and learning delay in children, and residual motor or visual deficits. They often result in hospital readmission [6].

Long-term follow-up of treated patients may show residual neurological deficits [84], including dysnomia and impaired learning of verbal and visual material, despite normal performances on standard mental status examination [85].

Postencephalitic epilepsy is often refractory to medical treatment, contributing to an unfavorable clinical outcome. Seizures during acute disease represent the main risk for the development of postencephalitic epilepsy. They occur in 40–65% of patients with HSE and may be the presenting symptom [43]. This high rate is in part due to the predilection of HSV for areas highly epileptogenic such as the mesial

temporal lobes and the orbitofrontal cortex. Epilepsy surgery is a potential treatment option but only in a subgroup of patients suffering from unilateral mesial temporal lobe epilepsy and congruent neuropsychological impairment.

Rehabilitation

Although there are few studies on the outcome of rehabilitation following encephalitis [33], all patients should have access to rehabilitation services. A multidisciplinary assessment and rehabilitation are desirable, including specialists in neuropsychology, neuropsychiatry, speech and language therapy, physical therapy, and occupational therapy. Access to specialists in brain injury rehabilitation is the key to recovery in many cases. The support provided by voluntary sector organizations is helpful for these patients and their families [10].

Varicella Zoster Virus (VZV)

Primary infection with VZV causes varicella (chickenpox), and once the illness resolves, the virus remains latent in the dorsal root ganglia, usually for many years or decades. The virus can reactivate later, often with advanced age or immunosuppression, coinciding with a decline in viral immunity, resulting in a painful dermatomal rash (shingles). Herpes zoster is the most common infection of the nervous system, with one million new cases each year in the United States, mainly elderly [86]. Herpes Zoster may be complicated by postherpetic neuralgia as well as meningoencephalitis, myelitis, retinal necrosis, and vasculopathy, including a multifocal VZV vasculopathy with temporal artery infection [87, 88]. All these neurologic and ocular disorders may develop in the absence of rash, including radicular pain (zoster sine herpete).

Hematogenous VZV dissemination gives rise to small- or large-vessel vasculopathy. The latter is a granulomatous angiitis that occurs weeks or months after the appearance of zoster vesicles in the first branch of the trigeminal nerve (zoster ophthalmicus) in immunocompetent individuals and may result in ischemic or hemorrhagic stroke. Small-vessel vasculopathy appears in immunosuppressed subjects without a preceding skin lesion and causes small ischemic, hemorrhagic, and demyelinating lesions located on the gray–white matter interface of the brain. Finally, periventriculitis in immunosuppressed patients may occur as a consequence of ventricular viral dissemination or of ischemic or demyelinating lesions in the periventricular region and is often associated to hydrocephalus [89].

The prevalence of VZV vasculopathy is unknown, although recent studies showed an increased risk of stroke after herpes zoster. One study found that the risk of stroke one year after herpes zoster ophthalmicus was increased 4.3 times as compared with controls [90, 91].

VZV is the second most common infectious etiology of encephalitis after herpes simplex virus (HSV) in the western world [92–94].

The clinical manifestations in zoster encephalitis are similar to other viral encephalitis. CSF examination shows a mild lymphocytic pleocytosis (around 100 cells per mm^3) with increased proteins and normal glucose. Diagnosis is confirmed by the detection of viral genome in the CSF by PCR or by the demonstration of the presence of specific IgM in the CSF or of an increase in the ratio of viral antibodies in the CSF to that in the blood [87]. Shingles episodes are often accompanied by asymptomatic CSF pleocytosis, as revealed by lumbar punctures performed for other reasons, and this likely reflects a more frequent CNS involvement than clinically suspected in varicella zoster virus infection.

The incidence of varicella zoster virus encephalitis is estimated in 1–2 individuals per every 10,000 cases of varicella. The risk of viral reactivation increases with age, immunosuppressive states, and HIV infection [95, 96]. Despite a lack of randomized therapy trials, the use of intravenous acyclovir (10 mg/kg/8 h) is recommended for 14–21 days. When vasculitis is present, steroids are usually added.

The mortality rate of VZV encephalitis in treated patients is 9–20%, and prognosis seems similar to HSE (Varicella-zoster virus infections of the central nervous system – Prognosis, diagnostics and treatment. [97]. Therapy of herpes zoster is based on antiviral drugs (e.g., valacyclovir, 1 g. 3 times daily for 7–10 days) that accelerate the recovery of rash and acute pain. In immunocompromised patients, intravenous acyclovir (5–10 mg/kg three times daily for 5–7 days) is recommended. A short course of corticosteroids, e.g., oral prednisone, 1 mg/kg for 5–7 days may be added [98].

Cytomegalovirus

Cytomegalovirus (CMV), another member of the *Herpesviridae* family, may cause encephalitis in immunosuppressed patients, particularly with HIV infection, although it occasionally occurs in immunocompetent patients. CMV is the commonest opportunistic infection in AIDS patients. Clinical presentation is similar in the immunocompetent and immunosuppressed, although it tends to be more severe in the latter [99]. Patients with CNS complications by CMV often had prior CMV infection, most commonly retinitis, but encephalitis can be the presenting CNS manifestation in AIDS. More commonly, CMV causes a lower-limb ascending polyradiculopathy with marked involvement of the cauda equina and lumbosacral nerve roots. It also results in meningoencephalitis with evidence of ventriculitis with subependymal enhancement as shown by MRI. Presentation as a Wernicke's encephalopathy-like syndrome has been reported [100].

Therapy is often disappointing and includes intravenous ganciclovir (5 mg/12 h) for 2 weeks followed by a maintenance dose of 5 mg/kg/day for one more week. Some experts recommend adding foscarnet (60 mg/kg every 8 h or 90 mg/kg intravenously every 12 h) during the first 2 weeks. Therapy in immunosuppressed patients should continue for 6 weeks.

In the era before combined antiretroviral therapy (cART), the prognosis of central nervous system CMV infections in HIV patients was poor, even with CMV antiviral

combined therapy such as ganciclovir and foscarnet [101]. Nowadays, with preservation or reconstitution of cellular immunity, the prognosis has improved [99].

Enterovirus

They are RNA viruses of the *Picornaviridae* family transmitted by the fecal–oral route and through respiratory secretions and are the agents of hand, foot, and mouth disease, skin rash, myocarditis and pericarditis, and pleurodynia, among others. As for the CNS complications, they are responsible for 10–20% of encephalitis cases in which an etiologic agent is identified [2]. They more commonly cause aseptic meningitis in the summer and are responsible of approximately one-half of aseptic meningitis cases in children [102].

The initial classification divided them into five subgenera: polioviruses, group A coxsackieviruses, group B coxsackieviruses, echoviruses, and newer enteroviruses. A classification based on RNA homology within the capsid divides the nonpolioviruses into four classes, designated A through D.

Coxsackie and echovirus are the most common causes of viral meningitis [103]. Of the 96 current human serotypes, the most commonly implicated in encephalitis are echoviruses (6, 9, and18) and coxsackieviruses (A9, B2, and B5). They usually cause a benign disorder with nonspecific clinical manifestations, although infection in agammaglobulinemia patients may be severe (echovirus 11 is usually responsible). CSF examination reveals a moderate lymphocytic pleocytosis (usually < 1000 cells per mm^3) with normal glucose and slightly elevated proteins. Brain MRI is often normal or shows meningeal contrast enhancement. Confusion with partially treated bacterial meningitis is frequent, so antibiotics should be maintained until CSF culture results are obtained.

It is well known that a poliovirus infection can result in poliomyelitis, but in addition to polioviruses, other enteroviruses, such as Enterovirus 71 and enterovirus D68, can cause polio-like paralysis [104]. Epidemics of infection due to enterovirus 71 have been identified in Taiwan and other Southeast Asian countries, Eastern Europe, and the United States [105]. Enterovirus 71 has been associated with acute flaccid paralysis and bulbar and brainstem encephalitis that may be fatal. Children with enterovirus 71 infection and CNS involvement often have long-term neurological sequelae and delayed neurodevelopment [106].

Arboviruses: Tick-Borne Encephalitis

Arboviruses (arthropod-borne virus) are transmitted by ticks or mosquitoes and cause heterogeneous clinical presentations that include asymptomatic infection, febrile syndrome, hemorrhagic fevers, and meningoencephalitis [107]. Although most arbovirus infections are mild or asymptomatic, they represent the most frequent cause of epidemic encephalitis worldwide. After replicating in the vectors, arboviruses spread to salivary glands and are inoculated by vector bite.

Arboviral infections occur in sporadic or epidemic zoonoses that involve birds and rodents as reservoirs. Humans are accidentally infected and are usually dead-end hosts. There are over 150 arboviruses that are pathogenic to humans and belong to different RNA virus families that include the *Togaviridae*, *Reoviridae*, *Bunyaviridae*, and *Flaviviridae* (Table 5.2).

The neurological complications of arboviral infections include aseptic meningitis or encephalitis, and the diagnosis is mainly based on the serological demonstration of specific antibodies in serum and CSF. The presence of specific IgM or a rise in the titer of IgG is highly suggestive of active infection in paired serum specimens. Viral genome can be detected by PCR in the CSF of patients with certain arboviruses [108]. Viral isolation is possible in laboratory animals or in tissue culture depending on the viral load in the blood. There is no specific therapy for arboviral infections, and arthropod-bite prevention and vaccination when possible are the most effective measures.

Flaviviruses are particularly important to human disease, since they include many pathogenic agents, including West Nile virus, yellow fever, Japanese encephalitis virus, and dengue virus. All these infections are discussed together with other tropical encephalitis in Chap. 6. We will center here on tick-borne encephalitis, which is also caused by a flavivirus frequent in Europe, particularly in Russia, Austria, and other countries of Central and Western Europe.

Tick-borne encephalitis virus is transmitted by *Ixodes* ticks, the same vector that transmits the spirochetal agent of Lyme disease. Infection occurs most often in summer, when tick activity is high and exposure (leisure activities) is more frequent. Many countries show an increasing number of reported cases with important oscillations between years [109]. About 10,000 cases of tick-borne encephalitis are reported annually in Europe and Russia [110]. Approximately one-third of persons infected with tick-borne encephalitis virus develop clinical symptoms [111]. The disease follows a biphasic course. After an incubation period of about 8 days (range 4–28 days) following the tick bite, viremia occurs and is accompanied by fever, headache, and malaise. Tick bite can go unnoticed (only two-thirds of patients remember the tick bite), and serology at this point is negative, complicating the diagnostic suspicion. After an asymptomatic period of 1 week, encephalitis develops, sometimes accompanied by flaccid paralysis. At this point specific, IgM against the virus should be present in the serum, and IgG starts to rise. A serum sample taken 4 weeks later will show a three- to fourfold rise in the IgG titer. The CSF shows a moderate pleocytosis (usually less than 100 cells/mm3), initially polymorphonuclear and later lymphocytic, with normal glucose and increased proteins.

Brain MRI shows abnormalities in 20% of patients, more often in the cerebellum, thalamus, caudate nuclei, and brainstem. The electroencephalogram shows nonspecific abnormalities.

These viruses have a predilection for gray matter, particularly the anterior horn of the spinal cord, and some patients develop a flaccid paralysis that bears some resemblance to poliomyelitis, although in this case, upper limbs are preferentially involved in contrast to poliovirus infection.

Table 5.2 Differential diagnosis of herpesvirus encephalitis

Acute viral encephalitis	
Sporadic	
Herpesviruses	Varicella zoster virus Epstein–Barr virus Cytomegalovirus Human herpesvirus 6 Human herpesvirus 7
Enteroviruses	Enterovirus 70 Enterovirus 71 Poliovirus Coxsackieviruses Echoviruses Parechovirus
Paramyxovirus	Measles virus Mumps virus
Others	Influenza virus Adenovirus Erythrovirus B19 Rubella virus Choriomeningitis virus HIV
Arthropod-borne and zoonotic	
Flaviviruses	West Nile virus Japanese encephalitis virus Tick-borne encephalitis virus Dengue viruses
Alphaviruses	Western equine encephalitis virus Eastern equine encephalitis virus Venezuelan equine encephalitis virus Chikungunya virus
Others	Lacrosse virus Colorado tick fever virus Rabies virus Chandipura virus Nipah virus Toscana virus
Nonviral encephalitis Zika	
Bacteria	
Mycoplasma pneumoniae *Rickettsiae* *Coxiella burnetii* *Tropheryma whipplei* *Bartonella henselae* *Brucella* spp. *Listeria monocytogenes* *Treponema pallidum* *Borrelia burgdorferi* Nocardiosis Actinomycosis	

(continued)

Table 5.2 (continued)

Parasites	
Trypanosoma brucei	
Naegleria fowleri	
Balamuthia mandrillaris	
Angiostrongylus spp.	
Fungi	
Coccidioidomycosis	
Histoplasmosis	
Blastomycosis	
Para-/postinfectious encephalitis	
Acute disseminated encephalomyelitis (ADEM)	
Acute hemorrhagic leukoencephalopathy (AHLE)	
Acute necrotizing encephalitis (ANE) in children	
Bickerstaff's encephalitis	
Noninfectious causes	
Vascular	Systemic lupus Primary angiitis of the central nervous system Subarachnoid hemorrhage Subdural hematoma Ischemic stroke Behcet's disease
Neoplastic	Paraneoplastic encephalitis
Metabolic encephalopathy	Hepatic encephalopathy Renal encephalopathy Hypoglycemia Toxics (alcohol, drugs) Septic encephalopathy Mitochondrial diseases
Antibody-mediated encephalitis	VGKC complex NMDA encephalitis Encephalitis lethargica
Others (*may mimic the clinical picture*)	
Cysticercosis	
Trichinosis	
Cryptococcosis	
Neurosarcoidosis	
Reye's syndrome	
Primary brain tumor	
Brain metastases	
Mycobacterium tuberculosis	
Brain abscess	
Brain empyema	
Parameningeal infections	
Endocarditis	

Modified from [10]

There are successful vaccines, although their effectiveness has not been shown in controlled studies. The mortality rate of tick-borne encephalitis is low, but a considerable proportion of patients with more severe disease show incomplete recovery [109].

Postinfectious Encephalitis or Encephalomyelitis (PE)

This condition is characterized by CNS inflammation and demyelination after viral infection but without the evidence of viral presence or persistence that characterizes viral encephalitis. It also occurs after vaccination and less commonly after infection with other pathogens [112]. In the California Encephalitis Project, which evaluated over 1500 patients with encephalitis, 8% were thought to represent a postinfectious disease process [3].

PE is supposed to be caused by an abnormal immune reaction against CNS self-antigens in response to the eliciting pathogen, and therefore, no evidence of viral presence in the CNS by CSF PCR can be demonstrated. An etiologic agent is only seldom identified, usually serological or clinical demonstration of prior viral infection.

PE is most frequent in children, often associated to childhood exanthematic diseases, and its clinical spectrum is protean, encompassing acute disseminated encephalomyelitis or acute hemorrhagic leukoencephalitis. Importantly, adult patients with PE often present with typical features of acute infection of the CNS.

The CSF in PE shows slightly increased protein levels, moderate pleocytosis, normal CSF glucose levels, and sterile cultures. It shows normal values in up to one-third of patients. MRI shows diffuse areas of abnormal signal involving the brain, brainstem, and spinal cord (Fig. 5.3).

Treatment of severe cases includes pulses of methylprednisolone (1 g daily for 3–5 days) followed by oral steroids (starting 1 g/kg daily and tapering for 4–6 weeks) [112]. Plasma exchange or intravenous immunoglobulin (IVIG) is usually the second step in severe cases.

PE appears as a complication of rubella and mumps, usually as a reversible encephalitis, and less often in the form of Guillain–Barré syndrome or myelitis. Measles complications are discussed in Chap. 6.

Varicella zoster infection in children can be complicated by an immune-mediated acute cerebellar ataxia, which occurs in approximately 1 in 4000 infections. Ataxia appears after the cutaneous lesion and has no specific therapy.

Human herpesvirus 6 infections are responsible for febrile seizures in infancy and rarely can be complicated with encephalitis.

Epstein–Barr virus infection occasionally complicates with acute disseminated encephalomyelitis, Guillain–Barré syndrome, or cerebellitis, among other neurological problems.

Rotavirus infection can also be complicated with encephalitis, seizures, and cerebellitis.

Neurological complications of influenza appear more often in young children, particularly from Asia, and include myelitis, seizures, Guillain–Barré syndrome, and encephalitis.

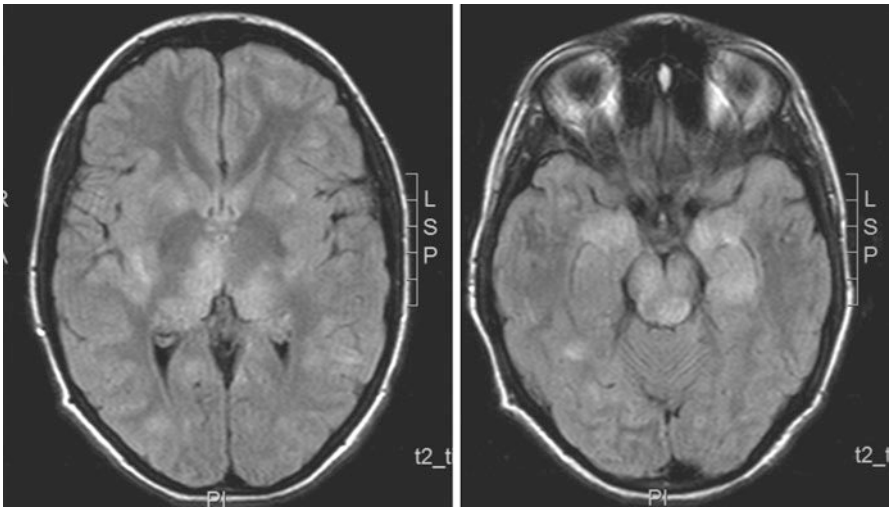

Fig. 5.3 Brain MRI (T2-weighted sequences) from a 16-year-old girl with acute demyelinating encephalomyelitis following a nonspecific upper respiratory infection. There was an extensive involvement of the gray and white matter both supra- and infratentorial. She presented with fever, seizures and decreased level of consciousness, and CSF lymphocytic pleocytosis. The clinical picture and MRI abnormalities normalized over several months after initial intensive steroid therapy.

Recently a variant of PE has been described following herpes simplex virus (HSV) encephalitis (read above).

Reversible Splenial Lesion Syndrome

The presence of transient lesions involving the splenium of the corpus callosum (SCC) has been described in patients with encephalitis or encephalopathy of varied etiology, including infections, high-altitude cerebral edema, metabolic disorders (hypoglycemia and hypernatremia), or antiepileptic drug withdrawal [113].

Most patients with this disorder are children or young adults from Japan. When identified, the most common infectious agents were influenza virus, Epstein–Barr virus, rotavirus, and a miscellaneous of less common bacterial pathogens.

It is characterized by the presence of round, nonenhancing lesions involving exclusively the splenium of the corpus callosum as revealed by magnetic resonance imaging. The lesions are hyperintense on T2-weighted, FLAIR, and DWI sequences and hypointense on T1 sequences and on the ADC map, findings consistent with cytotoxic edema.

The pathophysiology is unclear, and it represents a benign disorder except in those patients with an underlying severe disorder.

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Tropical Viral CNS Infections

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Abstract

Viral infections of the CNS in the tropics and Indian subcontinent are not only different from that encountered in the western world, but many types are constantly emerging. While age-old scourges like polio have recently been contained in these geographical areas to a great extent, thanks to effective vaccination programs, others like Japanese encephalitis, rabies, and measles in the form of subacute sclerosing panencephalitis have been inadequately controlled. In recent times some viruses causing predominant CNS symptoms such as West Nile, Chandipura, and Nipah have emerged. Emerging viruses also include others that may occasionally cause CNS symptoms such as enterovirus, dengue, and chikungunya. The CNS manifestations of most of these viruses may be in the form of aseptic meningitis, encephalitis, or myelitis either in isolated form or in combination. Many of these viruses such as Japanese encephalitis cause large-scale epidemics with high mortality and morbidity. This chapter discusses the current status of many of these viral infections of the CNS predominant in these geographical areas.

Keywords

Viral encephalitis • Myelitis • Meningitis • Tropics • Japanese encephalitis • West Nile • Dengue • Enterovirus • Nipah virus • Rabies • Measles • Chandipura Chikungunya • CNS infection • Viral myelitis • Vaccine derived polio virus Vaccine associated paralytic poliomyelitis

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Viral infections of the central nervous system (CNS) in the tropics are different than those seen in the western developed countries. This is due to different climatic conditions and environment, different insect and animal vectors, different host immunity, and different social and agricultural practices with contribution from inadequate health-care and sanitation facilities in many tropical countries. Climatic and environment changes in recent times have led to the emergence of many other viruses that can cause either altered or fresh CNS disease or spread into new geographical destinations.

The CNS is protected from viral invasion by anatomic barriers and virus-specific and nonspecific host immunity. When viruses do invade the CNS, they can infect the brain, meninges, spinal cord, or cranial nerves either in isolation or in combination, very often with devastating consequences. This is due to the fact that virus-specific treatment does not exist in most instances and adequate supportive treatment cannot be given on time. The silver lining to this scenario is the existence of effective preventive measures chiefly in the form of vaccines that have been used by some countries to control these infections.

This chapter discusses the prevalent viral infections of the CNS in the tropics and the challenges of emerging viral infections of the CNS in the tropics with emphasis to the Indian subcontinent.

Viral Meningitis

Viruses can infect the meninges leading to acute viral meningitis (VM), the most common cause of aseptic meningitis. The responsible causative agents in more than half the cases are enteroviruses (Coxsackie viruses, echoviruses, and polioviruses). Other responsible viruses include the arboviruses, herpes family viruses, and respiratory viruses such as adenoviruses, mumps, and HIV [1]. The etiological profile and incidence of VM in tropical countries like India are unknown because the cost of diagnosis, lack of diagnostic facilities, and benign nature of the disease lead to underreporting. However, epidemics of enterovirus (EV) meningitis in children have been reported from India [2]. Increased incidence of benign neurological illness possibly due to meningitis is seen in patients especially in children during epidemics of Japanese encephalitis (JE) in India [1]. Mumps meningitis is still prevalent in India, possibly due to inadequate vaccination [1]. While all age groups can be affected by the disease, children and elderly are more susceptible to VM. Both EV and mumps meningitis are more common in males.

Some clinical features are common to all VM, and these include headache, fever, myalgia, malaise, chills, sore throat, abdominal pain, nausea, vomiting, photophobia, stiff neck, and drowsiness. Altered consciousness, focal neurological deficits, and seizures suggest associated encephalitis. Meningeal signs can be elicited, and some VM are accompanied by a rash. Parotitis accompanies mumps meningitis, while EV is reported to be associated with hand, foot, and mouth disease, encephalitis, and flaccid paralysis in India as elsewhere. Most cases are self-limiting and

recover completely within 5–14 days. Persistent severe illness should prompt exclusion of other causes which may be difficult [1].

Diagnosis is by characteristic changes in the cerebrospinal fluid (CSF). CSF pressure is usually increased. There is initial increase in polymorphonuclear leukocytes followed by a mononuclear or lymphocytic pleocytosis, usually less than 500/cumm. CSF protein is elevated, while glucose may be normal or decreased. Definitive diagnosis is by virus isolation or demonstration of virus-specific IgM in the CSF. In recent times the polymerase chain reaction (PCR) test has become available for specific viral agents. Rise of specific antibody in convalescent serum of more than fourfold can provide a diagnosis but is time-consuming [1]. Imaging by computed tomography (CT) and magnetic resonance imaging (MRI) usually fails to show abnormalities. Meningeal enhancement on MRI was reported in 9 out of 23 patients in one study from China [3, 4]. However, it is prudent to do imaging as it may help differentiate VM from other clinical mimics such as tubercular meningitis and pickup complications such as hydrocephalus.

Treatment is supportive, symptomatic, and aimed at preventing complications. Analgesics, antipyretics, and antiemetics may be given and fluid balance maintained. Those with more severe disease, altered sensorium, or seizures need more aggressive treatment with hospitalization. Specific treatment with antivirals is indicated if the causative agent is HSV, varicella, or cytomegalovirus. There is available effective vaccination for viruses like measles, mumps, varicella, rubella, and JE and should be used for prevention [1].

Viral Encephalitis

Viral encephalitis (VE) refers to infection of the brain by a virus causing usually a diffuse inflammatory process. Acute VE commonly presents with fever and altered sensorium with or without focal neurological deficit. It may be accompanied by meningeal inflammation as well when the term meningoencephalitis is used. VE may less commonly present as a slower indolent process when the term slow viral infection is used. VE has to be distinguished from acute disseminated encephalomyelitis (ADEM) which is an altered immune response to viral illness or vaccination. This chapter discusses acute viral encephalitides that are endemic to the South Asian region and the Indian subcontinent. It also discusses the problem of emerging viruses of the region with CNS invasiveness. Table 6.1 gives a list of common viruses that are known to cause viral encephalitis in the Indian subcontinent.

The true incidence of VE is difficult to determine as in most cases a viral etiology cannot be confirmed. The term acute encephalitic syndrome (AES) which is defined as acute-onset fever with altered mental status with or without seizures is considered for surveillance purposes. Most AES is due to viral encephalitis. In a review of 25 studies of AES, 28–85% of cases did not have a confirmed viral etiology. There was a wide range of reported incidences varying from 0.9 to 185 per 100,000 in different age groups from both tropical and western settings. In two robust prospective studies of AES, the reported incidence was 6.34 and 7.4 in a tropical and western

Table 6.1 Common causes of viral encephalitis in the Indian subcontinent.

Herpes viruses – HSV (1 and 2), varicella zoster, CMV, EBV, HHV6
Adenoviruses
Influenza (including H1N1)/parainfluenza
Enteroviruses – Poliovirus, echovirus, Coxsackie, EV71, EV75, EV76, EV89
Mumps, measles, rubella
Rabies
Arboviruses – JE, WNV, dengue, Kyasanur forest disease, chikungunya, Chandipura
Paramyxoviruses – Nipah

HSV herpes simplex virus, *EV* enteroviruses, *JE* Japanese encephalitis, *WNV* West Nile virus

setting, respectively [5]. In a recent study from Central India, the incidence of AES reported was 16 per 100,000 [6]. In the Indian subcontinent, the etiological profile of AES has been changing over the years. While most studies reported from India during the period of 1975–1999 identified Japanese encephalitis virus (JEV) as the main cause of AES, studies published after 2000 have identified Chandipura and EV as the most common causes, in both outbreaks and surveillance studies. This may be due to vaccination campaigns against JEV, unmasking of other etiological agents after incidence of JE has come down, and advancement of diagnostic techniques over the years [7].

Most viruses gain entry into the CNS through the hematogenous route (e.g., JEV) and less commonly through the neuronal route (e.g., HSV). Despite the variety of viruses that can cause encephalitis, there is some uniformity in the pathology they produce in the immunocompetent host. All encephalitides are accompanied by cell death or "neuronophagia" involving destruction of neurons with disruption in their cell membranes and to some extent the glial cells. The dead cells disappear, and the remnants are surrounded by microglial cells and lymphocytes forming so-called glial stars, nodules, clusters, or knots. The rate at which cells undergo neuronophagia varies and can take no more than a few days in acute encephalitis to months to years in slow viral infections. The scale of neuronophagia also varies between different encephalitides. A second type of cell death without lysis is called apoptosis and is seen in some encephalitides. Another common feature of viral encephalitis is the development of inflammatory response to the viral infection. This occurs within few days in the site of infection and is accompanied by variable degree of edema. The perivascular spaces are filled with inflammatory cells, mostly mononuclear cells, macrophages, lymphocytes, and plasma cells forming so-called perivascular cuffs. While necrosis occurs in all encephalitides, the distribution of necrotic lesions within the CNS depends on the selective vulnerability of a particular cell to the invading virus, chiefly due to the requirement of virus-specific receptors that must be present in the cell for it to be susceptible to the virus. For example, poliovirus invades the anterior horn cells binding to the CD155 receptor protein. Not all instances of anatomic distribution of lesions of viral encephalitis can be

explained on the basis of this, however. The temporal lobe specificity of lesions of HSE may have more to do with the neuronal route of spread than viral tropism, as the receptor for the HSV exists in all neurons. Healing of the encephalitic lesions and edematous areas occurs by glial reaction which may continue for weeks to months after the infection. Focal or diffuse atrophy, shrinkage of white matter, and healing of encephalitic and edematous areas by glial reaction are late sequels of the disease [8]. The targeted involvement of some areas of the CNS and associated inflammatory changes are reflected on imaging especially on MRI which is a more sensitive investigation due to its superior contrast resolution in comparison to computed tomography (CT). Late sequels can be picked up on MRI as well.

Japanese Encephalitis

Japanese encephalitis (JE) is a mosquito-borne flaviviral encephalitis that is the most important cause of VE worldwide. It was first recognized in Japan since the 1870s, and despite the fact that JE is vaccine preventable, in the present day, it has spread across Southern and Eastern Asia and the Pacific Rim. The erstwhile term of Japanese B encephalitis was used to distinguish it from von Economo's encephalitis lethargica which was known as Japanese A encephalitis. The term "B" was later dropped. The Nakayama strain of JEV was isolated from a brain of a fatal case in 1935 [9]. In the later part of the 1980s, it was estimated that 50,000 new cases of JE occurred annually in 2.4 billion population in 16 countries affected by JE at that time with an annual incidence of 2 per 100,000 overall [10]. A recent study estimates 68,000 cases to occur annually in 24 JE endemic countries with an incidence of 1.8 per 100,000 overall. Seventy-five percent of the cases occur in children with an annual incidence of 5.4 per 100,000 in this group [11]. About one-third of patients die, while half of those that survive have severe neuropsychiatric sequels [9]. The true incidence of JE is however difficult to establish as the disease is underreported because of variable intensity of surveillance and availability of laboratory diagnostic facility in affected countries.

The JEV is a member of the genus *Flavivirus* and family Flaviviridae. The JEV virion consists of a single strand of positive-sense RNA of approximately 11 kilobase in length. It is wrapped in a nucleocapsid with a surrounding glycoprotein-containing envelope. The virion consists of three structural proteins (core [C], premembrane [PrM], and envelope [E]) and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [12]. Five genotypes of the virus have been described from different geographical areas [13–15]. Genotypes IV and V are the most divergent and have remained confined to their region of origin in Indonesia-Malaysia, while the newer genotypes I through III have spread across Asia.

JE is a zoonotic disease where man is incidentally infected and a dead-end host. The JEV cycle is maintained in nature between water birds and vertebrate hosts through the mosquito vector. Ardeid water birds such as herons and egrets serve as reservoirs and amplifiers of the virus and may be responsible for the spread of the

disease across continents [9]. Among the vertebrate hosts that have been implicated in the spread of JE, pigs are the most important hosts responsible for transmission to man as they can have high and prolonged viremia, are in close proximity to man, and reproduce in plenty providing hitherto uninfected hosts [9]. The virus is transmitted by culicine mosquitoes between birds and pigs. *Culex tritaeniorhynchus* is the principal vector responsible for transmission of JE in South, East, and Southeastern Asia. It breeds in stagnant water such as in rice fields. *C. annulirostris* is the main vector in North Australia. Many other species of Culex, Mansonia, and Anopheles mosquitoes are responsible vectors in India [16, 17]. Man becomes incidentally infected when bitten by an infected mosquito. Only 1 in 25 to 1 in 1000 infections with the JEV are clinically apparent [18]. This is a dead-end infection as man-to-man transmission does not occur due to transient and mild viremia. Human activity such as rice cultivation and pig farming, conditions that are abundant in Asia, contributes to maintenance and spread of the disease.

JE is predominantly a disease of children and young adults. However, when it occurs in an area for the first time as has been reported from Sri Lanka, India, and Nepal, adults may be equally affected. Nonimmune travelers to endemic areas stand at risk of acquiring the disease [9]. Two epidemiological patterns of JE have been described. JE tends to occur in epidemic forms in the northern part of the tropical zone of Asia such as in China, Japan, Nepal, Northern and Northeastern India, Korea, North Vietnam, and Thailand. In southern tropical zones of Asia such as in Southern Vietnam, South Thailand, Indonesia, Malaysia, the Philippines, Sri Lanka, and Southern India, JE is endemic with peak cases occurring after the rainy season [19]. This pattern is possibly related to temperature rather than amount of rainfall or the strain of JEV [20].

The geographical area of JE prevalence has been steadily increasing in the past 70 years or so (Fig. 6.1). Though the mechanism of spread of JE into new areas is not fully known, changing land usage and agricultural practice, deforestation, increasing rice growing, windblown mosquitoes, bird migration, and movement of infected hosts are factors that possibly contribute to the spread [21]. Mass childhood vaccination programs in several countries like Japan, Korea, and Taiwan have virtually eliminated JE in them in the recent years. In other Asian countries that have been slow in implementing such programs, the disease still persists. Currently approximately half of the reported JE cases of the world are from China [11]. However, the annual incidence of JE in China is decreasing in the recent years. During the period of 2000 and 2005, the annual incidence of JE decreased from 0.9/100,000 to about 0.4/100,000 [22]. The other big contributor to JE cases of the world is India. During 2006–2009, out of approximately 27,000 cases of JE reported to the World Health Organization, 86% were from India and China [11]. Approximately 4000–8000 new cases occurred during the period 2007–2012 across several Indian states [23]. These figures may be an underestimate as many JE cases in India go unreported.

After the JEV gains entry into the human body through the bite of the infected mosquito, it multiplies locally and in the regional lymph nodes. Thereafter it spreads to secondary lymphoid organs before entering the blood circulation. There is a

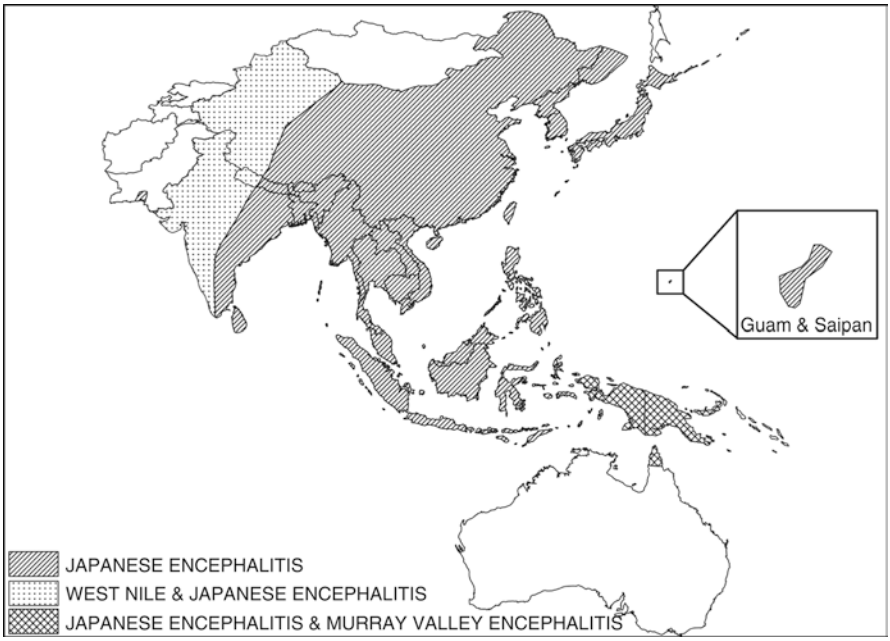

Fig. 6.1 Map showing distribution of Japanese encephalitis

transient viremia which spreads the virus to peripheral organs such as the kidney, liver, and spleen after which the virus spreads to the CNS by crossing the blood-brain barrier (BBB) [24]. JEV may cross the BBB by passive transport across the vascular endothelium, by an active replication process in the vascular endothelial cells or by a "Trojan horse" mechanism by which it is carried across by inflammatory cells [25]. The pathological changes in the brain in fatal JE cases include leptomeningeal haziness, vascular congestion, cerebral edema, and brain swelling. Histologically there is leptomeningeal mononuclear inflammation extending into the perivascular spaces with formation of perivascular cuffs. Two types of characteristic lesions are seen: the cell-rich gliomesenchymal nodule and the cell-poor necrolytic lesion. The gliomesenchymal nodule is formed by aggregates of microglial cells and lymphocytes around degenerating neurons. These lesions are seen in the medulla, thalamus, substantia nigra, pontine and reticular nuclei of the brainstem, cerebral cortex, dentate nuclei and Purkinje cells of the cerebellum, and Ammon's horn of the hippocampus. The necrolytic lesion is seen in the cerebral cortex, thalamus, corpus striatum, midbrain, and pons [26–28].

Clinically apparent JEV infection can present as encephalitis, aseptic meningitis, or acute flaccid paralysis. The incubation period of JE is 5–15 days [21]. The disease can occur in an acute or less commonly in a subacute form. The course of the disease can be divided into three stages: a prodromal stage, an encephalitis stage, and a convalescent stage. The prodromal phase precedes CNS features and is

characterized by constitutional symptoms such as malaise, fever which may be high grade and accompanied by chills, headache, nausea and vomiting, and diarrhea which is more common in children. This is followed by the encephalitic stage in 3–5 days. This is characterized by altered sensorium, convulsions, focal neurological deficits, behavioral changes, movement disorders, and associated meningitis. Focal neurological deficit may include motor paralysis and cranial nerve deficits. Behavioral changes may present in the form of restlessness, disorientation, delirium, and irrelevant talk. Movement disorders include head nodding, dystonia, coarse tremors, choreoathetosis, and parkinsonian features such as masklike facies, rigidity, and oculogyric crisis. Most deaths occur during the first 5 days of illness. The encephalitic stage may persist from a week to a few weeks if there are complications. Those that survive this stage either regain complete neurological function or may be left with residual neurological deficits in the convalescent stage that lasts from a few weeks to months [28]. Only one-third of the patients recover completely, while majority are left with mild to severe residua. Residual deficits include intellectual impairment, speech defects, and motor deficits. Secondary infections are frequent complications during convalescence [29]. Clinical features that have been associated with a poor outcome include short prodromal stage, deep coma, abnormalities in tone and breathing, decerebrate posturing, and seizures [9, 30].

Other than the classical encephalitic form of presentation of JE, few atypical presentations have been reported. JE can present with aseptic meningitis. Febrile seizure-like presentation has been reported in children. Adolescents can present with abnormal behavior as an initial presentation [29]. Acute flaccid paralysis has been reported in a subgroup of patients either as the lone presentation or with progression to subsequent encephalitis [31]. A biphasic illness pattern of JE has been reported where there is relapse of meningoencephalitic symptoms. In the second phase, symptoms may be different but still conform to the known features of JE, and MRI may show fresh areas of involvement, also conforming to JE lesions [32, 33].

Peripheral blood examination in JE may show polymorphonuclear leukocytosis. CSF examination shows elevated opening pressure. Increased CSF cell counts usually less than 1000/cumm. May be seen with lymphocytic predominance and at times with increased polymorphs. CSF protein is elevated in two-thirds of the patients [28]. Abnormal electroencephalographic (EEG) findings may be seen which include diffuse theta and delta waves, burst suppression, epileptiform activity, and alpha pattern coma. These findings are nonspecific and do not correlate with clinical status and outcome [34].

Imaging studies by CT or MRI reflect the pathological changes in the brain. The typical imaging findings are lesions in the thalami, substantia nigra, basal ganglia, and hippocampi (Fig. 6.2). Lesions can also be seen less commonly in the cerebral cortex, midbrain, pons, medulla, cerebellum, and white matter. MRI is more sensitive in picking up these lesions and should be the investigation of choice. Bilateral or unilateral, asymmetric thalamic lesions are the hallmark of JE and can be seen in 87–94% patients with abnormal MRI. JE lesions are hyperintense on T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) sequences and slightly hypointense to normal brain on T1-weighted images. Acute lesions have some

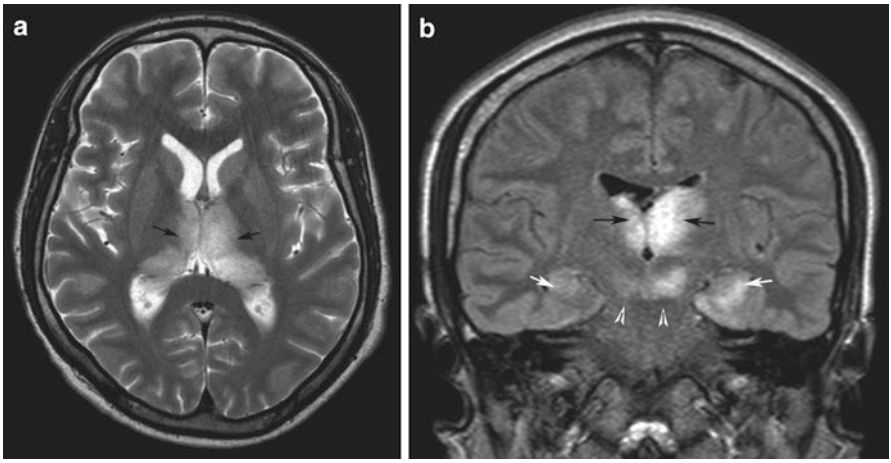

Fig. 6.2 A 50-year-old male with Japanese encephalitis. (**a**) T2-weighted axial MRI image showing bilateral thalamic lesions (*black arrows*). (**b**) Coronal fluid-attenuated inversion recovery sequence showing bilateral thalamic (*black arrows*), hippocampal (*white arrows*), and substantia nigra (*white arrowheads*) lesions. The lesions are asymmetric, even though they are bilateral and have local mass effect

amount of local brain swelling. Evidence of hemorrhage may be seen. The lesions do not enhance on post-gadolinium-enhanced images [3, 35–37]. A characteristic pattern of hippocampal involvement with the involvement of the tail and body and usual sparing of the rest of the temporal lobes with associated lesions of JE differentiates it from herpes simplex encephalitis (HSE) [37]. In an endemic area, the presence of thalamic lesions in a patient of AES is 100% specific and 23% sensitive for the diagnosis of JE with positive and negative predictive values of 100 and 42.1%, respectively [38]. When using a current generation 1.5 T MRI, sensitivity and specificity were 90.9 and 50%, respectively, in the first week of onset of JE which is comparable to the commonly used test for detection of JE, specific immunoglobulin (IgM) detection by immunoassay capture in the CSF (CSF Mac-ELISA) [3]. The presence of thalamic lesions on MRI can therefore be a rapid, sensitive, and fairly specific test for establishing a diagnosis of JE in AES in an endemic area. The JE lesions tend to be more conspicuous on conventional MRI sequences than on diffusion-weighted (DW) sequences [3]. No correlation between the radiological features of JE and clinical outcome has been found [39]. However, a significant association of thalamic lesions on imaging was found with development of dystonia [39].

The definitive diagnosis of JE is either by (1) virus isolation or (2) by demonstration of virus-specific antigen or antibody in the CSF/blood. JEV isolation can be done by intracerebral inoculation of clinical specimens in suckling mouse brain. Viral cell cultures used more recently include primary chick or duck embryo cells and lines of Vero. JEV antigen detection tests in the CSF include reverse passive

hemagglutination, immunofluorescence, and staphylococcal coagglutination tests using polyclonal or monoclonal antibodies [29]. JEV antibody detection by Mac-ELISA is currently the most widely used test to demonstrate the antibody in the CSF or blood [40]. However, it is to be noted that this test may be positive in the CSF in the first week of onset of the disease in only 50% of patients, although it is invariably positive beyond the first week [28]. Many newer modifications of this test are currently available which are simpler and more convenient to use especially in rural hospitals [9]. Viral genomic mapping by reverse transcriptase-polymerase chain reaction (RT-PCR) tests has been developed in recent times.

There is no definitive treatment of JE. A number of antiviral agents such as INF alfa-2a [41] and diethyldithiocarbamate [42] have been tried but have not shown any improvement of outcome of JE. Corticosteroids have not shown any benefit either [43]. Oral minocycline is a drug that has shown promise in some recent trails. Even though no statistically significant difference in outcome was observed in patients of AES receiving the drug versus those receiving placebo in a randomized control trial from India, a trend toward better outcome was observed in patients older than 12 years and in Glasgow Outcome Score in 3 months [44]. In another trial from India conducted in confirmed JE cases, minocycline was effective in reducing duration of symptoms like fever and altered sensorium and mean length of hospitalization [45]. In another feasibility randomized double-blind placebo-controlled trial of intravenous immunoglobulin (IVIG) containing JEV neutralizing antibody was conducted in Nepal. Though no significant difference in outcome between treatment and placebo group was demonstrated at discharge or follow-up, approximately 16 times higher JEV-specific neutralizing antibody was demonstrated in treatment group. The study concluded that IVIG treatment is an appealing option for JE treatment that warrants further study [46]. The above studies provide a silver lining for the therapy of JE in the future. Another drug that has been shown to be effective in vitro is N-methylisatin-beta-thiosemicarbazone [47]. Current treatment is supportive and is aimed at reduction of intracranial pressure, optimization of blood pressure to maintain adequate cerebral perfusion, and prevention of secondary infection [29].

Vaccination of the population at risk has been an effective means of controlling JE since the 1940s. Currently about 15 types of JE vaccines are in use, all based on genotype III virus JEV strain. Four major types of JE vaccine are in use:

1. Inactivated vero cell vaccines
2. Live attenuated vaccines
3. Chimeric vaccines
4. Inactivated mouse brain-derived vaccine

Currently there has been a shift away from the mouse brain vaccines used extensively earlier by several countries for mass immunization. This is because of increased reactogenicity, number of doses required, uncertain duration of protection, and need for repeat boosters. A detailed analysis of the properties, dosages, and proposed recommendations of JE vaccine use can be found in the background paper

on JE vaccines published by the Strategic Advisory Group of Experts of the WHO in 2014 [48]. Despite effective vaccines JE cases are being reported from endemic regions every year. This may be due to lack of awareness of the disease, lax immunization schedules, and infection of adults with low immunity especially in virgin areas [49]. Recently there have been reports of virus emergence in certain areas with a gradual shift from genotype III to I in many endemic areas in Asia [50, 51]. All currently available vaccines have been developed against the genotype III. With the emergence of other strains, there remains a concern for the effectiveness of these vaccines. Though preliminary reports indicate that some of the currently used vaccines are effective against genotype I as well [52], effectiveness against genotype V may be of concern [53].

Besides vaccination other measures such as prevention of exposure to mosquito bites, vector control measures, separation of piggeries from human dwellings, and vaccination of pigs have been used effectively for JE control.

West Nile Encephalitis

West Nile virus (WNV) is a positive-stranded RNA virus of the family *Flaviviridae* that is closely related to other flaviviruses such as JEV, Murray valley encephalitis virus, and St. Louis encephalitis virus. A closely related virus, the Kunjin virus, has now been classified as a subtype of WNV. Five lineages of WNV have been described out of which only lineage 1 is known to cause neuroinvasive disease [54]. WNV is transmitted to humans by mosquitoes. Various species of Culex mosquitoes have been implicated in the spread of WNV to man. In India, the vector implicated primarily is *Culex vishnui* besides other Culex species [55]. Man is a dead-end host like in JE due to low viremia which prevents further transmission of the virus. In nature, the virus is maintained in a cycle involving birds and mosquitoes. Several species of birds have been implicated as vertebrate carriers and amplifiers in different WNV prevalent geographical areas. In India ardeid birds like pond herons and cattle egrets have been implicated [55, 56]. Man-to-man transmission does not occur. However, the virus can spread transplacentally and by breast-feeding to newborns or by blood transfusion [54].

WNV was first isolated in the West Nile district of Uganda in 1937. It is today the most widespread flavivirus across the world and is distributed throughout Africa, the Middle East, Europe, many parts of Asia, Australia, and the USA. Outbreaks have occurred in several countries in the past 50 years with the largest outbreaks reported from Greece, Israel, Romania, Russia, and the USA [57]. In India, WNV was first reported in 1952 [58]. The virus has since been reported in Southern, Central, Western, and Northeastern India [54, 59]. Despite the abundant presence of the mosquito vectors of WNV and the neurovirulent strain of the virus, large-scale epidemics in the lines of those seen in the Western Hemisphere, Europe, and the Middle East are not seen in the Indian subcontinent. Though the cause for this is not known, the presence of other flaviviruses may offer cross protection for the WNV or dual infections of the vectors with JE, and WNV may lead to interference. Also, the

WNV vectors are zoophilic and do not prefer to feed on birds which may decrease the efficacy of the WNV transmission cycle [56]. However, epidemics of febrile illness and encephalitis due to WNV have been reported from Western India [55]. It is now being recognized in India that patients presenting with AES in the summer may also be due to WNV encephalitis. In one study of AES from Northeastern India where JE is endemic, 11% of patients were due to WNV [59].

Animal models suggest that the WNV replicates locally at the site of inoculation with subsequent spread to draining lymph nodes with resultant viremia and infection of the peripheral organs such as the spleen and kidney. Although it is likely that the CNS is invaded through the hematogenous route, other routes of entry are possible such as through the olfactory bulb, through passive transport through choroid plexus epithelial cells, through infected immune cells, or through retrograde axonal transport from infected peripheral neurons [60]. Fatal cases of WNV encephalitis show evidence of encephalitis and meningoencephalitis. Histologically there is evidence of perivascular inflammatory change with microglial nodule formation with neuronophagia involving the gray and white matter. The brainstem is typically involved with involvement of the temporal lobes, basal ganglia, cerebellum, and cortex. Spinal cord and cranial nerve root involvement may be seen [61, 62].

The incubation period in humans is approximately 2–15 days [54]. Most (80%) WNV infections are asymptomatic. Most symptomatic patients develop West Nile fever which is usually a self-limited disease characterized by fever, headache, fatigue, malaise, muscle pain, and weakness. GI symptoms and an upper trunk and extremity macular rash may sometimes manifest. CNS disease is seen in less than 1% of patients. This may manifest as aseptic meningitis, encephalitis, acute flaccid paralysis, or Guillain-Barré syndrome [54, 60].

CSF examination usually shows increased cells (mostly lymphocytes) with increased protein and normal glucose. Virus-specific Mac-ELISA test to detect IgM antibody in the CSF within 8 days of disease onset is the most efficient diagnostic test for WNV encephalitis as the antibody does not cross the blood-brain barrier [63].

CT usually does not show any abnormalities, whereas a third to more than half of MRI scans in WNV encephalitis are abnormal [63–65]. Leptomeningeal involvement may be seen as FLAIR hyperintensities or meningeal enhancement. White matter involvement mimicking demyelinating lesions may be seen in 10–50% of the patients. On MRI anatomic areas involved are the basal ganglia, thalami, mesial temporal lobe, midbrain, pons, and cerebellum [64, 65]. Diffusion-weighted imaging (DWI) abnormalities may be seen in the gray and white matter in as many as half of the patients. Patients with abnormalities on both DWI and T2-weighted imaging seem to have a poorer outcome when compared to patients with normal scans or with lesions seen only on DWI [64].Anterior horn cell involvement with nerve root enhancement has been seen in patients with acute flaccid paralysis [64, 65].

Treatment of the disease is mainly supportive and symptomatic as no specific treatment exists. There is anecdotal evidence of efficacy of intravenous immunoglobulin in the treatment of WNV CNS invasive disease (see section on viral

myelitis below). No approved vaccine is available for humans. Vector control methods described for control of Culex mosquitoes have been suggested in countries like India for the control of the disease [55].

Dengue

Dengue is the most rapidly spreading arboviral disease in the world. The actual incidence and prevalence of the disease is difficult to estimate due to underreporting and misclassification. A recent study estimates 390 million dengue infections to occur every year of which 96 million manifest clinically with any severity of the disease [66]. Another study estimates that 3.9 billion people in 128 countries are at risk for infection with dengue virus [67]. The disease is widespread throughout the tropics. In countries of the South Asian region such as India, Bangladesh, and Maldives, cyclic epidemics are being seen with increasing frequency with spread of the disease into new geographical areas like Bhutan and Nepal. The dengue virus is a *Flavivirus* transmitted to man by the bite of the infected *Aedes* mosquito. It is a single-stranded RNA virus consisting of four serotypes (DEN 1–4) [68].

Most infections may be asymptomatic. Classically the clinical manifestations of dengue have been classified as dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. This has been reclassified by the WHO in 2009 as dengue without warning signs, dengue with warning signs, and severe dengue [68]. This resulted from the observation that many life-threatening dengue cases did not meet the criteria for dengue hemorrhagic fever or dengue shock syndrome [69, 70]. Dengue should be suspected when a high fever is accompanied by two of the following: severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands, or rash. Warning signs that herald development of severe dengue include abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, and increasing hematocrit with decreasing platelets. Severe dengue is characterized by plasma leakage leading to shock, severe bleeding, severe organ impairment (which may include the liver, CNS, heart, or other organs), or a combination of the above [71]. The revised dengue classification has been shown to be useful to describe each phase of disease progression and define different levels of disease severity with warning signs helping identify patients in risk for shock. It also helps in the diagnosis, treatment of individual cases, follow-up of the disease, reorganizing health-care services for management of outbreaks, and epidemiological surveillance of the disease [72]. Atypical manifestations may involve the CNS, gastrointestinal, renal, cardiac, respiratory, musculoskeletal, or lymphoreticular systems [73]. CNS complications can occur in 0.5–6.2% [74]. A study from Eastern India has shown CNS complications in as high as 28% [75]. The new WHO classification includes CNS complications in the definition of severe dengue. Neurological complications have been shown to result in poor outcome in dengue [76]. However, the new WHO classification does not define the diagnostic criteria for CNS complications in dengue. A recent classification divides CNS complications in dengue into dengue encephalopathy, encephalitis, immune-mediated

neurological syndromes, dengue-associated muscle dysfunction, and neuro-ophthalmic disorders. In practice this classification might be difficult as clinical features overlap and clinical data (such as CSF tests) are not always available [77].

Dengue encephalopathy is the most common neurological manifestation of dengue. It may result from the systemic complications of dengue infection. Multiple factors such as cerebral edema, hemorrhage, hyponatremia, hepatic or renal failure, cerebral hypoxia, and shock may contribute to the pathophysiology of encephalopathy. CSF analysis is usually normal.MRI has been reported to show cerebral edema, scattered focal lesions, and hemorrhage [74, 77]. Without supportive treatment mortality and morbidity can be high. Mortality was 47% in a series of dengue encephalopathy from Sri Lanka [78].

In the past decade, there has been increasing evidence of a neurotropic effect of the dengue virus which has expanded the clinical spectrum of the disease to include encephalitis, myelitis, or aseptic meningitis. This is supported by virus isolation from the CSF, detection of the virus in the brain, lymphocytic pleocytosis, and demonstration of virus-specific IgM [74]. Dengue virus serotypes 2 and 3 have been reported to cause CNS invasive disease [73]. Clinical features of dengue encephalitis resemble that of other viral encephalitis and manifest with fever, dizziness, altered sensorium, seizures, and behavioral changes. In severe cases tetraparesis may be seen. These features are indistinguishable from dengue encephalopathy, and associated hypovolemic shock, organ failure, metabolic derangement, and intracranial hemorrhage may help in distinguishing the two entities. Seizures are more common in encephalitis that in encephalopathy. CSF examination, if feasible, can help in the differentiation by showing pleocytosis and presence of dengue virus RNA, IgM, or NS1 antigen in cases of encephalitis [78]. MRI has been reported to show JE-like lesions in the thalami, globus pallidus, temporal lobe, and pons in dengue encephalitis. These lesions are focal suggesting possible encephalitis rather than encephalopathy which shows more global change [79] . A recent publication has reported a consistent pattern of cerebellar involvement with presence of microbleeds besides lesions elsewhere in the brain [80].

Postinfectious immune-mediated effects of dengue on the CNS include acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome, and acute transverse myelitis. ADEM has been reported in the convalescence stage after classical dengue fever and dengue hemorrhagic fever. MRI may reveal demyelinating lesions in the brain with hemorrhagic changes which are fairly characteristic. Spinal cord involvement in dengue possibly occurs due to direct viral invasion or as an autoimmune process. Myelitis due to direct viral invasion is typically seen in the parainfectious stage within the first week of onset of symptoms, whereas autoimmune myelitis occurs in the postinfectious stage typically 1–2 weeks after the onset of symptoms. Detection of virus-specific antibodies or demonstration of the virus has been reported in neuroinvasive myelitis. MRI of the cord may be normal or show T2 hyperintense focal or long-segment lesions [74, 77].

Dengue-associated muscle dysfunction (DAMD) may be commoner than CNS involvement in dengue. In a study of 116 patients from India, 45% had DAMD with DEN 2 and DEN3 the commonest causative serotypes. CNS involvement resulted in

poorer outcome [81]. In a study from Saudi Arabia in 101 patients of dengue, myalgia was present in 63% with mild proximal muscle weakness in 3%; raised creatine phosphokinase was seen in as high as 91% [82]. DAMD may manifest with transient myalgia of variable severity, consisting of muscle tenderness on stretching, motor weakness, and even rhabdomyolysis in severe cases. Muscle enzymes are raised. Usually there is spontaneous recovery in 1–2 weeks [77].

Ocular involvement in dengue though uncommon is being increasingly reported and is of great significance in view of the possibility of loss of vision. The posterior segment is more commonly involved in comparison to the anterior segment. Common anterior segment manifestations include subconjunctival hemorrhage. Posterior segment involvement includes most commonly dengue maculopathy consisting of edema, hemorrhage, and foveolitis. Besides this exudative retinal detachment and focal chorioretinitis has been reported. Rarer manifestations include retinal vascular occlusion, vitreous hemorrhage, panophthalmitis, and ischemic maculopathy. Optic neuropathy is a rare but significant complication that may result in permanent visual loss [83]. Ocular involvement was seen in 40% of patients in a series of patients with dengue from India [84]. About 10% of patients in a series from Singapore had dengue maculopathy [85]. The pathogenesis of ocular involvement in dengue is not clear but thought to be immune mediated or due to direct viral invasion. Ocular manifestations occur about a week after onset of symptoms coinciding with the nadir of thrombocytopenia and increased immunological response. Most cases are fortunately self-limiting and resolve spontaneously [83].

Both hemorrhagic and ischemic stroke has been reported is dengue. Hemorrhagic stroke may result from vasculopathy, thrombocytopenia, and platelet dysfunction in dengue infection. Ischemic stroke can also be seen due to coagulopathy and vasculopathy [74]. The true incidence of stroke in dengue is unknown and has been reported to be less than 1% in large series from India and Brazil [86, 87]. This may however be underestimated. Both intra-axial and extra-axial intracranial hemorrhage have been reported [77].

The definitive diagnosis of dengue is by detection of the viral antibody {by IgM antibody-capture enzyme-linked immunosorbent assay (Mac-ELISA), IgG ELISA, or by plaque reduction and neutralization test (PRNT)} or by molecular tests {reverse transcriptase-polymerase chain reaction (RT-PCR) and detection of dengue nonstructural protein 1 (NS1)} in serum. Molecular tests detect genetic material of the virus and offer earlier and more specific diagnosis (80–90% sensitivity after 1–3 days of illness) but are not useful beyond the first week of disease. Mac-ELISA tests are typically positive after 5 days of disease onset. IgG ELISA can be used to detect recent or past dengue infection but require acute and convalescent samples. The antibody tests do not allow serotyping of the virus, are susceptible to cross reaction with other flaviviruses and pathogens, and need precise timing and at times multiple samples, reasons for which molecular tests are preferred. Virus isolation can be done but is used less commonly [88, 89].

There is no specific antiviral treatment for dengue at present. Management is mainly supportive. For supportive management of patients with neurological complications, possible causes of encephalopathy should be looked for and corrected.

Role of steroids for the treatment of CNS and neuro-ophthalmic involvement in dengue though tried has not been established by randomized control trials [77].

Prevention of the disease has been largely through the integrated vector control method recommended by the WHO. Though studies have shown improvements of entomological indicators after implementation of these measures, there is little data to show the impact of different forms of vector control on the incidence of dengue [88]. Recently a live-attenuated (recombinant) tetravalent vaccine (CYD-TDV or Dengvaxia®) has been registered for use in several countries. It is given in a 3 dose series on a 0/6/12 month basis. The indication for the first licenses is for prevention of dengue caused by serotypes 1,2,3, and 4 in individuals of 9–45 or 9–60 years of age (depending on the license) living in a dengue-endemic area. The WHO recommends that countries should consider introduction of the vaccine only in geographic settings (national or subnational) where epidemiological data indicate a high disease burden. Currently there are at least five more vaccines under evaluation in clinical trials [88, 90].

Enterovirus

Enteroviruses (EVs) belong to a genus of single-stranded RNA viruses that include Coxsackie viruses, echoviruses, polioviruses, and newer enteroviruses. In the past, poliomyelitis was the most significant CNS disease caused by EVs. With extensive intervention by way of vaccination in recent times, polio cases have decreased by over 99% since 1988 from an estimated 3,50,000 cases to 37 cases in 2016 with only three countries (Afghanistan, Pakistan, and Nigeria) remaining endemic to polio in 2017 [91]. Extensive use of live-attenuated vaccine for polio eradication has led to the emergence of circulating vaccine-derived polioviruses (cVDPV) in nature which have caused outbreaks in several parts of the world notably in Southeast Asia. Poliomyelitis-like disease has been reported in children with cVDPV with fever and asymmetric paralysis (see below). With the submergence of the poliovirus, newer EVs with the ability to cause CNS disease like aseptic meningitis, encephalitis, and acute flaccid paralysis have emerged in the recent past. Notable among these is EV71 which is an emerging virus that has significantly expanded its geographical range. It causes hand, foot, and mouth disease (HFMD) in children. There have been several outbreaks of EV71 disease in Southeast Asia and Pacific region since 1997 [92]. In China the disease was first seen in 1981, and in India, the first outbreak was reported in 2004. Many small-scale outbreaks have been reported from India after the first outbreak [93]. Over the past decade, EV along with Chandipura virus has emerged as the most common cause of AES in India [7]. Severe outbreaks are followed by milder attacks and periods of decreased disease activity and vice versa as has been seen in China and Taiwan [93]. In rare cases HFMD can progress to manifest in severe complications such as CNS involvement, respiratory and cardiovascular involvement, cardiopulmonary failure, and fulminant neurogenic pulmonary edema with high mortality [94]. According to clinical studies conducted in Taiwan, symptomatic infection of EV71 can be divided into four stages: stage 1 with HFMD/

herpangina, stage 2 with CNS involvement, stage 3 with cardiopulmonary failure, and stage 4 or convalescence. Most infections are contained in stage 1, some advance to stage 2, and few advance to stage 3. Survivors of stage 3 can progress to stage 4 with long-term sequelae [95]. Occurrence of CNS disease in EV71 infections is variable. The reason for this is not well understood but could be due to high spontaneous mutation rate of the virus and presence of numerous subtypes [92]. Majority of patients with neurological complications are under 5 years of age. Neurological complications typically occur 3–5 days after fever onset or appearance of skin lesions. Some patients may show neurological complications without appearance of skin or oral lesions [95, 96].EVs are transmitted by the feco-oral route although respiratory oral spread and spread through fomites are possible. Invasion of the CNS is through hematogenous route following viremia. Up to 30% of patients with EV71 infections may show CNS disease. This commonly includes aseptic meningitis, encephalitis, and acute flaccid paralysis and may also include cerebellitis, brainstem encephalitis, opsoclonus-myoclonus syndrome, Guillain-Barré syndrome, and transverse myelitis [92]. Brainstem encephalitis is the most common neurological manifestation (58%) with aseptic meningitis (36%) and brainstem encephalitis with cardiorespiratory dysfunction (3%). Brainstem encephalitis can be accompanied by fluctuating blood pressure and pulmonary hemorrhage/edema due to autonomous dysfunction. Fatalities due to pulmonary hemorrhage usually occur within 24 h. Brainstem encephalitis in EV71 is characterized by myoclonus, ataxia, nystagmus, oculomotor palsies, and bulbar palsy or a combination of these. Myoclonus is the most common symptom and is an early indicator of brainstem involvement. It can occur during deep or light sleep and when awake [95, 96].

Laboratory confirmation of the disease can be done by virus isolation (from the throat, skin ulcer, rectal swabs, serum, or CSF) or by detection of virus-specific antibody. The latter can be done by IgM ELISA which is fast and a cost-effective technique. Reverse transcriptase-PCR tests are able to detect serotypes of the virus [93]. Presently RT-PCR tests sequencing the *VP1* gene are preferred. For CNS infection detection rates of the virus in CSF are very low (0–5%), and detection of the virus from skin lesions, throat or rectal swabs, or stool may be the only option. CSF may also show a mild lymphocytic pleocytosis or be normal [95]. MRI of EV71 encephalitis from Taiwan has shown brainstem involvement in the posterior medulla and pons and in the midbrain. Cerebellar dentate nuclei, thalami, putamina, and cervical cord were also involved [97]. In a study from North India, brainstem (midbrain and pons) lesions were the most common. Other lesions were seen in the thalami, cerebellum, cortex, basal ganglia, and substantia nigra [98].

Though antiviral treatment against EV71 is currently ineffective, a treatment protocol for brainstem encephalitis using milrinone and intravenous immunoglobulin (IVIg) has been recommended from Taiwan. In a recent prospective, open-label, randomized control study using this drug combination, patients with brainstem encephalitis with pulmonary edema and/or neurogenic shock had a significantly lower 1 week mortality rate in comparison to controls [99]. Currently inactivated whole-virus EV71 vaccines have been approved for use in China. Phase III clinical

trials of these vaccines have shown high safety and immunogenicity. Protective efficacies were over 90% for HFMD and over 80% for serious EV71-associated diseases [94, 95].

Other EVs that have been reported to cause outbreaks of encephalitis in India include EV76 and 89 from North India and EV 75 from South India [100, 101]. Numerous other non-polio EVs have been identified in association with acute flaccid paralysis in India [102].

Basic prevention for the feco-oral spread should be practiced, and these include personal hygiene such as hand washing, cleaning of utensils, and prevention of contact with infected patients [93].

Nipah Virus Encephalitis

Nipah virus encephalitis (NVE) is an emerging zoonosis that was first reported from Malaysia and Singapore in 1998. The Nipah virus (NV) is closely related to the Hendra virus. Both viruses are species of the genus *Henipavirus*, a new class of virus in the *Paramyxoviridae* family. It has the ability to cause potentially fatal encephalitis in humans with case fatalities of 40–75%. Other domestic animals such as pigs are also susceptible to the virus. Fruit bats of the Pteropodidae family are the natural hosts of the virus but do not suffer from NV disease. Farm animals possibly get infected from bat urine or saliva. In the first outbreaks reported from Malaysia, the disease was transmitted to man from contact with infected pigs or their contaminated tissues. Most of the initial outbreaks occurred in pig farm workers or residents of pig-farming villages. Transmission may have occurred through respiratory droplets, contact with throat or nasal secretions of pigs, or contact with a sick animal. Following the initial attacks in Southeast Asia, outbreaks of NVE have occurred in the sub-Himalayan region of the state of West Bengal in India and in the adjoining areas of West Central Bangladesh since 2001. In India and Bangladesh, consumption of fruit or fruit juices such as raw date palm juice contaminated by bat urine or saliva was the possible source of infection. Direct human-to-human transmission has been documented in Bangladesh and India possibly through close contact with patient secretions and excretions. In North Bengal, transmission of NVE was reported in a health-care setting with 75% cases occurring in hospital staff or visitors. Approximately half of the reported cases from Bangladesh occurred due to human-to-human transmission in the period of 2001–2008 [103, 104]. Pathologically an unusual feature is systemic and CNS vasculitis with associated thrombosis and parenchymal necrosis in the CNS. This is accompanied by other usual features of encephalitis like neuronophagia, microglial nodule formation, and perivascular cuffing [104].

The incubation period varied from 4 days to 2 months in the Malaysian outbreak, while in Bangladesh this was shorter at 6–11 days [105]. Human infections may range from asymptomatic to fatal encephalitis. Patients may present with influenza-like symptoms such as fever, headache, muscle pain, vomiting, and sore throat. This may be followed by signs and symptoms of AES [103]. AES has been associated with segmental myoclonus, areflexia, hypotonia, and autonomic dysfunction [106].

Atypical pneumonia with respiratory distress can be seen in some patients. Patients from Bangladesh had high prevalence of respiratory symptoms compared to the Malaysian outbreak. Indications of poor outcome in Bangladesh were fever with temperature of >37.8 °C, altered mentation, respiratory distress, and abnormal plantar reflex [107]. Relapse of encephalitis was reported in 7.5%, and delayed encephalitis was reported in 3.7% patients who initially presented with non-encephalitic infection from Malaysia [108]. In contrast to this, in a study of 22 patients from Bangladesh, delayed encephalitis after Nipah fever was not observed. However, neurological sequelae and new neurological dysfunction in the form of nerve palsies and cervical dystonia were seen. There was long-term neurological and functional morbidity in survivors [109].

The definitive diagnosis of NV infection can be done by serum neutralization, ELISA tests, PCR assay, immunofluorescence assay, and viral culture [103].

Somewhat different MRI findings have been described in acute NVE from Malaysia and Bangladesh. In Malaysia, discrete T2 and FLAIR hyperintense lesions measuring 2–7 mm were seen all over the brain but with a subcortical and deep white matter predominance. These lesions showed no mass effect and did not correlate with focal neurological sign, depth of coma, or with outcome [110]. Similar findings have been reported from Singapore. Acute NVE patients showed <1 cm hyperintense lesions in the cerebral white matter including the corpus callosum and external capsules, cortex, pons, and cerebellar peduncles. On diffusion-weighted imaging, larger lesions showed restricted diffusion resembling microinfarcts. Some lesions showed contrast enhancement. On follow-up many of these lesions resolved over time with transient appearance of T1 hyperintense lesions similar to laminar cortical necrosis [111]. These lesions are thought to represent microinfarcts due to small vessel angiopathy described in postmortem studies [110]. In patients from Bangladesh, however, disseminated multifocal and confluent gray and white matter lesion has been described [109, 112]. Confluent cortical lesions have also been described in relapsed- or delayed-onset NVE. The pathological correlates of these lesions were changes typical of acute encephalitis rather than vasculitis [110].

There is no vaccine or definitive treatment for NV infection. Supportive and symptomatic treatment is the main approach to the management. Preventive measures include cleaning and disinfection of pig farms and establishing animal health surveillance systems. During outbreaks, restricting animal movement and culling may be necessary. Education of people to reduce exposure to the virus should focus on cleaning and peeling of fruits and boiling raw palm juice for consumption, avoiding contact with infected people, wearing protective equipment during patient care or animal handling, and hand hygiene [103].

Rabies

Rabies is one of the oldest diseases known to mankind. It is a zoonotic encephalomyelitis with a near 100% fatality. The virus is a single-stranded RNA virus of the genus *Lyssavirus* and family Rhabdoviridae. Out of seven known genotypes of

virus, only genotype 1 is prevalent in India and other Asian countries [113]. Though the disease is prevalent worldwide, many geographically isolated areas mainly islands and peninsulas are free of the disease. Worldwide, about 55,000 people die annually of the disease mostly in Asia and Africa [114]. More than 30% of these deaths, estimated at about 25,000–30,000, occur in India alone [115]. Human infection results from bites of infected animals, dog bites being the most common mode of infection in developing countries such as India. If sufficient nerve endings are exposed through the bite, the virus may directly invade the nerves. The incubation period in this case tends to be short. Alternatively the virus replicates in the muscles and then enters the nerves supplying the muscle. This is followed by retrograde axoplasmic spread into the spinal cord and then to the brain. There is initial involvement of areas such as the hippocampus, hypothalamus, and limbic system which explains the presenting symptomatology. There is eventual involvement of the entire brain. The pathological hallmark of infection is the presence of neuronal inclusion bodies called Negri bodies. The relative lack of pathological brain changes suggests defective neurotransmitter function or neuronal apoptosis rather than necrosis plays a role in the pathogenesis of rabies.

The progression to rabies encephalitis after exposure of an individual depends on several factors such as site and severity of the bite, host immune factors, and viral contents in the animal's saliva. Bites in the head, neck, and upper extremity carry the highest risk of disease and have a shorter incubation period. However, in India, it is more common to have bites in the legs. The incubation period is variable and may range from 7 days to 6 years. This extreme variability may be due to variable viral quantity inoculated, properties of the rabies virus strain, availability of viral receptors in the tissue, and degree of tissue innervations. In as many as 5% of cases from India, no history of dog bite may be elicited.

Classic neurological symptoms may be preceded by a prodrome consisting of nonspecific symptoms with or without paraesthesia or itching at the site of bite. This may last for a few hours to days. This is followed by the acute neurological manifestations of rabies which are of two forms, the more classical and common encephalitic or furious form and the dumb or paralytic form. The encephalitic form starts with fever and agitation followed by classic symptoms of phobic spasms characterized by hydrophobia and aerophobia, fluctuating consciousness progressing to coma, and signs of autonomic dysfunction such as hypersalivation, papillary abnormalities, piloerection, excessive sweating, priapism, and spontaneous ejaculation. Paralytic or dumb rabies may present in approximately 20% patients and may be more difficult to diagnose due to lack of classic phobic spasms. This presents with ascending paralysis starting from the bitten extremity and progresses to involve all limbs, face, pharyngeal, and laryngeal muscles. Features of furious rabies may at times present in the terminal phase. The cause for pathogenesis of the two clinical forms of rabies is unknown. As the paralytic form is more common in partially immunized patients, a superadded immune response to virus-infected cells may be responsible for this.

There is surprisingly less imaging literature on rabies, probably because of the difficulty in imaging these patients. CT imaging may either be normal or reveal hypoattenuated lesions in the basal ganglia, hippocampi, periventricular white

matter, and brainstem. No difference was found between the MRI features of paralytic and dumb rabies in a small series of five patients. T2 hyperintense ill-defined non-enhancing lesions were seen in the brainstem, hippocampi, hypothalami, deep and subcortical white matter, and deep and cortical gray matter in non-comatose patients. Once patients became comatose, gadolinium-enhancing lesions were seen in the hypothalami, brainstem nuclei, spinal cord gray matter, and intradural cervical nerve roots. Enhancement of the brachial plexus may however be seen in the prodromal phase of the disease [116].

In recent times more sensitive and specific tests for the antemortem detection of rabies have been developed. The antigen or antibody can be detected or viral isolates obtained from biological material such as serum, CSF, and saliva or from tissues such as nuchal skin or corneal swabs. The rabies virus antigen can be detected by fluorescent antibody tests in corneal smears or nuchal skin, the latter being more sensitive. Viral nucleic acid can be detected by PCR test. Both conventional reverse transcriptase-PCR and real-time PCR tests can be done and appear to be promising for antemortem diagnosis. Virus isolation can be done by mouse inoculation or rapid tissue culture infection tests. This is reliable but time-consuming. Demonstration of high titer of antibodies in nonimmunized patients or rising titer of antibodies in immunized patients in tests done 7–10 days apart provides indirect evidence of infection. Antibody detection can be done by the mouse neutralization test or the rapid tissue culture infection test, the latter being more sensitive. Antemortem diagnosis may not always be successful, and it has been seen that postmortem diagnostic tests are more sensitive and specific. Negri bodies can be demonstrated in more than 70% of brain specimens. The viral antigen can be detected in brain smears by direct immunofluorescence tests or ELISA-based techniques.

In spite of reports of occasional survival of patients, rabies should be considered a fatal disease and treated conservatively with isolation of the patient. Antiviral agents (such as ribavarin), interferon, or intrathecal immune globulin has not been effective in treatment of rabies. In paralytic rabies, when the diagnosis is not definite, more active therapy in an intensive care unit is advisable giving the benefit of doubt to the patient. Health-care personnel should take adequate precautionary measures in handling patients and take adequate preexposure prophylaxis.

Despite the eventual fatality of rabies, there is scope of effective disease control through postexposure prophylaxis. This consists of effective wound toilet, passive immunization with rabies immunoglobulin, and active immunization with rabies vaccine. Postexposure treatment should be started immediately for category II and III contact (see Table 6.2). Whereas no treatment other than wound toilet is necessary for category I contact, immediate vaccination along with wound toilet is recommended for category II contact. For category III contact, immediate vaccination with adequate wound toilet followed by administration of rabies immune globulin is recommended. Depending on vaccine types, the postexposure schedule recommended is intramuscular doses of 0.5 or 1 ml given as 4–5 doses over 4 weeks. Cell-derived vaccines recommended by the World Health Organization have been used intradermally for postexposure prophylaxis in countries like Thailand, Sri Lanka, and the Philippines, advantage being in reduced costs due to reduced dosages.

Table 6.2 World Health Organization guidelines for the postexposure prophylaxis of rabies.

Category of bite	Description of contact	Treatment
I	Touching, feeding of animals, or licks on intact skin	None, if history is reliable
II	Minor scratches or abrasions without bleeding and/or nibbling of uncovered skin	Immediate vaccination Stop treatment if animal remains healthy after 10 days of observation or if animal is euthanized and found to be negative for rabies by appropriate laboratory techniques
III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva (i.e., licks), and suspect contacts with bats	Immediate administration of rabies immunoglobulin and vaccination Stop treatment if animal remains healthy after 10 days of observation or if animal is euthanized and found to be negative for rabies by appropriate laboratory techniques

From [118]

Local wound treatment should be given at the earliest. The wound should be washed in running tap water and washed with soap for at least 10 min which helps eliminate the virus. Local antiseptics should then be applied and suturing avoided as far as possible. The World Health Organization recommended dosage of rabies immunoglobulin is 40 IU/kg body weight for equine rabies immunoglobulin and 20 IU/kg body weight for human rabies immunoglobulin. This can be used for infiltrating around the wound, and the remainder can be injected intramuscularly at a site distant from the vaccine inoculation. Highly potent and safe vaccines are currently available for rabies prophylaxis. Tissue culture or duck embryo vaccines of at least 2.5 IU per single immunization dose should be used for vaccination. Intramuscular schedules involve injection of 1 dose into the deltoid region (or the anterolateral thigh in small children) on days 0, 3, 7, 14, and 30. The abbreviated multisite schedule which is a 2-1-1 regimen may be applied whereby 2 doses are given (one in each arm) on day 0 followed by 1 dose in the deltoid on days 7 and 21. This schedule is helpful in patients who do not receive rabies immunoglobulin, and an early immune response is necessary. The World Health Organization also recommends a two-site intradermal regimen (2-2-2-0-2) which may reduce costs by 60–80%. About 0.1 ml of purified vero cell rabies vaccine or purified chick embryo cell vaccine is given intradermally in the left and right upper arm on days 0, 3, 7, and 28 [117, 118].

Preexposure vaccination is recommended for persons who have continued exposure risk like veterinarians, dog catchers, etc. Three doses of any modern vaccine are given as one standard intramuscular dose (0.5 or 1 ml) or 0.1 ml intradermally on days 0, 7, and 28. For reexposure of any person who has been previously immunized with a modern cell culture vaccine, two doses (intramuscular or intradermal) on days 0 and 3 are recommended. No immunoglobulin is applied. Use of brain tissue vaccine is no longer recommended by the World Health Organization [117, 118].

Measles

Measles is a highly infectious disease of children characterized by fever, respiratory symptoms, and a characteristic rash. The measles virus is a negative-stranded RNA paramyxovirus that is transmitted by droplet infection. Though measles is endemic to virtually all parts of the world, in recent years, an appreciable reduction in deaths due to measles has been seen, principally due to effective vaccination. During the period 2000–2015, there was a drop in the incidence of measles by 75% from 146 to 36 cases per million population. The same period also saw a decline in measles mortality by 79%. Despite this, the African region and India continue to have the highest number of deaths due to measles. In 2015, estimated deaths from measles were 61,600 in Africa and 49,200 in India [119].

CNS infection by the measles virus can result in acute measles encephalitis (AME), subacute measles encephalitis (SME), or subacute sclerosing panencephalitis (SSPE). CNS complications in measles are rare. Approximately 0.5–1 in 1000 cases of measles result in AME [120]. In North India, approximately 7–22% of viral encephalitis in children is caused by the measles virus [97, 121]. SSPE is rarer still and occurs in a frequency of one to four cases in a million in developed countries and up to 21 cases in a million in developing countries like India [122, 123]. In recent times, however, with the introduction of mass immunization programs, the incidence of SSPE may be decreasing in India [124]. SME, also known as measles inclusion body encephalitis, is a still rarer complication of measles that occurs in the immunocompromised host and is caused by wild-type measles virus [120].

Acute measles encephalitis occurs at any time during the appearance of measles rash, usually within 8 days of onset of illness. There is controversy regarding the mechanism of AME with some studies suggesting direct viral invasion on the CNS, while others suggest autoimmune mechanisms after having failed to show viral-specific RNA in the brain of infected patients. However, an early onset may suggest direct viral invasion, while a delayed onset may suggest an autoimmune mechanism [120]. The onset is abrupt with irritability, fever, headache, vomiting, altered sensorium, seizures, and coma [125]. Mortality rate is between 10 and 20%. The CSF may show mild pleocytosis, usually mononuclear, elevated protein, and normal sugar. Myelin basic protein in the CSF may suggest an autoimmune process, while detection of virus-specific genome in the CSF may suggest direct viral invasion [120]. MR imaging in children from Korea revealed bilateral T2 hyperintense lesions in the cerebral cortex, corpus striatum, and white matter with mild mass effect in the acute phase of the disease. These lesions showed restricted diffusion on DWI. Petechial hemorrhage, and cortical gyriform and leptomeningeal enhancement, was also seen. Encephalomalacia and atrophy was seen in the chronic phase [126]. Treatment is largely supportive, but immunomodulatory treatment with corticosteroids, immunoglobulin, and plasmapheresis has been employed with variable results [125].

SSPE is a slow virus infection of the CNS due to measles virus infection. The name is derived from the insidious nature of onset (subacute), the type of pathological lesions (sclerosis), and the involvement of the entire brain (panencephalitis)

[127]. The disease develops 6–8 years after the initial measles attack and is more common in males (male/female = 3:1). Risk factors of acquiring SSPE include younger age (highest risk under age 1), living in a rural area, overcrowded environments, more number of siblings, mental retardation, and lower birth order, all factors that may predispose to intensive measles exposure. A close temporal relationship of measles virus to other viruses may modify the course of measles infection and has been suggested as a risk factor for SSPE [128].

The exact pathogenesis of SSPE is not well understood. Measles virus possibly gains entry into the CNS by infection of the endothelial cells or through circulating inflammatory cells. There is evidence that an inadequate cell-mediated immune response and a resultant ineffective humoral response probably play an important role in the pathogenesis of SSPE. Once inside the neuron, the virus changes the cell machinery to bypass the immune system, and it undergoes mutations to avoid recognition. The virus remains dormant for several years before an eventual inflammatory response leading to widespread CNS destruction [127]. Despite the long latency, there is evidence that the virus gains entry into the brain soon after the acute infection with subsequent spread through the brain [128]. Early in the disease, there is variable inflammation of the meninges, cortex, deep gray matter, and white matter. This is associated with neuronophagia, gliosis, astrocytic proliferation, perivascular cuffing, lymphocytic and plasma cell infiltration, demyelination, and inclusion bodies in the neurons and glial cells. In the late stages, inflammatory changes decrease with severe loss of neurons of the cortex and deep gray matter with thinning of white matter and severe gliosis. Inclusion bodies are scanty at this time [129].

Clinically, the disease presents with minor behavioral and intellectual changes in a previously healthy child. This is followed by development of motor dysfunction and characteristic myoclonic jerks. Focal paralysis, seizures, autoimmune dysfunction, and rigidity also develop, finally leading to akinetic mutism and death [127, 128]. Four clinical stages have been described by Jabbour et al. In stage I there are personality changes and behavioral disturbances. Myoclonus, seizures, and severe intellectual decline are seen in stage II. Stage III is characterized by rigidity and progressive unresponsiveness. In stage IV there is mutism and coma; rigidity and myoclonus decrease [130]. Visual and ocular manifestations have been reported in 10–50% patients and include cortical blindness, chorioretinitis, and optic atrophy [128].

The diagnosis of SSPE is based on clinical features associated with typical electroencephalographic (EEG) findings, presence of anti-measles antibody in the serum or CSF, MRI findings, and brain biopsy. CSF analysis may be normal or show elevated cells, total protein, gamma globulins, and an oligoclonal band pattern. Elevated titers of anti-measles antibody of 1:256 in the serum and 1:4 or greater in the CSF is considered diagnostic for SSPE. There is a lowered CSF-to-serum ratio of the titer ranging from 1:4 to 1:128 compared to normal ratios of 1:200 to 1:500 [128].

The characteristic EEG findings in SSPE are periodic complexes, known as Radermecker complexes, which are found in 65–83% of SSPE (Fig. 6.3b). Periodic complexes are 100–1000 mv, 1–3 Hz waves, intermingled with spikes and sharp and

slow waves of 1–3 s duration. The interval between complexes varies from 2 to 20 s. In early stages, they can recur every 5 min. They can occur during sleep and can be elicited by external stimuli. They are secondary to widespread neuronal excitability, pathological hypersynchronization, and rhythmic triggering by a pacemaker, potentially in the brainstem or perithalamic area [127]. Morphology of the complexes is highly stereotyped within one individual but differs between patients [128]. EEG background is normal in early stage of the disease. As the disease progresses, there are slowing, disorganization, and asymmetry with increasing diffuse slow-wave activity in the background. At times there may be focal spikes coinciding with underlying pathology. In the progressive stage of disease, polymorphic delta activity or intermittent frontal dominant monorhythmic slow activity may be present. In the later stage, recurrence of periodic complexes increases, and amplitude reduction of complexes occurs. Finally EEG becomes flat, or in rare instance, an alpha coma pattern may be seen.

Neuroimaging with MRI is preferred over CT, as CT underevaluates the disease [131]. MRI shows involvement of the white matter, gray matter, and deep gray matter with cerebral atrophy. MRI seems to follow a constant pattern with white matter changes appearing first followed by cerebral atrophy. Early in the disease, T2 hyperintense white matter changes are seen (Fig. 6.3). These are more common in the parieto-occipital than in the frontal regions. Gray matter changes are also noted that are hyperintense on T2- and hypointense on T1-weighted images. The brainstem, cerebral and cerebellar peduncles, and cerebellum may be involved. In advanced stages, cerebral atrophy is more pronounced with diffuse white matter changes and thinning of the corpus callosum [131–133]. Despite this set progressive pattern on conventional MRI, the changes do not correlate well with clinical stages of the disease [131] (Fig. 6.3). Newer MRI techniques such as diffusion-weighted imaging (DWI), MR spectroscopy (MRS), diffusion tensor imaging (DTI), and diffusion tensor tractography (DTT) have been reported to be of more help in early detection and staging of the disease. DWI has shown a significant difference in apparent diffusion coefficient (ADC) values between clinical stages II and III of the disease with the highest ADC values in stage III [134]. Similar ability to differentiate stage II from III has been reported with MRS. In one such study, there were differences in brain metabolites of stage II and III disease in relation to controls. Stage II disease revealed elevated myoinositol (MI) and choline levels with normal *N*-acetyl aspartate (NAA), while stage II disease revealed decreased NAA with increased choline and MI with increased lactate and lipid peaks. The findings possibly reflect the inflammation in stage II and the demyelination, gliosis, cell necrosis, and anaerobic metabolism in stage III [135]. DTI has been shown to detect abnormal mean diffusivity (MD) and fractional anisotropy (FA) values in normal-appearing white matter in stage II patients. Tract-specific FA values in some major white matter tracts have been shown to correlate inversely with clinical grades II through IV [136, 137].

No adequate therapy for SSPE exists in the current time. Three drugs, Isoprinosine, interferon-alpha (INF-α), and ribavirin, have been reported as effective but not curative of the disease. Isoprinosine, an antiviral drug that acts by increasing CD4+ lymphocytes, has been shown to prolong survival and cause clinical improvement in some patients. A dose of 100 mg/kg/day is given daily, and it needs to be continued

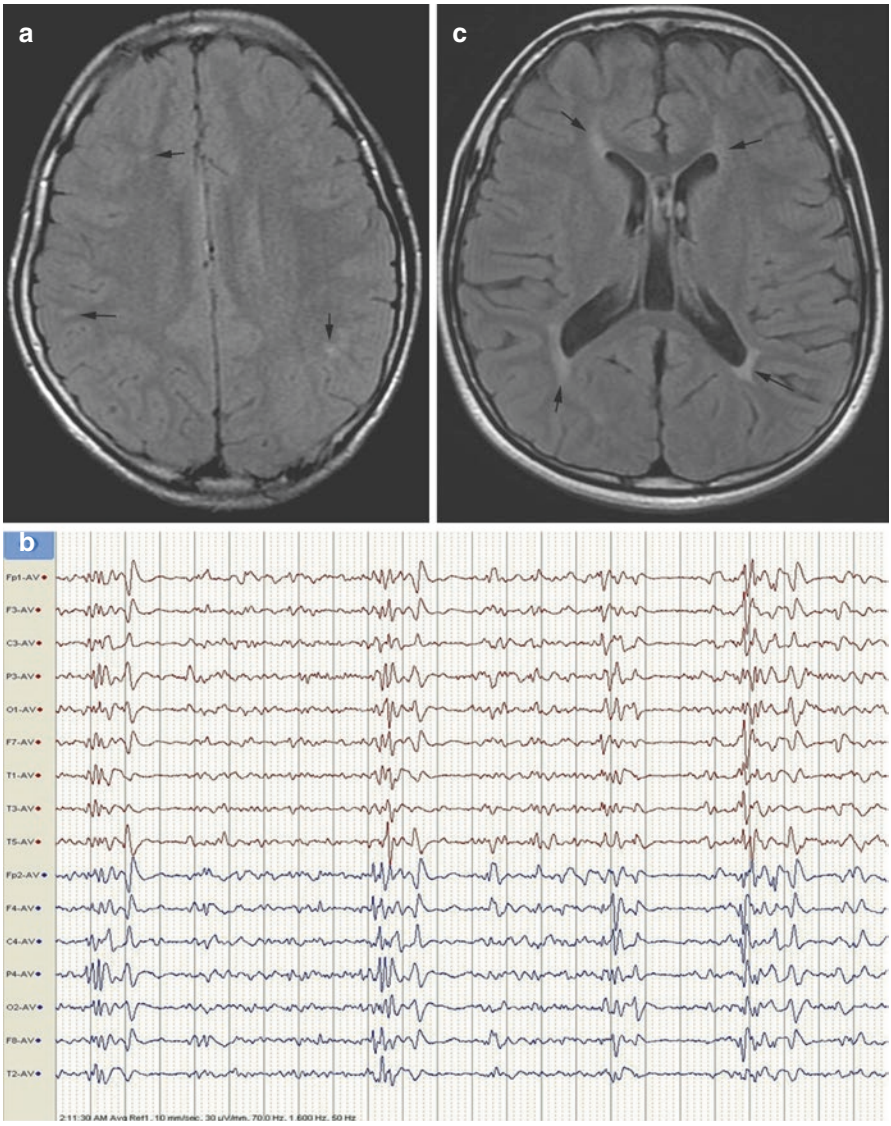

Fig. 6.3 (**a**) A 12-year-old male with subacute sclerosing panencephalitis (SSPE) in clinical stage III. Axial fluid-attenuated inversion recovery MRI image. Note subtle white matter lesions in the subcortical regions (*arrows*). There is no cerebral atrophy. MRI changes do not correlate well with the clinical stage of disease. (**b**) Electroencephalography of the same patient as (a) showing characteristic periodic complexes, appearing in 6 s and lasting for 2 s on a slow background. Focal frontal slow waves are also recorded. (**c**) Axial fluid-attenuated inversion recovery MRI in a different 13-year-old male patient with stage II SSPE. White matter lesions (*arrows*) are seen in the parieto-occipital periventricular and frontal periventricular white matter. There is cerebral atrophy. The patient had a worse looking MRI than the patient in (a) despite being clinically better

even during remissions and possibly for life [128]. INF-α did not meet with much success when used through the intravenous or intramuscular route. However, the intraventricular route has been successful in showing improvement in patients [138, 139]. Combination therapy with intraventricular INF-α and oral Isoprinosine has been found to be effective in treating SSPE. Combination of weekly intrathecal INF-α offered a benefit of 35% compared to the 34% benefit with Isoprinosine monotherapy in one study. This was more beneficial than the 5–10% spontaneous remission reported in literature. Even though no statistical difference in combination therapy versus Isoprinosine monotherapy was seen in the study [140], the combination therapy is still considered the most effective treatment available for SSPE today [138]. Intraventricular administration of ribavarin, another antiviral drug, has also shown efficacy in the control of SSPE. Used in high doses, it has shown doubtful results; but used in combination with INF-α, it has shown better results [141, 142]. At the current time, SSPE remains a fatal disease with a case fatality of 95% and mean survival in children being 1 year and 9 months to 3 years [127].

Subacute measles encephalitis (SME) also known as measles inclusion body encephalitis (MIBE) or immunosuppressive measles encephalitis (IME) is an uncommon complication of measles in immunocompromised children, primarily occurring in patients of acute lymphocytic leukemia but also seen in other immunosuppressive conditions such as AIDS, organ transplantation and immunosuppressive therapy, or immunodeficiencies. Unlike SSPE which has a latency of several years, SME presents a few weeks to 7 months after the acute measles infection [143]. Recently, a cluster of eight patients of SME in HIV-positive patients have been reported during a large outbreak of measles in South Africa underscoring the importance of immunization programs in an HIV-endemic population. Unlike SSPE, the brain virus was similar to the epidemic strain, possibly due to the short time from infection to brain disease in these patients [144, 145]. CSF analysis, EEG, and measurement of measles antibody in the serum and CSF are not helpful in the diagnosis. Brain biopsy and measles polymerase chain reaction on brain tissue are required for diagnosis of SME. Brain biopsy reveals eosinophilic inclusion bodies in neurons and oligodendrocytes with non-necrotizing encephalitis with paucity of inflammation [143, 144]. Patients present with partial seizures often with epilepsia partialis continua, altered sensorium, and variable neurological deficits. It has a mortality rate of 85%, and survivors frequently have severe psychomotor deficit. CT is not helpful in imaging these patients. On MRI, cortical T2 hyperintense lesions are seen with patchy involvement of the parieto-occipital, frontal, and temporal regions and in the deep gray matter. White matter abnormalities are infrequent [144, 146, 147]. Intravenous ribavarin therapy is effective if administered early [143].

Chandipura

Chandipura virus (CHP) is an emerging rhabdovirus that has recently been associated with a number of outbreaks of encephalitis in India.. Sandflies of the *Sergentomyia* and *Phlebotomus* species have been implicated as possible vectors of

the disease that are responsible for the transmission and maintenance of the disease. Though the *Aedes Aegypti* mosquito has been suspected to be a vector, definite proof of this lacking [148]. The virus was first isolated in 1965 during an outbreak of febrile illness in a village called Chandipura in the state of Maharashtra in India [149, 150]. Its epidemic potential was realized only during large outbreaks of acute encephalitis reported from South India in 2003 and West India in 2004 with high case-fatality rates [151, 152]. Earlier believed to be prevalent only in Asia, CHP today is today known to be prevalent in India, Sri Lanka, and Western Africa [149]. There is some controversy regarding the CHP etiology of epidemic encephalopathy. One investigating group did not find any conclusive evidence of invasion by any pathogen as the cause of the outbreak. They suggested that the outbreak was not of encephalitis but because of "epidemic brain attacks" presumably due to a vascular cause [153]. Nevertheless in recent years, CHP may have emerged as one of the most common agents causing acute encephalitis syndrome in India [7]. CHP encephalitis is characterized by acute-onset fever, altered sensorium, seizures, diarrhea, and vomiting. Death or recovery occurs within 2–3 days with no sequel in survivors. Most deaths occur within 24 h of illness. The symptoms have been attributed to brainstem encephalitis. CSF and blood parameters are usually normal. High-grade fever, absent oculocephalic reflex, and a Glasgow Coma Scale of less than 7 are poor prognosticators of the disease [154, 155]. The diagnosis is established by (1) virus isolation in cell culture, infant mice, and embryonated eggs, (2) antigen detection by ELISA and immunofluorescence assay, (3) genome detection by reverse transcriptase-polymerase chain reaction (RT-PCR), and (4) serological tests: IgM and IgG ELISA, hemagglutination inhibition, complement fixation, and virus neutralization test [150, 151]. As the disease has a rapid course and high fatality, RT-PCR is the diagnostic method of choice with the advantage of high sensitivity, speed, accuracy, and reproducibility [156]. Neuroimaging by CT and MRI was found to be normal in a study from South India [153]. However, there is incidental mention that one group of investigators saw lesions in the cortical regions of the frontal and temporal lobes in 11 MRI scans in patients from South India [157]. CT scans of eight patients in another study from South India showed diffuse brain swelling and dilated ventricles [158]. No specific treatment exists. Treatment is symptomatic, aimed at symptoms and complications. Early treatment with mannitol to reduce brain edema is lifesaving [159]. Currently a recombinant vaccine and inactivated vaccine are in the development stage and have shown promise by inducing high immunogenicity in mice [148].

Chikungunya

Chikungunya (CHIK) is an emerging virus infection that has resulted from enhanced vector competence. It is caused by a togavirus. *Aedes aegypti* mosquito was the principal vector in earlier times. Later the viral host range extended into the *Aedes albopictus* mosquito, presumably due to favorable mutation of the virus that increases infectivity of the virus for *A. albopictus*, facilitates entry into the salivary

gland, and increases efficiency of transmission from mosquitoes to vertebrates [160]. It was first detected in modern-day Tanzania. Initially it was limited to sub-Saharan Africa, India, and parts of Southeast Asia. Subsequently in 2005–2006, large outbreaks have been reported from La Réunion, with subsequent spread to the Indian subcontinent and Indonesia. There were an estimated 1.5 million cases in India in 2006. A small outbreak was reported in Italy where the disease spread from an index Indian traveler through native *A. Albopictus* [104, 161]. Currently it is prevalent in Asia, Africa, and the Indian subcontinent with outbreaks in Pakistan and India in 2016. A major outbreak affected several regions in the Americas in 2015 [162].

CHIK is a dengue-like illness characterized by fever, malaise, body ache, joint pains, rash, headache, and nausea. The illness is self-limiting. Fever may last for 36 days, but arthropathy may last for 3–6 months. Neurological complications are not uncommon and have been reported in 10–16% cases in recent large series from India [163, 164]. The neurological complications of CHIK include meningoencephalitis, meningo-encephalo-myeloradiculitis, myeloradiculitis, myelitis, myeloneuropathy, Guillain-Barré syndrome (GBS), external ophthalmoplegia, facial palsy, sensorineural deafness, and optic neuritis [161, 164]. Encephalitis appears to be the most common neurological complication occurring within a few days of onset of symptoms corresponding to the viremia period. Myelitis, GBS, and optic neuritis typically occur after more than 2 weeks [161]. In a large series from India, neurological complications occurred within 20 days of onset. In patients of encephalitis altered sensorium, behavioral abnormalities, extrapyramidal features, and convulsions were commonly seen [164].Altered sensorium, headache, seizures, sensory abnormalities, and motor dysfunction have been reported in patients with neurological disease from La Réunion [165]. In children with neurological manifestations, febrile seizures, meningitis, and acute encephalopathy have been reported [166]. Overall mortality in studies from India and La Réunion was similar at 10% [129, 130]. Vertical transmission of the CHIK virus has been reported from La Réunion. Vertical transmission rate was close to 50% in viremic mothers with encephalopathy being the most common complication in the infected neonates [167].

MRI abnormalities in patients with encephalopathy from India were in the form of multiple punctuate white matter lesions that are more prominent on diffusion-weighted MRI than on T2- or T1-weighted images. Although these resembled those of Nipah viral encephalitis, the prominence on diffusion imaging and lack of brainstem or cortical lesions differentiated CHIK from Nipah viral encephalitis. Occasional contrast enhancement of the lesions was seen. MRI rarely showed cord changes in CHIK with myelopathy. Nerve root enhancement involving the ventral cauda equina nerve roots has been reported in patients with neuropathy [161, 168]. MRI abnormalities reported from La Réunion were somewhat different. Brain MRI was abnormal in 5 out of 14 children with neurological complications. Two out of ten patients more than 1 month of age showed abnormal MRI with increased T2 signal in the cingulate, limbic areas, and white matter. No diffusion abnormalities were seen. Three out of four patients of less than 1 month age showed abnormal MRI, with areas of restricted diffusion in the white

matter and regions of increased signal in the white matter and/or cortex on T1- and T2-weighted images. Areas of hemorrhagic change were also noted. Patients with MRI abnormalities and severe clinical symptoms had more sequel or fatalities [166]. No imaging abnormalities were seen in another study of 23 patients from La Réunion [165].

While almost all patients of neurological CHIK from India showed lymphocytic pleocytosis and elevated protein [161], those from La Réunion showed variable pleocytosis [165, 166]. Electroencephalogram (EEG) was nonspecific and showed diffuse slowing [165]. In children EEG showed diffuse slowing that was anteriorly predominant in half of the cases and paroxysmal polyspikes in 40% [166]. The diagnosis can be confirmed by immunological techniques such as immunofluorescence assay (IFA) and ELISA tests for the detection of antibodies to the CHIK virus. IgM tests are positive 2–3 days after onset through several weeks to 3 months. Type-specific IgG antibodies appear after IgM antibodies (2–3 days) and persist for several years. Molecular tests for the CHIK virus are rapid and sensitive. Conventional reverse transcription polymerase chain reaction (RT-PCR) is available along with other RT-PCR real-time assays. These are useful in the initial viremic phase up to 10 days [169]. Due to variable sensitivity of RT-PCR, both serological and virological (RT-PCR) tests should be done in the first week of onset of symptoms. Virus isolation can also be done during the first few days of infection [162].

No specific antiviral therapy for the disease is currently available. The WHO guidelines recommend supportive treatment aimed at administering fluids, antipyretics, and analgesics with rest and physiotherapy [170, 171]. Steroids, plasmapheresis, and intravenous immunoglobulin have been tried in neurological complications of CHIK with no obvious demonstrable benefits [161, 164]. No vaccine is recommended for disease prevention at present. However two vaccines, a CHIK virus-like particle-based vaccine and a recombinant live-attenuated measles virus-vectored vaccine, have qualified recently for clinical phase II trials [171].

Viral Myelitis

Viral myelitis may involve the spinal cord gray matter, white matter, or both, extending through variable vertebral segments. If the anterior horn cells are involved, acute flaccid paralysis (AFP) can result. When both halves of the spinal cord are involved, acute transverse myelitis (ATM) can result. A chronic from of myelitis that is associated with human immunodeficiency virus 1 (HIV-1) and human T-cell lymphotropic virus 1 (HTLV-1) has also been described.

AFP is characterized by rapid-onset progressive weakness that may involve muscles of respiration and swallowing with maximum severity within days to weeks. If untreated, AFP may not only persist but lead to death. Poliomyelitis is the prototype AFP. It is of great public health importance in the context of the global polio eradication program. With poliomyelitis on the wane in endemic areas, other emerging

viruses are gaining importance in the etiology of AFP. These include non-polio enteroviruses, West Nile virus, Japanese encephalitis virus, Coxsackie viruses, and tick-borne encephalitis virus [172, 173]. Out of over 110,000 AFP cases reported worldwide in 2017, more than 46,000 were reported from India alone. India has one of the highest annualized non-polio AFP rates in the world at more than 12 per 100,000 population compared to the global annualized non-polio AFP rate of 5.79 per 100,000 population in 2017 [174]. The incidence of non-polio AFP in India has been increasing since the year 2000. This has been linked to oral polio vaccination with a causative association of the number of oral polio vaccine doses used and the rate of non-polio AFP [175]. The exact incidence of viral myelitis is unknown [173]. Viral myelitis may accompany several of the tropical CNS viral infections described above.

In AFP due to poliomyelitis, there is a prodrome consisting of headache, fever, or altered mental status. Within days, motor deficit involving one or more limbs occurs. There are no sensory abnormalities or bladder dysfunction. AFP caused by non-polioviruses may be associated with other symptoms which may provide a clue to the viral etiology of symptoms. AFP caused by enterovirus 71 may be associated with hand, foot, and mouth disease, aseptic meningitis, or acute hemorrhagic conjunctivitis. Muscle weakness and wasting associated with enterovirus 70 may be severe and permanent [172]. Acute myelitis, on the other hand, presents with sensory disturbances, urinary retention, and weakness with decreased or increased reflexes. The involvement may be asymmetric when a part of the transverse extent of the cord is involved and bilaterally uniform when both halves of the cord are involved, when it is called acute transverse myelitis. Typically viral myelitis occurs in a matter of days. Faster evolution of symptoms in the order of minutes or hours may represent a vascular event such as anterior spinal artery infarct. Clues to the viral etiology can again be provided by symptoms such as prior vesicular rash in the buccal mucosa and on the hands and feet 3–7 days before in enterovirus 71; dermatomal zoster up to 2 weeks prior in varicella-zoster virus; fever, petechiae, and rash with dengue myelitis; and fever and arthropathy with chikungunya. Associated aseptic meningitis, meningoencephalitis, and neuritis can be seen with several types of tropical viral myelitis (see above).

Differential diagnosis of myelitis includes nonviral infective myelitis and structural, vascular, traumatic, metabolic, hereditary, and autoimmune causes. These can be distinguished by appropriate clinical evaluation and laboratory tests [172, 173].

MRI is the imaging modality of choice and should include the entire spine as the clinical level may not always be accurate. The brain should be included when clinically indicated or at least screened because this may provide important clues to the diagnosis in acute transverse myelitis (e.g., silent demyelination in multiple sclerosis and demyelination typical of acute disseminated encephalomyelitis). MRI in viral myelitis may be normal or show the level and extent of lesions and vertebral segments involved. Cord swelling and hemorrhagic changes may be seen. Gadolinium enhancement of the cord, meninges, or nerve roots may be evident. In patients with AFP due to enterovirus 71 etiology, unilateral or bilateral anterior horn cell T2 hyperintense lesions and ventral nerve root enhancement in post-gadolinium

images have been reported [176]. T2 hyperintense lesions in the anterior horn cells in AFP due to poliomyelitis have also been reported [177]. Spinal cord involvement has also been seen on MRI in Japanese encephalitis [178].

The CSF may show elevated protein and lymphocytic pleocytosis. A definitive diagnosis can be arrived at by demonstration of the virus, viral genome, and antibodies in the CSF or serum. Virus culture is difficult and rarely successful. The viral genomic sequence can be demonstrated by polymerase chain reaction (PCR) for DNA viruses and reverse transcriptase-PCR (RT-PCR) for RNA viruses. The yield is highest if CSF testing is done within 5 days of onset of symptoms [179]. Intrathecal antibody detection by demonstrating virus-specific IgM is a complementary test to PCR/RT-PCR. A ratio of virus-specific serum/CSF IgG antibody titers of less than 100:1 may be suggestive of CNS antibody synthesis. More than fourfold rise of serum antibody titers against a virus may also be diagnostic of viral CNS infection [173]. The definitive diagnosis of viral myelitis is nevertheless elusive and is arrived at by the exclusion of other differential diagnosis.

Electrodiagnostic tests may provide supportive diagnostic evidence, clues to the differential diagnosis, and prognostic information in AFP and ATM. In AFP due to poliomyelitis, non-polio enteroviruses, Japanese encephalitis virus, and West Nile virus, nerve conduction tests indicate anterior horn cell disease with reduced compound muscle action potential (CMAP) amplitude with evidence of denervation on electromyography (EMG). Differentiation of AFP from Guillain-Barré syndrome (GBS) may be possible as the latter shows reduced CMAP amplitude and demyelination on nerve conduction tests but usually does not show denervation on EMG up to 3 weeks [172]. Electrodiagnostic tests may suggest peripheral nerve demyelination or less commonly a compound demyelination and axonal process in GBS [180, 181]. ATM does not show abnormalities on nerve conduction or EMG [172]. It may not be possible however to differentiate between various etiological types of ATM on the basis of electrodiagnostic tests. Prognostic information from electrodiagnostic tests in ATM has been reported. In a large series of patients of ATM, outcome was correlated to somatosensory evoked potentials, EMGs, and central motor conduction times to the tibialis anterior and abductor digiti minimi muscles.

Though the treatment of HSV myelitis is with the antiviral drug, acyclovir, administering acyclovir for all cases of viral myelitis till HSV-2 is excluded is not advisable unless there is a history of recurrent genital infection [173]. Treatment of enterovirus myelitis is mainly supportive. There are anecdotal reports of the efficacy of pleconaril, a drug that blocks enterovirus receptor interaction and viral uncoating, and intravenous immunoglobulin against acute flaccid paralysis caused by enterovirus [182]. Similarly anecdotal reports for efficacy of intravenous immunoglobulin for the treatment of West Nile virus neuroinvasive disease exist [183]. Few drugs have shown promise for the treatment of Japanese encephalitis. However, the efficacy of these drugs in the treatment of JE virus myelitis is yet unknown (see above). Corticosteroids have a doubtful role in the treatment of neuroinvasive viral disease (see sections on JEV, measles, chikungunya). High

doses of intravenous methylprednisolone may have to be started in acute transverse myelitis as it is usually impossible to differentiate between postinfectious (immune-mediated) myelitis and viral myelitis in the acute setting. A dose of 1 g daily for 5–7 days is given [173].

Vaccine-Derived Poliovirus and Vaccine-Associated Paralytic Poliomyelitis

In 1988 the World Health Assembly resolved to eradicate poliomyelitis worldwide. The main tool used for this purpose has been the live-attenuated oral polio vaccine (OPV). The use of this has brought the wild poliovirus (WPV) to near eradication with only three countries, Pakistan, Afghanistan, and Nigeria, remaining endemic at present [91]. WPV occurs in three serotypes (types 1,2, and 3), and currently all residual activity is with type 1. A fallout of the widespread use of OPV has been the emergence of genetically divergent vaccine-derived poliovirus (VDPV) whose genetic drift from the parent OPV strains indicates prolonged circulation and replication. In areas of inadequate OPV coverage, circulating VDPV (cVDPV) can emerge and cause outbreaks of poliomyelitis. In addition in patients with primary B-cell immunodeficiencies, immunodeficiency-associated VDPV (iVDPV) can replicate for years. Ambiguous VDPVs (aVDPV) are isolates that cannot be definitely classified. The incidence of AFP due to VDVP outbreaks have been declining. Thirty-five cVDPV cases were reported worldwide during January 2015–May 2016. During the same period, 11 iVDPV cases and 15 aVDPV cases were reported worldwide. Out of the 721 cases of cVDPV cases detected worldwide during January 2006–May 2016, more than 94% have been of type 2 (cVDPV2) followed by type 1 (cVDPV1) (4%). High OPV coverage can prevent cVDPV outbreaks, but iVDPV infections can only be stopped by stoppage of OPV use. The WHO has responded to the continued cVDPV2 risk incorporating the following in its strategic plans: (1) shifting from trivalent OPV (of types 1, 2, and 3) to bivalent OPV (of types 1 and 3) by April 2016 and (2) including ≥1 dose of injectable inactivated poliovirus vaccine into immunization schedules worldwide to maintain the immunity to type 2 poliovirus. With global eradication of WPV2 declared in 2015 and no detection of WPV3 since 2012, the key long-term goal is that of termination of OPV use starting with the OPV2 which will ultimately tackle the problem of cVDPV outbreaks, new iVDPV infections, and vaccine-associated paralytic poliomyelitis (see below). High levels of routine immunization will have to be maintained to reduce the risk of iVDPV spread from long-term chronic excretors [184–186].

Vaccine-associated paralytic poliomyelitis (VAPP) is an adverse event of exposure to OPV. It occurs in those recently vaccinated individuals or their close contacts. It is sporadic and rare occurring at low rates in countries that use OPV. It is caused by the Sabin strains of attenuated virus in the OPV mutating to a more genetically stable variant that may become neuroinvasive and cause paralysis

indistinguishable from WPV infection. A recent review estimated the global risk of VAPP at 4.7 cases per million births with a global annual burden of 498 cases. When only countries using OPV were considered, the risk was at 3.8 per million births and burden of 399 cases. In low-income countries, VAPP was associated in individuals receiving more than three doses of OPV, whereas in middle- or high-income countries, VAPP was more common in recipients after the first OPV dose or close contacts [184, 187].

In conclusion, CNS viral disease in the tropics presents a challenging task to the treating physician due to several offending endemic and epidemic viruses that are different from those seen in the western world. This is frequently compounded by inadequate health-care systems and adverse sociopolitical conditions that have posed a challenge to the control of several of these diseases. Issues such as emergence of viruses, climate, and environmental change pose fresh challenges to their control. Though commendable strides have been taken in the control of age-old problems such as poliomyelitis, much needs to be done for the control of Japanese encephalitis, rabies, and measles. Fresh challenges have been presented by the emergence of West Nile, Chandipura, Nipah, and occasional neuroinvasive viruses like dengue and chikungunya. The recent emergence of the Zika virus has posed new challenges in the recent past. The reader is directed to Chap. 6 for further details on this virus.

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Fungal Infections of the Central Nervous System

7

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Abstract

Fungal infections of the central nervous system (CNS) represent a diagnostic and therapeutic challenge and are associated with high morbidity and mortality. The incidence of invasive fungal infections has increased over time with the rise of at-risk populations including organ transplants, chemotherapy, and human immunodeficiency virus infections among other conditions. Respiratory tract or sinuses are usually the most common port of entry, and then fungi spread hematogenously or by contiguity to the CNS. Infection may also occur after neurosurgical procedures and catheters, trauma, skin burns and penetrating wounds, and near drowning. CNS fungal infections may present as an acute or chronic meningitis, brain abscess, occupying space lesions, hydrocephalus, stroke, vasculitis, and arachnoiditis. In this chapter, the most common etiologies of CNS infections will be reviewed, including *Cryptococcus*, *Candida*, *Aspergillus*, *Mucor*, endemic dimorphic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*), and other more rare pathogens including *Exserohilum rostratum* and *Scedosporium* spp. Management include the use of amphotericin B, flucytosine, triazoles (voriconazole, posaconazole, fluconazole, itraconazole), and surgery for large brain mass. Long-term azole therapy may be needed for chronic infections to avoid recurrence.

Keywords

Amphotericin B • Aspergillosis • Brain abscess • *Candida* • Cryptococcal meningitis • Fungal infections • *Histoplasma* • Molds • Mucormycosis Phaeohyphomycosis

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Introduction

Fungi are ubiquitous saprophyte organisms that can be found in soil and water. They have an important role in the decomposition of organic material and decaying vegetation. Of the 100,000 fungi species, around 300 are pathogen to humans. Fungal infections of the central nervous system (CNS) represent a diagnostic and therapeutic challenge and are associated with high morbidity and mortality. CNS fungal pathogens can be classified as yeasts (small unicellular organisms), filamentous or hyphae fungi (molds) that grow in colonies and dimorphic fungi (Table 7.1).

Some endemic fungi have specific geographic distribution in template and subtropical regions. However, other fungi may have a worldwide distribution and be ubiquitous. In the last decades, the epidemiology of fungal infections has rapidly changed. Involvement of the CNS is now a more frequent complication of disseminated mycosis in susceptible hosts. The incidence of invasive fungal infections has increased over time with the rise of at-risk populations including organ transplants, chemotherapy, and human immunodeficiency virus (HIV) infections [1].

There are specific risk factors for CNS fungal infections, as these affect mostly immunocompromised individuals. Acquired immune deficiency syndrome (AIDS), solid organ transplantation, chronic diseases (diabetes, renal failure, and cirrhosis),

Table 7.1 Most common CNS fungal pathogens

1.	Yeasts	
	(a)	*Cryptococcus neoformans*
	(b)	*Cryptococcus gattii*
	(c)	*Candida* spp.
2.	Molds (filamentous fungi)	
	(a)	Septate molds
		• *Aspergillus* spp.
		• *Scedosporium* spp.
	(b)	Aseptate/minimally septate
		• *Mucorales* (Mucor)
		• *Rhizopus*
		• *Rhizomucor*
		• *Absidia*
		• *Cunninghamella*
	(c)	Dematiaceous or pigmented molds
		• *Exserohilum rostratum*
		• *Cladophialophora bantiana*
		• *Rhinocladiella mackenziei*
		• *Ochroconis gallopava*
3.	Dimorphic fungi	
	(a)	*Histoplasma capsulatum*
	(b)	*Coccidioides immitis*
	(c)	*Blastomyces dermatitidis*
	(d)	*Paracoccidioidies brasiliensis*

hematological malignancies, chronic corticosteroid or immunosuppressive therapy, some congenital immune deficiency conditions, and the use of intravenous drugs are well-known risk factors. However, some pathogen fungi may also affect to healthy immunocompetent people, and predisposing factors include trauma, near drowning, skin burns and penetrating wounds, and the use of catheter and neurosurgical devices [2].

Cryptococcus is the most frequent cause of fungal meningitis. Cryptococcal meningitis is now an AIDS-defining illness, and the incidence rose dramatically with the pandemic of AIDS. During the pre-highly active antiretroviral therapy (HAART) era, thousands of people yearly died from cryptococcal meningitis in sub-Saharan Africa [3]. The incidence of HIV-associated cryptococcosis has diminished in developed countries since the introduction of antiretroviral therapy [4].

Geographical differences have been observed in the frequency of CNS fungal infections, too. In a 2-year study performed in a reference hospital in northern India, the most common cause in 50 CNS fungal infections was mucormycosis (50%), followed by *Cryptococcus* (34%), and aspergillosis (16%) [5]. However, incidence of invasive aspergillosis continues to rise in Middle East countries among immunocompromised patients [6].

Meningitis and meningoencephalitis are the most frequent forms of presentation of CNS fungal infections. *Cryptococcus* is the most common cause of chronic lymphocytic fungal meningitis. *Candida albicans* is the most frequent etiology of acute or neutrophilic fungal meningitis. CNS fungal infections may also present as space-occupying focal lesions, brain abscesses, or granulomas. Some angioinvasive fungi such as *Aspergillus* may cause ischemic stroke secondary to vasculitis. In rare occasions, myelopathy and epidural abscess, and osteomyelitis may happen.

There are new clinical phenotypes of fungal infections in special immunosuppressed hosts. New groups at risk include patients with acquired immunodeficiency due to immunosuppressive therapies such as anti-tumor necrosis factor-α (TNF-α) treatment. Patients who have severe burns and damage of skin barrier protection are also susceptible to disseminated *Candida* and filamentous fungal infections (*Aspergillus spp*., *Mucorales*). Some recently discovered primary immunodeficiency conditions can also predispose selectively to invasive CNS fungal diseases [1].

Respiratory tract is the most common port of entry, and fungi spread through hematogenous dissemination to the CNS. In some cases, direct fungal inoculation in the CNS may occur as consequence of trauma, infected wounds, neurosurgery, and use of intravenous drugs or contaminated corticosteroid injections. Local spread from sinuses, orbit, and vessels may also occur, and blood vessel invasion is common in immunosuppressed patients [7].

Microscopy, culture, and histopathological identification of fungal organisms are the standard strategies for the diagnosis of fungal pathogen infection. Recently, new diagnostic techniques have emerged such as lateral flow immunoassays, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), and multiplex polymerase chain reaction techniques (PCR) [8]. Neuroimaging (CT scan and MRI of brain) have been very useful to detect and

evaluate progression of cerebritis, abscess formation, large mass lesions, vasculitis and ischemic infarctions, mycotic aneurysms, and the presence of leptomeningeal enhancement [9].

Timely antifungal therapy may avoid long-term neurological sequel. In patients with focal mass lesions, neurosurgical therapy may also be needed. Reversal of immunosuppression and early detection and treatment of immune reconstitution inflammatory syndrome (IRIS) are other basic management points. Antifungal agents include amphotericin B formulations, flucytosine, and triazoles [10].

In this chapter, the most common fungal pathogens affecting the CNS will be reviewed.

Yeasts

Cryptococcosis

Epidemiology and Risk Factors

Cryptococcus is a worldwide spread yeast that is usually found in soils contaminated with bird feces which are an environmental reservoir for the fungi. Cryptococcosis is a fungal infection caused mainly by two pathogen species which belong to the group of basidiomycete, *Cryptococcus var. neoformans* and *Cryptococcus var. gattii*. *Cryptococcus* is a leading cause of meningitis in those areas of the world in which HIV infection is endemic. One decade ago, it was estimated that *Cryptococcus* caused annually around 1 million cases of meningitis and half million deaths per year in sub-Saharan HIV-endemic countries [11]. In the last decade, the introduction of HAART caused a significant reduction in the number of cases of HIV-associated cryptococcal meningitis in developed countries. Prevalence of cryptococcal meningitis remains still high in HIV-endemic African countries, and patients at high risk are those with CD4 T cell count <100 cells/ul and not taking HAART.

Cryptococcus gattii has also caused outbreaks in the region of the United States (US) Pacific Northwest, British Columbia, and Vancouver, affecting mainly healthy immunocompetent population and causing involvement of lungs and the CNS [12]. *C. gattii* infection is usually found in tropical and subtropical areas among healthy people exposed to plant propagules.

Risk factors for cryptococcal meningitis in HIV non-infected patients are receiving solid organ transplantation [13], having cell-mediated immunity disorders, chronic liver, kidney or lung disease, and malignancy [14]. In addition, *Cryptococcus* is associated with sarcoidosis [15] and some autoimmune diseases (lupus, dermatomyositis) [16]. However, a confounding factor in these cases may be the chronic use of steroids.

Cryptococcal meningitis has also been reported in health immunocompetent people. Nevertheless, it is thought that many "normal" or "healthy" hosts may harbor unknown primary immune defects [11]. Idiopathic CD4+ lymphopenia, pulmonary alveolar proteinosis with antibodies to granulocyte-macrophage

colony-stimulating factor, and the presence of autoantibodies against interpheron-gamma have been associated with cryptococcosis [17].

Recently, cryptococcal meningitis/meningoencephalitis and disseminated cryptococcosis have been reported in several patients with relapsing remitting multiple sclerosis treated with the immunosuppressive drug fingolimod [18–20].

Pathogenesis

Cryptococcus genome displays plasticity and high capacity for microevolution, which can happen in the stressful environment of the human subarachnoid space [21]. *C. neoformans* is found in purine-rich bird guano and suffers a dramatic change in nutrient availability during host infection when disseminating to colonize the purine poor CNS [22]. The virulence of this human fungal pathogen is complex, and multiple factors have been identified including the ability to growth in higher temperatures, the capsule and melanin production, and the phospholipase/urease activity.

Cryptococcus can grow at 37 °C and survive in relatively hypoxic environments such as the brain and produces a polysaccharide capsule that protects from host. *Cryptococcus* has a high tropism for the brain and uses the virulence factor laccase which has a predilection for the dopaminergic tracts, particularly in the basal ganglia, to produce melanin. The oxidation of catecholamines within dopaminergic tracts produces melanin which acts as an immunosuppressive compound. The high concentration of inositol in the CNS seems also to be necessary for the survival of the fungus in the brain. Recently, it has been shown that guanosine monophosphate (GMP) synthase, the second enzyme in the guanylate branch of de novo purine biosynthesis, is required for virulence factor production and infection by *Cryptococcus* [22].

Clinical Features

Cryptococcus is usually acquired by inhalation, and the yeast reaches the alveolar spaces. Following a latent period in which *Cryptococcus* is contained within the lymph nodes of the lung, the organism may spread and involve the lungs, CNS, skin, urinary tract, and bones. During the primary infection, dissemination from lungs to the blood and CNS may cause a life-threatening meningoencephalitis in immunosuppressed patients. Dissemination may also happen after reactivation of a granuloma upon immunosuppression [23].

Acute cryptococcal meningitis may present with headache, fever, nausea and vomiting, and mental changes. Blurred vision, seizures, and decreased level of consciousness may occur as a consequence of raised intracranial pressure. In rare cases, visual loss may occur through direct optic nerve, chiasm, or tract invasion by the fungi [24]. Focal brain granulomas are called cryptococcomas and may present as focal neurological deficit [25].

In some patients, a significant delay in diagnosis may happen; chronic infection is associated with cognitive dysfunction, gait disturbances, and even dementia in these cases. Visual and hearing problems, cranial nerve involvement, and either obstructive or non-obstructive hydrocephalus may also occur. HIV-negative

patients may have a more prolonged and chronic course of the disease [7]. In a case-control study, the main predictors of cryptococcal meningitis were positive blood culture, detection of cryptococcal antigen in serum, current malignancy, and headache [26].

Diagnosis

Cerebrospinal flow (CSF) analysis may demonstrate raised protein, low glucose levels, and lymphocyte pleocytosis. However, the CSF white cell count can be low in HIV patients. Confirmatory diagnosis is based on detection of cryptococcal antigen (the capsular polysaccharide called glucuronoxylomannan) and/or the direct visualization of *Cryptococcus* in the CSF using India ink stain, which has 70–90% sensitivity. In those patients having negative CSF culture, antigen titters from serum and CSF can be detected by means of enzyme immunoassay, latex agglutination tests, or lateral flow assay. In non-HIV patients, CSF culture and latex agglutination tests can be negative, and repeated CSF samples may be indicated, mainly for *C. gattii* [11].

The CT and/or MRI of the brain may reveal leptomeningeal enhancement, hydrocephalus, and cryptococcomas. In negative CSF culture patients and in those who present with cryptococcomas, diagnosis can be done by pathological examination of meningeal biopsy sample. Encapsulated cryptococcomas, although rare, may happen in immunocompetent hosts. These are large cystic lesions, usually related to *C. gattii* and may mimic a glioblastoma [27]. Vasculitis causing small vessel infarctions in the basal ganglia, thalamus, and posterior circulation has also been described in cryptococcal meningoencephalitis [28–30] (Fig. 7.1).

IRIS, resulting in worsening of cerebral edema and neurological deterioration have been reported during early stages of treatment in both HIV and non-HIV patients [31]. IRIS may happen in HIV patients with cryptococcosis after initiation of the HAART. Paradoxical cryptococcal IRIS associated with the development of intracranial cryptococcomas have been described in HIV patients following treatment of cryptococcal meningitis [32]. Cryptococcal-IRIS findings include focal meningeal and parenchymal enhancement, linear perivascular enhancement in the brain sulci, and enhancement of the distended Virchow-Robin space pseudocysts [33].

Treatment

Crptococcosis of the CNS is associated with significant mortality and morbidity among HIV and non-HIV infected patients, despite antifungal therapy. Early diagnosis and treatment are needed to avoid long-term neurological sequelae and death. Raised intracranial pressure should be treated soon as it is significantly associated with poor neurological outcomes [34, 35].

The three-steep therapeutic approach (induction, consolidation, and maintenance) has been used in the last two decades. Amphotericin B (Amb) with or without flucytosine is the treatment of choice. Amphothericin B plus flucytosine showed better outcomes, with increased survival ratio and quicker clearance of infection,

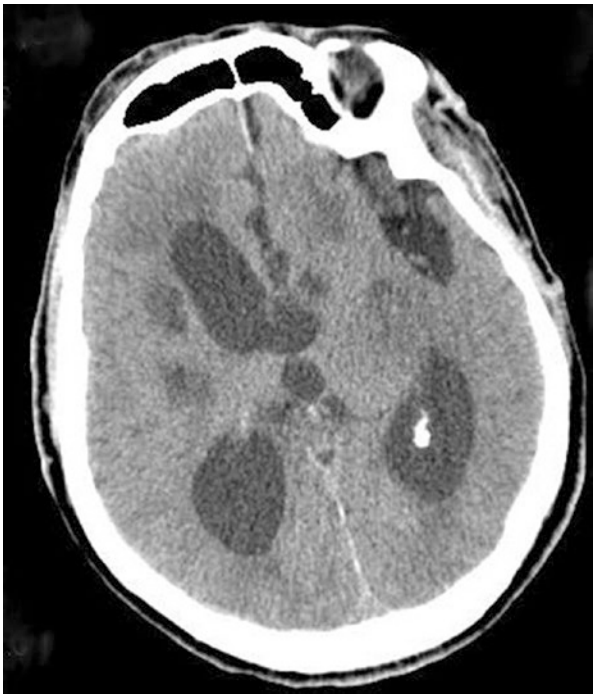

Fig. 7.1 CT scan of the brain. Hydrocephalus and ischemic infarcts in cryptococcal meningitis

compared to single therapy with amphotericin B. Flucytosine dose should be adjusted if renal impairment secondary to amphotericin occurs [11].

Amphotericin B deoxycholate (D-Amb) may cause side effects including hypokalemia, hypomagnesemia, renal dysfunction, and anemia. The intravenous (IV) lipid amphotericin B formulations (L-Amb), either liposomal AmB (dose: 3–4 mg/kg/day IV) or lipid complex AmB (5 mg/kg/day IV) have a better tolerability profile and can be used in those patients having kidney dysfunction [11].

Initial intravenous fungicidal therapy (D-Amb dose: 0.7–1 mg/kg/day) plus flucytosine (100 mg/kg/day orally in four divided doses) is recommended for at least 2 weeks. The initial induction phase may be longer (4–6 weeks) in non-HIV patients and is followed by a consolidation therapy with fluconazole (400 mg/day) for at least 8 weeks. Fungistatic oral drugs such as fluconazole (200 mg/day) or itraconazole are also recommended as subsequent oral treatment to complete a 12–18 months course. *Cryptococcus gattii* may become fluconazole-resistant [11].

In some patients, serial high-volume lumbar punctures may be indicated to control CSF pressure during the first weeks of treatment. Cerebral edema, outflow obstruction secondary to arachnoiditis, and obstruction within the Monro, Luschka, and Magendie foramen may happen. In severe hydrocephalus cases, a shunt may be required.

CNS Candidiasis

Epidemiology and Risk Factors

Candida spp., a yeast that forms part of the normal commensal human microbial flora, can be found frequently in the skin, oral cavity, and the digestive and genitourinary tracts. There are more than 80 species and the most common are *Candida albicans*, *Candida tropicalis*, *Candida glabatra*, *Candida krusei*, and *Candida parapsilosis* [36].

Candida spp. can cause invasive disease in immunocompromised patients, and the main risk factors are neutropenia and AIDS [37]. In immunocompetent patients, invasive candidiasis is associated with critical illness, the use of central venous catheters, prosthetic material and other indwelling catheters, prolonged use of broad-spectrum antibiotics, and burns [38].

Data from the Prospective Antifungal Therapy Alliance registry, a multicenter observational study of HIV patients, showed that *Candida* (33%) was the second most common infection after *Cryptococcus* (50%), and followed by *Histoplasma* (9%), and *Aspergillus* (4.4%) [39]. Disseminated *Candida* infections in HIV patients occurred mainly as candidemia [39].

Candida spp. meningitis occurs mostly in neonates, and also in patients that underwent neurosurgical procedure such as ventriculostomy, had an infected wound or a shunt placed, and also in immunocompromised subjects [2, 40].

Invasive fungal infection rates are highest among neonates, especially those of low birth weight. The Neonatal Infection Surveillance Network in England study (2004–2010) reported that the overall incidence was 2.4/1000 neonatal unit admissions and was highest among babies <1000 g. The majority of infections were caused by *C. albicans* ($n = 59$; 69%) and *C. parapsilosis* ($n = 17$; 20%). Identified risk factors were the use of central venous catheters, parenteral nutrition, and previous antibiotic use [41]. Mortality and neurodevelopmental outcome of extremely low birth weight infants who suffer CNS candidiasis is very poor, and severe neurodevelopmental impairment or death has been reported [42]. In the England study, the case fatality rate was 21% [41].

Caspase recruitment domain-containing protein 9 (CARD9) deficiency is an autosomal recessive primary immunodeficiency disorder which confer human susceptibility to invasive fungal disease [43]. Cases of congenital CARD9 deficiency have been associated with chronic mucocutaneous candidiasis including spontaneous CNS candidiasis [44]. In some cases, CNS candidiasis occurred in adulthood and was confounded radiologically with brain malignancies [44]. Inherited CARD9 deficiency in otherwise healthy children and adults may present with *Candida* spp. meningoencephalitis, colitis, or both [45]. Chronic *C. albicans* meningitis has also been reported in a 4-year-old girl harboring a homozygous mutation in the CARD9 gene (Q295X) [46].

Clinical Features

C. albicans initially infects the oral cavity and esophagus; submucosal blood vessels become involved when infection progresses. Hematogenous dissemination may

cause meningitis and also multiple embolic micro-abscesses in the brain parenchyma in neutropenic patients. CNS involvement may occur in at least half of cases of disseminated candidiasis, and mortality is very high [7]. *Candida* endophthalmitis may happen following bloodstream infections. After *Staphylococcus aureus*, neurocandidiasis is the second most common etiology of scattered cerebral micro-abscesses. *Candida* micro-abscesses may present with non-specific symptoms including headache, fever, and encephalopathy. Cerebral abscesses may also happen in preterm infants [47].

There are other less common forms of presentation such as large solitary brain abscesses, basilar artery thrombosis, ischemic stroke secondary to vasculitis, and subarachnoid hemorrhage following the rupture of a mycotic aneurysm [30]. Shunt dysfunction can be the first manifestation once the device is infected.

Diagnosis

CSF analysis may reveal low glucose levels, increased CSF adenosine and protein levels, and monocytic or neutrophilic pleocytosis, although in immunocompromised patients the inflammatory response can be absent. Diagnosis is based on the identification of *Candida* spp. in the CSF culture. Negative culture cases are seen commonly and for this reason large volume CSF samples, around 30 ml, may be needed [7]. The detection of 1,3-β-D-glucan, a fungal cell wall component, is not specific and can also be detected in *Aspergillus* infections [48, 49].

MRI is a helpful technique to detect multiple parenchymal micro-abscesses, hydrocephalus, or diffuse meningeal gadolinium enhancement. CNS candidiasis may also present radiographically as bilateral punctate areas of restricted diffusion in the basal ganglia on the brain MRI [50].

Treatment

The treatment of choice of CNS candidiasis is liposomal Amb (3–5 mg/kg/day) with or without flucytosine (25 mg/kg four times a day) for several weeks, followed by a maintenance therapy with fluconazole (6–12 mg/kg; 400–800 mg daily) [2, 51].

Echinocandins such as caspofungin, micafungin, or anidulafungin, although commonly used in disseminated candidiasis, have very low detectable levels in the brain and can be even undetectable in the CSF. Echinocandins are not active against *Cryptococcus*. For these reasons, echinocandins are not usually used to treat CNS fungal infections.

Removal of prosthetic material such as contaminated shunts, indwelling catheters, and other neurosurgical devices and the drainage of collections is also necessary. Restitution of immune function is also important. Clinical remission of CNS candidiasis was obtained in a CARD9 deficiency patient with adjunctive granulocyte-macrophage colony-stimulating factor therapy [44]. Interferon-gamma immunotherapy has been used in patients with refractory disseminated candidiasis [52]. Ruptured mycotic aneurysms may be treated with coil embolization [53].

Molds

CNS Aspergillosis

Epidemiology and Risk Factors

Aspergillus spp. is a genus of filamentous and septated molds that can be found throughout the world. *Aspergillus* is a ubiquitous airborne saprophytic fungus. *A. fumigates* is the most common species, and other pathogens from the same genus are *A. flavus*, *A. niger*, and *A. terreus*. Immunocompetent hosts usually eliminate the inhaled *Aspergillus conidia* by means of the innate immune mechanism.

Aspergillosis is a relatively infrequent opportunistic infection of the CNS that may account for around 10% of all fungal infections of the CNS and it is associated with high mortality and morbidity [54]. Risk factors for invasive CNS aspergillosis [2] include neutropenia, hematological malignancies, AIDS, chronic treatment with corticosteroids, transplant recipients [55], and severe debilitating conditions such as chronic granulomatous diseases [56], tuberculosis, cancer, diabetes, or alcoholism. CNS aspergillosis has also been described in patient with Crohn's disease after treatment with infliximab and corticosteroids [57].

Rarely granulomatous cerebral aspergillosis may happen in immunocompetent adult patients [54]. Sinocranial aspergillosis has also been described in inmunocompetent patients in temperate countries [2].

Clinical Features

The involvement of the CNS may occur either by direct propagation from sinuses, nose or ear canal, or by hematogenous spread from a primary pulmonary focus. It is estimated that around 40% of patients with pulmonary aspergillosis may develop extrapulmonary involvement, mostly brain abscesses and sinusitis [58]. Mortality rate can be higher than 50% [59–61].

Intracranial mass lesions and skull base involvement may happen in CNS aspergillosis [2]. Intracranial fungal granulomas are rare space-occupying lesions, and among these, *Aspergillus* granuloma is the most frequent. Aspergillomas may result in focal neurological deficit (hemiparesis) or symptomatic seizures, and headache, fever, and altered mental status are common. The involvement of the base of skull may cause multiple cranial nerve palsies [7]. Sinucranial aspergillosis may present with nasal stuffiness, periorbital pain, and can be followed by diverse degrees of ophthalmoplegia, proptosis and visual loss, and orbital apex or cavernous sinus syndrome. Optic nerve aspergillosis has been reported, and enlargement of optic nerve at the level of the cavernous sinus and extending into the optic chiasm has been described [62]. Rare cases of primary *Aspergillus* sellar abscess simulating pituitary tumor in immunocompetent patient have also been described [63].

Aspergillosis is the most common invasive fungal infection affecting cerebral blood vessels. Hematogenous dissemination can cause ischemic infarctions and brain hemorrhages [30]. *Aspergillus* is an angioinvasive pathogen, and the enzyme elastase is able to digest the internal elastic lamina of cerebral arteries leading to

focal micro-hemorrhages. As a consequence, mycotic aneurysm may occur in the weakened walls of the cerebral arteries and their rupture may cause subarachnoid hemorrhage. Cerebral aneurysms associated with *Aspergillus* infection are highly vulnerable to rupture. Recurrent cerebral aneurysm formation and rupture due to invasive aspergillosis of the nasal sinus have also been reported [64].

Occlusive thrombosis and hemorrhagic infarctions can happen once *Aspergillus* invade and fill brain vessels [30]. Aspergillosis usually blocks the cerebral blood flow at the origin of the small perforating arteries and frequently affects the basal ganglia, thalamus, and the corpus callosum [65]. The anterior and middle cerebral arteries are also frequently involved.

Aspergillus vertebral osteomyelitis, spinal epidural abscess, and intramedullary infections have described less frequently [66].

Diagnosis

The galactomannan antigen test and the PCR technique in CSF are helpful to establish the diagnosis. Another potentially helpful biomarker is (1 → 3)-β-D-glucan, a cell wall component found mainly in *Candida* and *Aspergillus* spp. The detection of (1 → 3)-β-D-glucan in the CSF may also contribute to the diagnosis, although validation studies are needed [49]. In some patients with invasive aspergillosis [67], CSF and serum 1,3-β-D-glucan test may be positive, in contrast to galactomannan antigen.

In many occasions, a definitive diagnosis can be only done by means of pathological exam [68] or a positive culture obtained from the brain tissue. CNS biopsy followed by histopathological examination and/or culture can contribute to an early diagnosis and timely treatment and improve survival rate [69].

The brain MRI may show multiple brain abscess, ring-enhancing lesions, and dural or blood vessel infiltration from near surrounding areas from orbit region or paranasal sinus, and/or ischemic lesions [70]. The CT scan is helpful to identify any subarachnoid hemorrhage.

Treatment

Voriconazole is the recommended treatment for invasive aspergillosis and has a good penetration in the CNS [71]. Invasive *Aspergillus* sinusitis and otitis with meningeal extension have been successfully treated with voriconazole [67]. Initial dose (6 mg/kg IV every 12 h the first day) should be followed by 4 mg/kg IV every 12 h and then oral dosage 200 mg twice a day. Nevertheless, this drug has a non-linear pharmacokinetics and extensive inter and intra-patient variation in serum levels is common. As some of the voriconazole adverse effects may be related to high serum concentrations, therapeutic drug monitoring is advisable. Periostitis and alopecia have been associated with prolonged use [71]. Liposomal Amb (3–5 mg/kg/day IV), posaconazole [72, 73], itraconazol, or micafungin [74] are alternatives for refractory cases, and adjunctive surgery should be considered when needed as this could reduce mortality [75, 76].

Azole-resistant *Aspergillus fumigatus* is a concern and experts recommend switching in these cases from voriconazole to liposomal amphotericin B. L-Amb is

recommended as first-line therapy for azol-resistant CNS aspergillosis in regions with environmental resistance rates of ≥10%, and the addition of a second agent such as flucytosine should also be considered [77].

Mucorales (Mucormycosis)

Epidemiology and Risk Factors

Traditionally, it has been considered two orders of *Zygomycetes*, the *Mucorales* and the *Entomophthorales*. Recently, a change in nomenclature has been proposed. Now it is accepted as more appropriate the term mucormycosis, as the old concept "zygomycosis" has been discarded following molecular reclassification using sequence-based DNA phylogeny [78]. These fungi are ubiquitous in soil and can be found frequently in decaying vegetation and in decomposing organic matter such as fruit and bread [2]. *Mucorales* are aseptate molds and have broad, ribbonlike nonseptate hyphae.

The most pathogenic are *Mucor*, *Rhizopus*, *Absidia*, *Cunninghamella* spp., and *Lichtheimia corymbifera*. In a review of 96 mucormycosis cases from literature, the most frequent pathogens were *Rhizopus* spp. (31%), followed by *Mucor* spp. (15%) [79].

Risk factors for *Mucor* infection are hematological malignancies, immunosuppression states, prolonged neutropenia, chronic corticosteroid therapy, hematopoietic stem cell and kidney transplantation, diabetes, renal failure, injectable drug users, trauma, malnutrition, iron overload, and the use of deferoxamine chelation therapy. Uncommonly, mucormycosis can affect immunocompetent subjects, mainly when the skin barrier is affected in wounds and burns.

Clinical Features

The port of entry of sporangiospores is through inhalation. There are several forms of the disease including pulmonary, cutaneous and soft tissues, renal, gastrointestinal, rhino-orbital-cerebral, and disseminated disease [80]. CNS involvement can occur as sino-orbital infections or through hematogenous dissemination from pulmonary mucormycosis. In a review of published cases, rhino-orbital was the predominant site of infection (38.5%, of which 43% also had CNS involvement), followed by disseminated disease (22%) [79]. Rhinocerebral mucormycosis is the most common form of the disease in diabetic ketoacidosis, followed by the cerebral form. Hematogenous spread and cerebral involvement are more common in IV drug abusers [81].)

Rhinocerebral mucormycosis constitutes a medical emergency. A sequential involvement from nasal cavity and ethmoidal sinuses to the orbital region, eye, bone, and brain usually occurs [82]. Ethmoidal mucormycosis can extend into cavernous sinuses because the venous drainage of ethmoidal sinuses extends to the cavernous sinuses. Cavernous sinus thrombosis is characterized by the involvement of ocular motor nerves and the first and second branches of trigeminal nerve. Diplopia secondary to ophthalmoparesis, loss of vision or blurred

vision, and paranasal sinus symptoms are initial symptoms, and may be followed by contralateral hemiparesis if internal carotid artery thrombosis occurs [7]. Rhino-orbito-cerebral mucormycosis may sometimes present as orbital apex syndrome initially [83].

Isolated cerebral mucormycosis and disseminated mucormycosis with cerebral involvement are other forms of presentation of the disease. Temporal bone mucormycosis may affect elderly diabetic patients and present as facial palsy [84]. Cerebral mucormycosis may present with fever, headache, impaired vision, lethargy, seizures, and focal symptoms such as hemiparesis, aphasia, or Gerstmann syndrome [85]. This condition can be complicated with multiple cerebral infarctions and abscesses [86]. Mucormycosis with cerebral involvement without sinus disease may result in ischemic stroke [87].

Mucormycosis has a very poor prognosis. Mortality rate for rhinocerebral infection is more than 60%, whereas mortality associated with disseminated infection in the CNS is 98%. Differential diagnosis includes other mold infections as those caused by *Aspergillus*.

Diagnosis

Pathological assessment and culture of tissue samples may show lack of septa in the hyphae, and this fact allows the distinction with aspergillosis. The Grocott-Gomori methenamine-silver stain and the calcofluor white fluorescent stain are the stains of choice to confirm the lack of septae. Cultures may become positive in only 40–70% of biopsy-proven cases [2].

The CT scan of the sinuses and/or craniofacial MRI may detect sinus opacification, fluid-filled sinuses, bone erosions, and obliteration of deep fascia planes [82] (Fig. 7.2). Bony destruction may happen as the disease progresses. MRI and MR venogram are helpful to identify thrombosis of cavernous sinus and perineural intradural spread. Neuroimaging techniques are also helpful to visualize the best area for the biopsy.

Treatment

The principles of treatment of rhinocerebral mucormycosis include antifungal therapy, the control and reversal of host conditions (control of diabetes and neutropenia), and appropriate surgical debridement of necrotic tissue. High-dose amphotericin B (1.2–1.5 mg/kg/day) or AmB lipid complex (3–10 mg/kg/day) is the antifungal treatment of choice, and total dose of AmB may range between 2 and 4 *g* [88]. Posaconazole has in vitro activity against *Mucorales* and may also be an effective therapy, although CNS penetration is poor; recommended oral daily dose is 800 mg divided in 2 or 4 doses.

A case of disseminated mucormycosis with cerebral involvement owing to *Rhizopus microsporus* has been successfully treated in a kidney recipient with combined liposomal amphotericin B and posaconazole therapy [89]. Case reports have also highlighted isavuconazole as effective treatment for disseminated mucormycosis [90]. Mucor usually has a poor response to voriconazole which is the treatment of choice for cerebral aspergillosis.

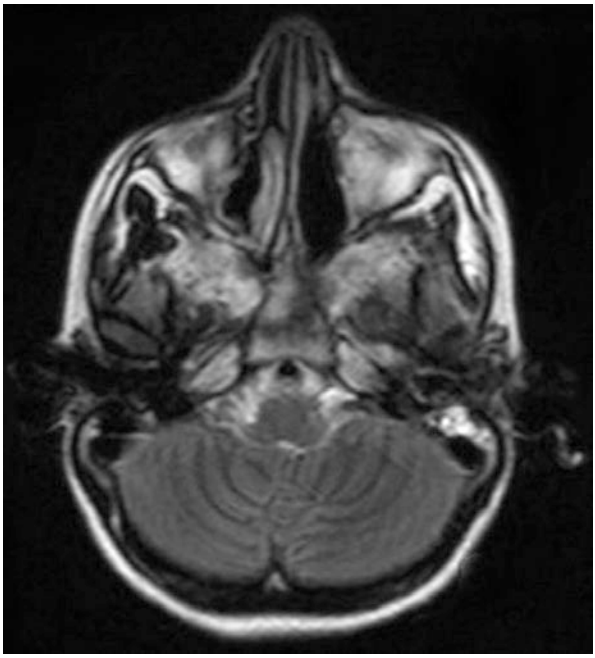

Fig. 7.2 CT scan of the brain. Rhino-orbito-cerebral mucormycosis

Dimorphic Fungi

Histoplasmosis

Epidemiology and Risk Factors

Histoplasmosis is probably the most common endemic mycosis in South and Central America, Mexico, and the USA. In the USA, the disease is endemic in Ohio and Mississippi river valleys. Endemic areas have also been described in Southeast Asia, India, and along the Yangtze River in China [91]. Factors that account for specific endemicity in these geographical areas are moderate temperature and the presence of bird or bat guano containing soil. Activities at risk of *Histoplasma* infection include farming, working as geologist in caves, demolition of old buildings, exposure to chicken coops or caves, or travel to endemic areas [91].

Infection occurs by inhaling microconidia and is usually asymptomatic in healthy subjects. However, inhalation of large inoculums may cause acute pulmonary histoplasmosis in immunocompetent individuals. Most of subjects develop a self-limited or subclinical disease. Immunocompromised patients who have impaired cellular immunity such as AIDS, lupus, and solid organ transplantation recipients [92] are at risk of developing the disease either pulmonary or disseminated [93]. Histoplasmosis can also affect infants, given their immune immaturity, and children [94] and main risk factors are malnutrition (37%) and environmental exposure (33%) [95].

Clinical Features

Fever, fatigue, weight loss, and respiratory symptoms can be observed in disseminated histoplasmosis. The lungs, kidney, liver, skin, and CNS can be affected. Chest X-rays may detect pulmonary nodules, hilar and mediastinal adenopathy, or pulmonary reticulonodular, interstitial, or military infiltrates [91]. Progressive histoplasmosis can present with hemophagocytic lymphohistiocytosis and epithelioid cell granulomatosis [96].

CNS histoplasmosis can occur in 10% of cases of disseminated histoplasmosis, although in children the proportion is higher (50%) [95]. CNS histoplasmosis can present as acute or subacute meningitis, brain and/or spine parenchymal lesions, and chronic meningitis with or without vasculitis and ischemic infarctions [97, 98]. Headache, focal deficits [99], seizures, stroke, and even cognitive dysfunction [100] are common forms of presentation. Hemichorea has also been reported as clinical presentation of HIV-associated CNS histoplasmosis [101]. Cases of histoplasmosis infecting ventriculoperitoneal shunt have been described [102].

Diagnosis

H. capsulatum can be visualized as ovoid yeast cells in tissues and body fluid specimens, including the brain parenchyma. Galactomannan antigen for *Histoplasma* can be detected in serum, urine, and the CSF, although cross-reactions with *Blastomyces* have been seen. CSF analysis may show low glucose levels, raised proteins, and myeloid pleocytosis. In occasions, the diagnosis is obtained by positive culture and/or histopathological analysis of brain tissue obtained by means of stereotactic biopsy. Cultures can be positive in 50–85% of cases of disseminated or chronic pulmonary histoplasmosis, and the highest culture yield is from bone marrow or blood with a positivity of 75% [91]. The brain MRI may reveal meningeal enhancement, hydrocephalus, or multiple lesions with a ring-enhancing pattern [99, 103] (Fig. 7.3).

Treatment

Recommended therapy for CNS histoplasmosis is liposomal amphotericin B (dose, 5 mg/kg/day; total dose, 175 mg/kg given over 4–6 weeks) followed by itraconazole (200 mg two or three times per day) for at least 12 months. *Histoplasma* antigen levels should be cleared, and CSF analysis should come back normal before deciding stopping itraconazole. Azole serum levels should be monitored during treatment. Fluconazole, voriconazole, and posaconazole are alternative treatments for salvage therapy. Relapses may occur, and in some patients, lifelong azole therapy is necessary, mainly for those patients for whom effective immune reconstitution is not observed.

In a multicenter retrospective study of outcomes and factors associated with relapse in 96 cases of AIDS-associated histoplasmosis, 67% of CNS histoplasmosis patients relapsed compared to 15% without CNS involvement [104]. Patients with antigenuria above 2.0 ng/mL at 1-year follow-up were also almost 13 times more likely to relapse. The following factors have been associated with safe

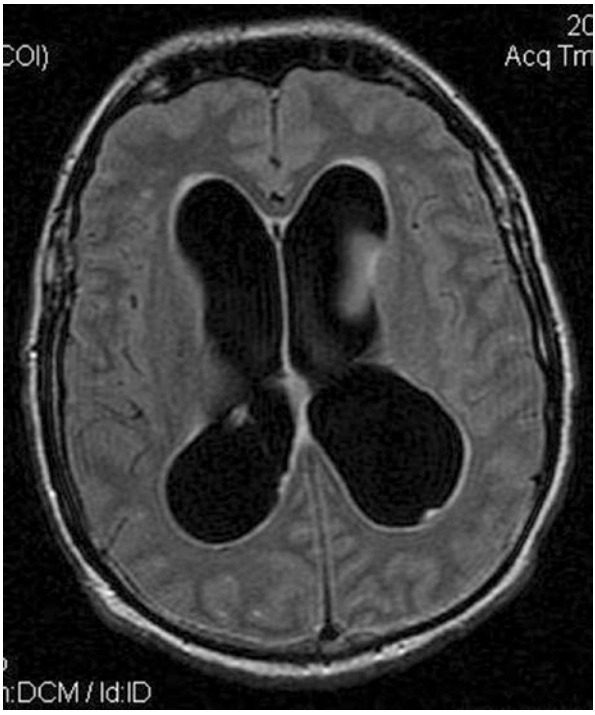

Fig. 7.3 MRi of the brain. Hydrocephalus in CNS histoplasmosis

discontinuation of antifungal therapy: (1) adherent patients who completed at least 1 year of antifungal treatment; (2) to have CD4 count >150 cells/mL, (3) HIV RNA < 400 c/mL, and (4) *Histoplasma* antigenuria <2 ng/mL; and (5) absence of CNS histoplasmosis [104].

Coccidioidomycosis

Epidemiology and Risk Factors

Coccidioides spp. are dimorphic saprophytic fungi that are common in dry and warm regions in Mexico, South America, and south-western USA. *Coccidioides immitis* is the most common cause of chronic meningitis in endemic regions for coccidioidomycosis. Risk factors are immunosuppression states, AIDS, diabetes, and chronic steroid therapy.

Prolonged soil exposure in dry hot areas is a risk factor in healthy people and population at risk include farm and construction workers and other professionals such as archaeologists. Pulmonary infection may happen after inhalation of *Coccidioides arthroconidia*, and disseminated state affecting the CNS occurs mostly in immunosuppressed patients [2].

Clinical Features

CNS involvement can present as chronic basilar meningitis with involvement of multiple cranial nerves. Initial clinical symptoms include low-grade fever, chronic daily headache, and memory and attention problems. Without treatment, the disease may progress and complicate with hydrocephalus, vasculitis, and ischemic infarctions in approximately 40% of cases.

Spinal coccidioidomycosis is less frequent and usually manifests as bone involvement leading to osteomyelitis and epidural abscess. A rare case of disseminated coccidioidomycosis who presented with rapidly progressive quadriparesis due to cervical intramedullary spinal cord involvement has been recently reported [105].

Diagnosis

Diagnosing coccidioidal meningitis can be difficult owing to delay in the positivity of a CSF culture or CSF antibody, particularly if the primary coccidioidal infection is unrecognized [106]. In many cases, there is a delay in the diagnosis, as patients may present with subacute meningitis in the absence of pulmonary symptoms, and CSF culture may be negative.

Coccidioidomycosis should be considered in the differential diagnosis of chronic meningitis in endemic areas. Diagnosis relies on the detection of positive antibodies or a positive culture in CSF. CSF Coccidioides antigen testing may be helpful in both the diagnosis and management of CNS coccidioidomycosis [107]. In occasions, the CSF may show eosinophilic pleocytosis and hypoglucorrachia. CSF (1,3)-β-D-glucan testing may also be useful in diagnosis of coccidioidal meningitis, and this test has a 96% sensitivity and 82% specificity [106]. Neuroimaging techniques are helpful to rule out hydrocephalus or ischemic complications. Post-contrast MRI sequences may reveal leptomeningeal enhancement around the basilar cisterns, and in some cases spinal nerve root enhancement [103].

Treatment

Induction treatment of choice can be either fluconazole (400–600 mg/day) or liposomal amphotericin B (3–5 mg/kg/day IV for 6–10 weeks; total dose, 100–150 mg/kg). Consolidation treatment requires the use of oral fluconazole (400–900 mg/day) for 1 year, and should be followed up by lifelong suppressive therapy (fluconazole 200–400 mg/day) to prevent recurrences. Recurrence of coccidioidal meningitis after discontinuation of fluconazole has been reported [108]. Hydrocephalus requires the placement of ventriculoperitoneal shunt. Despite of this therapy, mortality still remains high, and in the azole era has been estimated in 40%.

Paracoccidioidomycosis

Paracoccidioidomycosis is an endemic mycosis in South America caused by *Paracoccidioides brasiliensis* and is characterized by a chronic course with involvement of multiple organs mainly in immunocompromised patients.

In a retrospective study of 1219 paracoccidioidomycosis cases, the most commonly affected sites were the lungs (64%) and oral mucosa (50%). Generalized lymphadenopathy and skin lesions were observed in almost one-third of cases. Involvement of the larynx (16%), gut (7.5%), spleen (4.7%), CNS (3.4%), bones and joints (2.2%), and adrenal (2.1%) was also described [109]. Pulmonary and adrenal insufficiencies are common sequelae.

CNS paracoccidioidomycosis is potentially fatal and can occur in 12% of cases [110]. CNS paracoccidioidomycosis has also been described in AIDS patients [111]. Concomitant pulmonary and CNS paracoccidioidomycosis with cerebellar abscess [112] and also rare cases of encephalomyelopathy have been reported [113].

The CSF may reveal positive *P. brasiliensis* smear and culture. The brain MRI may show enhancing supra or infratentorial nodular lesions and meningeal enhancement [111, 114]. Itraconazole and amphotericin B have been advocated as treatments of choice [115].

Blastomycosis

Blastomycosis is a mycosis caused by *Blastomyces dermatitidis*, a dimorphic fungus endemic in Africa, Canada, and midwestern and southeastern USA, mainly in the Mississippi and Ohio River basins.

Blastomycosis may happen in both immunocompetent and immunosuppressed (AIDS, diabetes, transplant recipient) populations. Healthy humans become infected through the inhalation of airborne conidia. Pulmonary symptoms are common; however, dissemination to the skin, genitourinary system, bone [116], and CNS may occur.

CNS blastomycosis is a potentially fatal complication and usually present as subacute or chronic meningitis. Brain abscess, osteomyelitis, and mass lesions may also occur. Headache and focal neurologic deficits are the most common presenting symptoms [117]. Large cerebellar mass lesions [118] and enhancing cerebellopontine mass have been reported as rare intracranial manifestation of blastomycosis [119].

Diagnostic tests include CSF analysis and biopsy for tissue culture and pathology [117]. Enzyme immunoassay may detect *Blastomyces dermatitidis* antigen in the CSF [119]. There is a high cross-reactivity with *Histoplasma* antigen enzyme immunoassay. Brain biopsy may be needed in those cases of mass lesions.

Treatment is based on amphotericin B lipid formulation (5 mg/kg/day for 4–6 weeks) and extended course of azole therapy such as voriconazole (200–400 mg twice a day), itracozanole (400–600 mg/day), or fluconazole (800 mg/day). In occasions, surgical drainage of brain mass lesions or abscess may be necessary.

Rare and Emerging Fungi Affecting the CNS

Dematiaceous Molds

Dematiaceous molds are usually identified by the presence of melanin-like pigment within the cell wall. These fungi are well-known pathogen organisms to livestock or

plants, causing chromoblastomycosis and black-grain mycetoma. These black molds cause invasive infections and may affect the CNS in both immunocompetent and immunosuppressed subjects. The term phaeohyphomycosis has been used to describe the infection caused by these dark pigmented fungi. CNS phaeohyphomycosis agents include *Cladophialophora bantiana*, *Exserohilum rostratum*, *Rhinocladiella mackenziei*, and *Ochroconis gallopava* [120, 121]. Prognosis of CNS phaeohyphomycosis is poor, with mortality rates of 50–70%, despite combination therapy of surgery and antifungal treatment [122].

The largest phaeohyphomycosis outbreak was caused by *Exserohilum rostratum* in the USA in 2012. This outbreak was associated with the contamination of three lots of preservative-free methylprednisolone for musculoskeletal injection and resulted in 750 infections by *E. rostratum*. There were 151 cases with meningitis and paraspinal infections, 325 cases with paraspinal infections without meningitis, and 64 deaths following spinal methylprednisolone lumbar injections [120]. Spinal infections presented as epidural abscess, vertebral osteomyelitis, diskitis, arachnoiditis, and cauda equina syndrome. Around 5% of patients presented with posterior circulation stroke, affecting the vertebrobasilar system, and most of deaths (85%) were associated with the occurrence of stroke [120, 123]. Voriconazole, liposomal amphotericin B or both can be used as initial treatment.

C. bantiana has a marked neurotropism for the CNS, causing almost exclusively brain abscesses. Approximately 120 cases of cerebral *C. bantiana* have been reported in the literature [124], and 60% occurred in healthy subjects in the absence of pulmonary lesions. Cerebral cases have been described in hypogammaglobulinemia [125] and prediabetes [126]. Slowly expanding brain abscess (97.5%), coinfection of brain parenchyma and meninges (14%), and meningitis alone (2.5%) were the most common clinical manifestations. Melanised fungal cells can be seen in a brain biopsy and abscess materials [127]. Mortality rate has been estimated in 65%.

Ochroconis gallopava is a neurotropic dematiaceous mold responsible for life-threatening pulmonary and CNS infections in domestic poultry and in immunologically compromised humans [128]. *O. gallopava* is an emerging cause of mycosis in solid organ transplant recipients, and disseminated forms affecting the brain have been reported [129].

Other Molds

Scedosporium apiospermum (*Pseudallescheria boydii* is the sexual or perfect stage) is a soil fungus that cause severe cerebral infections in the form of brain abscess in trauma and near- drowning patients with aspiration of polluted water and also in immunosuppressed hosts such as lung transplant recipients. Incubation period is around 1–3 weeks in near drowning, whereas in transplant hosts may be up to 1 year [7]. Disseminated infection in near-drowning patients has also been reported [130].

The fungi may invade the CNS through the cribriform plate or from pneumonic foci [8]. Clinical picture resembles aspergillosis of the CNS, and the hyphal appearance may resemble septated *Aspergillus*. Multiple brain abscesses may also occur

[131]. Case reports of colitis, gastrointestinal manifestations, and CNS infection have also been described [132, 133]. Voriconazole has been advocated as initial therapy.

In Japan, a case of *Scedosporium aurantiacum* brain abscess after near drowning in a survivor of a tsunami has been published [134]. *Scedosporium prolificans* is a frequently fatal pathogen in immunocompromised subjects. Cases of CNS involvement by *Scedosporium prolificans* have been reported [135]. This fungus infects the CNS through hematogenous dissemination or through traumatic inoculation (Fig. 7.4).

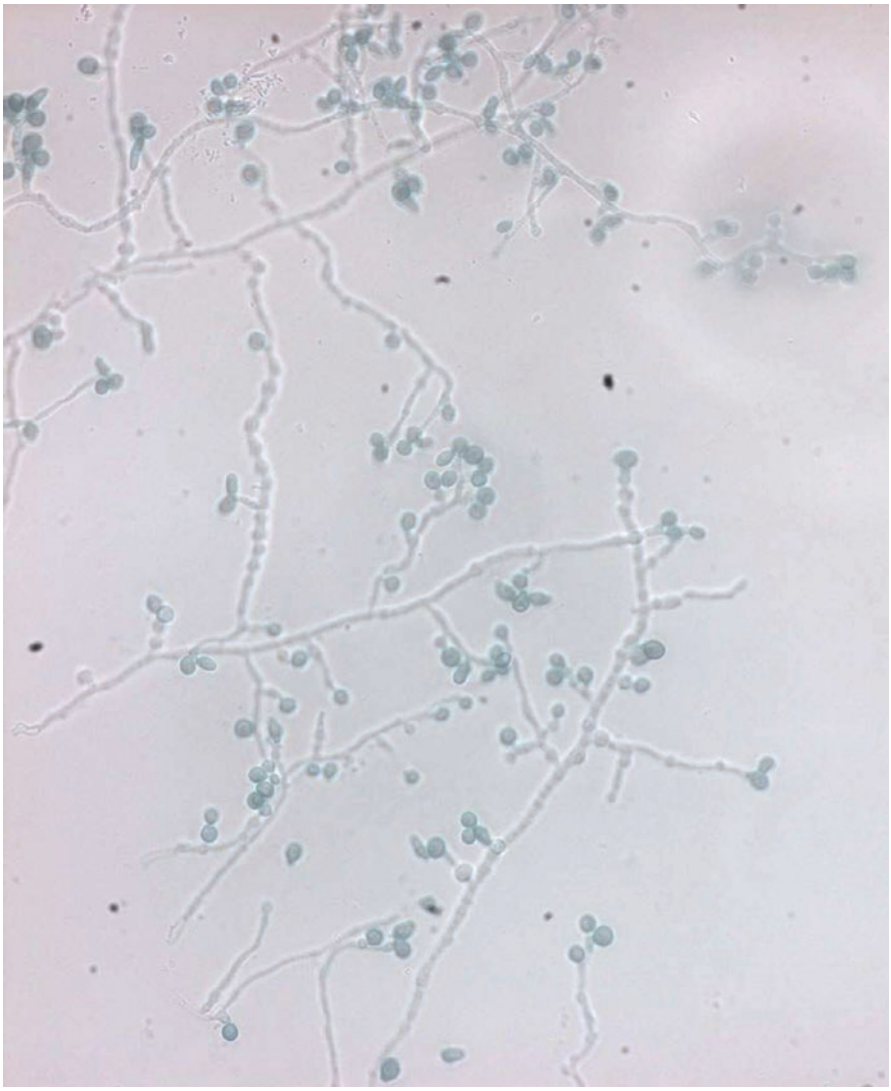

Fig. 7.4 *Scedosporium prolificans* stained with lactophenol cotton blue, ×100

Fusarium spp. is also a ubiquitous fungus that can cause fatal infection in immunosuppressed patients with persistent neutropenia. Sinuses and respiratory tract, catheters, and periungual lesions (paronychia) are common portals of entry. Disseminated fusariosis frequently causes fungemia and skin lesions. Fever, erythematous nodular cutaneous lesions, sinus and pulmonary infections, and septic arthritis are common manifestations. *Fusarium solani* brain abscess has been reported in acute lymphocytic leukemia and autologous peripheral stem cell transplant patients [136]. *Fusarium* is highly angioinvasive and can cause hemorrhagic infarctions. Other complications are bilateral endophthalmitis and chorioretinitis [8].

Other Rare Fungi

Case reports about other rare fungi that may affect the CNS have been published. Invasive infections have also described in *Saprochaete* and *Geotrichum* species [137]. *Phellinus* spp. is an emerging cause of refractory fungal infection in patients with X-linked chronic granulomatous disease [138]. *Bipolaris* spp. is dematiaceous fungus that usually affects the skin and nasal sinuses and rarely the CNS. Disseminated phaeohyphomycosis with brain abscess and biliary tree invasion due to *Bipolaris* spp. in an immunocompetent patient has been recently published [139].

Sporothrix schenckii and *Sporothrix brasiliensis* can also affect the CNS [140]. Sporotrichosis usually manifest as a lymphocutaneous form. Cases of disseminated infection have been reported in AIDS patients, and mortality has been linked with CNS involvement [141].

Conclusions

An increased incidence of CNS fungal infections is expected as the number of patients at risk due to AIDS and other immunosuppression states have risen. Early diagnosis and identification of fungal meningitis and specific pathogens are very important, and prognosis depends on opportune administration of antifungal treatment. The many different types of clinical presentations (ranging from acute and chronic meningitis to brain abscess and vasculitis), the diversity of microorganisms, and the resistance to treatment are additional challenges that need to be tackled.

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CNS Tuberculosis and Other Mycobacterial Infections

8

Juan Carlos García-Moncó and Aida Rodriguez-Sainz

Abstract

Tuberculous meningitis is the most severe form of tuberculous infection (*Mycobacterium tuberculosis*) and presents as a subacute syndrome with lymphocytic pleocytosis and low glucose in the cerebrospinal fluid (CSF) and meningeal enhancement of the basal cisterns and hydrocephalus on neuroimaging.

Diagnosis is challenging, since CSF cultures take long and are positive in less than two-thirds of patients. Empirical therapy is thus often employed. Mortality rate of this infection remains at approximately 25% of the patients.

Parenchymal involvement (tuberculomas and spinal cord damage) may also appear.

Nontuberculous mycobacteria affect AIDS patients. *M. avium* complex is most frequently implicated. CNS infection is rare and occurs with disseminated disease. Diagnosis is made by culture of involved tissues, and therapy requires a prolonged, multidrug regimen.

Keywords

Tuberculosis • *Mycobacterium tuberculosis* • Tuberculoma • Tuberculous abscess Tuberculous meningitis

Tuberculosis (TB) remains a major public health problem with approximately 9.2 million new cases and 1.7 million deaths throughout the world in 1 year (data from 2006). Thirty percent of the global population is infected with *M. tuberculosis*, 15 million people around the globe are coinfected with HIV and *M. tuberculosis*, and

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50 million are infected with multidrug-resistant tuberculosis [1]. Every untreated individual with active TB will infect 10–15 persons every year.

The HIV epidemic together with rising immigration, homelessness, and urban crowding and the increase in drug-resistant *M. tuberculosis* strains have contributed significantly to this burden. Tuberculosis is currently the leading infectious cause of death and undoubtedly represents a global public health priority.

Central nervous system (CNS) involvement occurs in 5–10% of extrapulmonary tuberculosis cases [2].

M. tuberculosis: The Etiologic Agent

Human tuberculosis is caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex, which consists of *M. tuberculosis*, *M. bovis*, and *M. africanum*.

M. tuberculosis is the main agent in humans, and the term *tuberculosis* should be reserved exclusively for infection caused by this organism. The other two species belonging to the *Mycobacterium tuberculosis* complex, *M. bovis* and *M. africanum*, are implicated in very few human cases.

M. tuberculosis is an obligate aerobic, slowly growing, acid-fast bacillus with a cell wall abundant in lipids and glycolipids that conform an external hydrophobic layer that interferes with antibiotic penetration, thus explaining its difficult and lengthy therapy.

Pathogenesis of CNS Tuberculosis

Human tuberculosis is acquired by inhalation of aerosolized droplet nuclei containing a few bacilli (1–10 are needed) that reach the alveoli where they multiply and interact with macrophages, resulting in cytokine and chemokine release with activation of T-helper immunity and granuloma formation.

Within 2–4 weeks, a silent hematogenous spread to extrapulmonary sites occurs, including the brain, where tubercles of mononuclear cells surrounding a caseous center are formed. Neuroimaging at this stage may reveal the presence of CNS granulomas in neurologically asymptomatic patients with miliary tuberculosis [3].

These tubercles, also known as Rich focus, remain latent for months or years until they reactivate for unclear reasons. Tubercles rupturing into the subarachnoid space cause meningitis. Those tubercles deeper in the brain or spinal cord parenchyma may expand resulting in tuberculomas or, more rarely, tuberculous abscesses.

Neurological Manifestations

Tuberculous meningitis (TBM) is the most frequent and severe manifestation of CNS involvement in tuberculosis [4]. Tuberculoma and abscess formation as well as spinal cord involvement can also occur.

Tuberculous Meningitis

The clinical characteristics of patients with TBM in adults and children have been pooled on Tables 8.1 and 8.2.

There is a consistent prodromal period of 2–4 weeks before presentation of non-specific symptoms, including fatigue, malaise, myalgia, and fever. Chest X-ray abnormalities, a history of close contact with tuberculosis patients, and tuberculin test positivity are present more frequently in children, reflecting the shorter period between contagion and development of meningitis. Hyponatremia is present in half of the patients, often due to inappropriate secretion of antidiuretic hormone (SIADH).

The most prominent clinical features of tuberculous meningitis in adults are fever, headache, vomiting, mental status abnormalities, and meningismus. Cranial

Table 8.1 Tuberculous meningitis: associated features

	Adults	Children
Mean duration of illness prior to admission (range)	2 weeks (1 day–9 months)	2 weeks (3 days–3 months)
Mean frequency of close contact with tuberculosis (range)	28% (2–50%)	56% (45–70%)
Prior history of tuberculosis	23% (5–45)	NA
Abnormal chest X-ray (range)	45% (25–55%)	61% (35–75%)
Positive tuberculin skin test (range)	51% (40–70%)	72% (50–95%)
Patients with hyponatremia (plasma sodium level <135 mEq/dL) (range)	46% (25–75%)	44% (25–65%)
Mortality	27% (7–45%)	19% (3–40%)

Modified from Garcia-Monco [4]
NA not available or incomplete data

Table 8.2 Signs and symptoms in patients with tuberculous meningitis

	Adults		Children	
	Mean (%)	Range (%)	Mean (%)	Range (%)
Fever	72	55–85	76	45–95
Headache	67	45–85	34	20–40
Meningismus	67	55–90	62	25–75
Abnormal mental status	59	30–80	42	25–75
Hydrocephalus (CT scan)	52	40–65	85	75–100
Vomiting	43	30–70	58	30–70
Malaise-anorexia	41	45–65	52	30–70
Cranial nerve palsies	24	20–40	29	10–45
Papilledema	15	5–30	9	9
Hemiparesis/hemiplegia	12	5–20	24	5–40
Seizures	11	7–10	25	10–55

Modified from Garcia-Monco [4]

nerve palsies occur in one-fourth of patients, involving mainly the sixth and, less frequently, the third, fourth, seventh, and eighth cranial nerves. Hemiparesis, papilledema, and seizures occur in 10–15% of the patients. Funduscopic evidence of choroidal tubercles is pathognomonic but is present in <10% of patients, most frequently in association with miliary tuberculosis [5].

Children presentation is similar except for a lower percentage of headache complaints and a higher frequency of hydrocephalus.

The severity of TBM is assessed by the British Medical Research Council into three stages [6]: from conscious patients with no neurological signs (stage 1) to confused patients with focal findings (stage 2) to patients in coma or with hemiplegia or paraplegia (stage 3).

CSF Findings

The CSF shows a lymphocytic pleocytosis with an average of 200 cell/μL, increased protein contents (around 200 mg/dL), and low glucose levels (Table 8.3). In 20–25% of non-HIV-infected patients, neutrophilic predominance is present; it shifts to lymphocytic predominance over the next 24–48 h [7]. Occasionally neutrophils persist, resulting in the so-called persistent neutrophilic meningitis, a syndrome of varied etiology in which tuberculosis has to be carefully excluded [8]. This syndrome seems more frequent in HIV-infected patients, particularly when meningitis is caused by multidrug-resistant mycobacteria [9].

On the other hand, an initial mononuclear pleocytosis may briefly change in the direction of polynuclear predominance when therapy is initiated, and this may be associated with clinical deterioration. This "therapeutic paradox" has been regarded by some authors as virtually pathognomonic of tuberculous meningitis [10] and manifests a few days after the start of antituberculous therapy by rapid deterioration. It likely represents an uncommon hypersensitivity reaction to the massive release of tuberculoproteins into the subarachnoid space.

Table 8.3 CSF profile in patients with tuberculous meningitis

	Adults	Children
Mean cell count (range)	223 cells/μL (0–4000)	200 cells/μL (5–950)
Mean percentage of patients with neutrophilic pleocytosis (>50% neutrophils) (range)	27% (15–55)	21% (15–30)
Percentage of CSFs with normal cell count	6% (5–15)	3% (1–5)
Mean protein level in mg/dL (range)	224 mg/dL (20–1000)	219 mg/dL (50–1300)
Percentage of CSFs with normal protein content	6% (0–15)	16% (10–30)
Percentage of patients with depressed glucose levels (<45 mg/dL or 40% of serum glucose)	72% (50–85)	77% (65–85)
Positive smear	25% (5–85)	3% (0–6)
Positive culture	61% (40–85)	58% (35–85)

Modified from Garcia-Monco [4]

Normal protein contents are seen in 5–15% of patients and normal glucose levels in less than one-third, and cells are absent in up to 16% of HIV patients as compared to 3–6% in non-HIV-infected patients. Acellular CSF samples may show pleocytosis if a spinal tap is repeated 24–48 h later [11].

Over time, CSF sugar levels seem to normalize first, followed by the cell count and the protein contents [7, 12]. In a series, the most rapid return to normal of CSF glucose was 19 days and the slowest 11 weeks [7].

Diagnosis

The diagnosis of TBM remains an important challenge, since clinical presentation is nonspecific and microbiological confirmation is often difficult and late. From a clinical standpoint, the best predictors of TBM are as follows: (a) duration of symptoms >6 days; (b) CSF total cell count <1000/μL with lymphocytic predominance; and (c) peripheral blood white cell count <15,000 × 10^3/mL [13, 14].

Acid-fast stains (Ziehl-Neelsen, Kinyoun, and auramine-rhodamine): These methods are fast to detect acid-fast bacilli with a conventional smear microscopy but have a low sensitivity (up to 20%). The reasons are that acid-fast dyes cannot stain *M. tuberculosis* once it enters into the cell and that high volumes (5–10 mL) of CSF are needed, since approximately 10^4 organisms are required for their reliable detection [15]. The sensitivity of Ziehl-Neelsen stain increases with large CSF volumes, but sensitivity rarely exceeds 60% [16].

Recently, a highly efficient Ziehl-Neelsen stain has been developed. It requires low CSF volumes (0.5 mL) that are first cytospinned to compactly collect the bacilli and cells in the CSF with permeabilization of the cells by a detergent, Triton X100, allowing the staining of the intracellular bacilli. This modified stain managed a 93.8% of intracellular detection rate and a 100% extracellular detection rate, results that need to be replicated [15].

Interferon-gamma release assays (*IGRAs*): This technique measures the interferon-gamma release in response to stimulation with specific *M. tuberculosis* antigens. In whole blood, it is useful for the diagnosis of active pulmonary tuberculosis or to distinguish between active and latent tuberculosis [17]. IGRA determination in the CSF requires high CSF volume samples, the results are commonly indeterminate, and its sensitivity (58–84%) and specificity (73–94%) vary among studies depending on the cutoff of the number of spots (interferon-gamma producing lymphocytes) [16]. A recent meta-analysis concludes that this technique has a moderate value, due to a sensitivity of 77% and specificity of 88%, i.e., a sensitivity similar to adenosine deaminase or nucleic acid amplification, but with lower specificity. Furthermore, it is more complex technically [18].

CSF culture: When productive, it takes 4–8 weeks for unequivocal identification. Their sensitivity in TBM ranges from 25 to 85% with an average of 50%. Newer culture media, either radiometric—such as BACTEC—or nonradiometric systems, may give positive results in 7–10 days [19]. The WHO has endorsed the

microscopic observation drug susceptibility (MODS) assay, a liquid culture with a sensitivity of 65% and specificity of 100% and a median detection time of 6 days. It can be used for diagnosis and for drug resistance [20].

Adenosine deaminase (*ADA*) *determination in CSF*: Increased ADA values are useful for the diagnosis of tuberculous meningitis [20–23], although false positives and negatives do occur in other infectious and neoplastic CNS disorders [23–25]. ADA values may increase during the first 1–2 weeks of therapy and then progressively decrease [26]. A recent systematic search on the value of ADA in the CSF of TBM patients found that values >8 U/l provided a sensitivity <59% and specificity >96% in TBM diagnosis [27].

Nucleic acid amplification test: The paucity of organisms in TBM and the availability of a completely sequenced genome of *M. tuberculosis* [28] made the polymerase chain reaction (PCR) an important diagnostic tool, but its sensitivity seems too low (56%, 95% CI 46–66) and perhaps not better than bacteriology [29]. Furthermore, performance of PCR assays is heterogeneous, which makes difficult the comparisons between different studies. PCR assays remain positive up to 1 month after antituberculous therapy [20]. The detection of mycobacterial proteins (GlcB, HspX, MPT51) in CSF by ELISA and qPCR in children with tuberculous meningitis has shown a 98–100% sensitivity and 96–98% specificity [30] and gives new perspectives in fast methods for TBM diagnosis. Metabolomic or gene-expression profiles in preliminary studies suggest a future role but are not in routine use at present [16].

Neuroimaging

The predilection of TBM for the basal cisterns is revealed on neuroimaging by intense meningeal enhancement (Fig. 8.1), corresponding to the thick exudate that is observed pathologically [31]. The interpeduncular fossa, the ambiens cistern, and the chiasmatic region are the sites of predilection. Meningeal enhancement is more common in HIV-infected patients. In one study, meningeal enhancement was present in 23% of HIV-positive patients but only in 6% of HIV-negative individuals [32]. Hydrocephalus is observed on CT scan and MRI, usually of the communicating type, although obstructive hydrocephalus may result from a focal parenchymal lesion and the associated mass effect. As mentioned before, hydrocephalus is more common in children.

Complications

Ischemic brain infarctions occur in about 25–40% of patients during the course of tuberculous meningitis [33], as a consequence of the inflammatory arterial occlusion. When there is basal ganglia involvement, abnormal movements result, including unilateral choreoathetoid movements, myoclonus, and dystonia [34, 35]. Hyponatremia or true SIADH frequently develops in TBM.

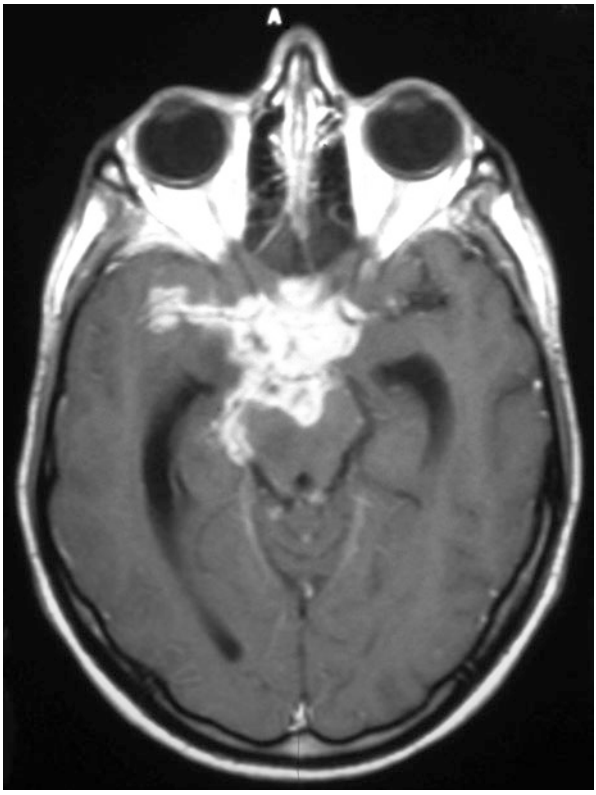

Fig. 8.1 Magnetic resonance imaging (T1-weighted sequence after gadolinium administration) of a patient with tuberculous meningitis showing a prominent exudate involving the basal meninges and extending toward the middle cerebral artery

Syringomyelia can occur several years after the initial infection, although a few acute cases have been reported [36]. Inflammatory edema and spinal cord ischemia appear to be the mechanisms implicated in early cases, whereas chronic arachnoiditis underlies late cases.

Management

Guidelines for therapy of tuberculosis have been established by the American Thoracic Society, the Centers for Disease Control and Prevention [37], the Infectious Disease Society of America [38], and the British Infection Society [39].

Unlike its pulmonary counterpart, from where it has often been extrapolated, the optimal therapy for TBM is not the result of controlled studies and therefore is not so well established. Many patients will be empirically treated due to the diagnostic difficulties of TBM. Not infrequently, the response to therapy constitutes a key to the diagnosis. Identification and early empiric treatment of patients at risk are critical to their outcome. TBM should be suspected in patients with subacute meningitis and moderate (<1000 cells/μL) lymphocytic pleocytosis in the CSF.

An initial four-drug course of 2 months is generally accepted, particularly in areas of multiple-drug resistance, with isoniazid, rifampin, pyrazinamide, and ethambutol (particularly appropriate in patients over 50 years of age or with renal disease), followed by 10 additional months with two drugs (isoniazid and rifampin) to a total duration of 12 months. Drug dosages and specific comments are described on Table 8.4. Isoniazid and rifampin as well as several second-line agents (aminoglycosides, capreomycin, and fluoroquinolones) are available in parenteral form if an altered mental status precludes oral intake. Isoniazid, the cornerstone of TBM therapy, and pyrazinamide readily cross the blood-brain barrier, while rifampin and ethambutol have significantly less penetration into the CNS. Isoniazid and rifampin are bactericidal against intra- and extracellular organisms and pyrazinamide against intracellular organisms at high concentrations, whereas all the other first- and second-line drugs are bacteriostatic (streptomycin is bactericidal in vitro, but it is bacteriostatic in vivo, acting only against intracellular bacteria).

In areas where the incidence of drug resistance to *M. tuberculosis* is lower than 4% (it is higher in Africa, Asia, and parts of South America), an initial regimen with three drugs (isoniazid, rifampin, and pyrazinamide, all daily) for 2 months and two drugs (isoniazid and rifampin, daily or twice a week) for 7–10 additional months is acceptable [40].

Liver enzymes should be monitored throughout the therapy; in the event of significant elevations of alanine aminotransferase (>5 times normal), isoniazid and rifampin are usually stopped, and ethambutol and streptomycin started and continued until enzymes return to normal, at which time isoniazid may be resumed with biweekly determinations. In most cases a combination of isoniazid, ethambutol, pyrazinamide, and streptomycin will be well tolerated. During pregnancy, streptomycin (can cause congenital deafness) and pyrazinamide (insufficient experience) should be avoided, and the preferred regimen is isoniazid, ethambutol, and rifampin.

Shorter regimens may suffice, although there have been few controlled trials of treatment in patients with extrapulmonary disease. Two studies reported that the 6-month therapeutic regimen resulted in a morbidity/mortality ratio similar to that found in the longer-course therapies [41]. Chemotherapy with isoniazid and rifampin for 9 months has also proven successful in 95% of patients, equivalent to conventional therapy with two to three drugs for 18–24 months [42]. The authors claimed that their twice-weekly regimen has the additional advantages of reduced cost, fewer doses, and ease of supervision when needed. A prospective study concluded that young children with TBM can be safely treated for 6 months with high doses of antituberculous agents (isoniazid, rifampin, ethionamide, and pyrazinamide) without overt hepatotoxicity and with a low risk of relapse [43].

Intensification of treatment in an attempt to reduce mortality has been recently evaluated. High dose of intravenous rifampicin (600 mg or 13 mg/kg) for the first 14 days resulted in significant mortality reduction (65% vs. 35%) [44]. A trial will be ended in the next few years comparing the use of high dose of intravenous rifampicin and oral levofloxacin as the fourth drug compared to conventional treatment [45].

Table 8.4 Drug therapy for tuberculous meningitis

Drug	Penetration into the CSF with normal meninges[a]	Penetration into the CSF with inflamed meninges	Daily dose (route)	Special remarks	Duration (months)
First-line drugs					
Isoniazid	+ (20% of plasma levels)	+++ (90% of plasma levels)	A: 300 mg/day (PO, IM) Ch: 10 mg/kg	Monitor for liver toxicity Add pyridoxine to avoid peripheral neuropathy	9–12
Rifampin	No	+ (up to 10% of plasma levels)	A: 600 mg/day (PO, IV) Ch: 10–20 mg/kg	Monitor for liver toxicity Interacts with protease inhibitors for HIV infection	9–12
Ethambutol	No	++ (10–50% of plasma levels)	15–25 mg/kg/day (PO)	Monitor for optic neuritis	2
Pyrazinamide	+++ (similar to plasma levels)	+++ (similar to plasma levels)	A: 20–35 mg/kg (PO) Ch: 20–30 mg/kg	Monitor for liver toxicity	2
Second-line drugs					
Streptomycin	No	++ (25% of plasma levels)	A: 15 mg/kg (IM) Ch: 20–30 mg/kg Maximum daily dose 1 g	Monitor for vestibular and auditory toxicity	2
Cycloserine	+++ (similar to plasma levels)	+++ (similar to plasma levels)	A: 10–15 mg/kg (1 g/day, PO) Ch: Same dosage	Neurologic side effects; avoid in epileptic patients	18–24
Ethionamide	+++ (similar to plasma levels)	+++ (similar to plasma levels)	A: 15–20 mg/kg (1 g/day, PO) Ch: Same dosage	Gastrointestinal adverse effects	18–24
Capreomycin Kanamycin	NO	++	A: 15 mg/kg (10 mg/kg if older than 50, IM or IV) Ch: 15–30 mg/kg (1 g/day, IM or IV)	Auditory (high-frequency hearing loss), vestibular, and renal dysfunction	6
p-Aminosalicylic acid (PAS)	NO	+	A: 8–12 g/day in 2–3 doses (PO) Ch: 200–300 mg/kg/day in 2–4 doses	Gastrointestinal adverse effects	18–24

(continued)

Table 8.4 (continued)

Drug	Penetration into the CSF with normal meninges[a]	Penetration into the CSF with inflamed meninges	Daily dose (route)	Special remarks	Duration (months)
Levofloxacin	+	+	A: 500–1000 mg/day Ch: Unknown	Gastrointestinal and neurologic side effects	18–24
Moxifloxacin Gatifloxacin	+	+	A: 400 mg Ch: Unknown	Gastrointestinal and neurologic side effects	18–24

A adult, *Ch* children, *PO* oral route, *IM* intramuscular, *IV* intravenous
[a]Penetration arbitrarily graded as low (+), intermediate (++), or high (+++)

Surgery in TBM patients is considered in patients with hydrocephalus in whom an external drainage is required. The most effective management of communicating hydrocephalus in these patients is unclear but requires neurosurgical consultation to alleviate hydrocephalus not responsive to medical therapy and intracranial pressure monitoring.

Corticosteroid therapy was suggested to improve neurologic outcomes of TBM of moderate severity [46]. Another study showed that corticosteroids significantly improved the survival rate and intellectual outcome of children with TBM, although they did not affect the intracranial pressure or the incidence of basal ganglia infarction [47]. A recent controlled trial in Vietnamese adults with TBM has shown that steroid therapy was strongly associated with a reduced risk of death (relative risk 0.69; 95% CI, 0.52–0.92), although it did not prevent disability in survivors [48]. Steroids were beneficial regardless of the severity grades of disease, but did not affect those patients with HIV coinfection; this aspect requires further study.

Therefore, dexamethasone use is warranted in TBM patients not infected with HIV, regardless of age and disease severity. The regimen employed in the most recent trial was 0.4 mg/kg of intravenous dexamethasone for the first week, tapering 0.1 mg/kg per week over the 3 ensuing weeks until a dose of 0.1 mg/kg was reached and then 4 mg daily PO, thereafter reducing 1 mg/kg per week to drug stop [48].

Drug Resistance in TBM

Although drug resistance does not seem to represent a serious threat for TBM at present since only occasional single cases of multidrug-resistant (MDR) meningitis (as defined by resistance to both isoniazid and rifampin) have been reported [49–51], this aspect requires utmost vigilance because it is associated with a decreased probability of cure. MDR meningitis should be considered in patients with prior antituberculous treatment, contact with a patient with MDR tuberculosis, or with a poor clinical response to first-line drugs within 2 weeks of therapy.

Therapy in MDR cases includes a combination of first- and second-line drugs (Table 8.4) and should be individualized and based on susceptibility studies. Second-line drugs include capreomycin, ethionamide, para-aminosalicylic acid (PAS), cycloserine, streptomycin (SM), some fluoroquinolones (levofloxacin and moxifloxacin mainly), and aminoglycosides (kanamycin and amikacin). Among these agents, ethionamide and cycloserine have a good CNS penetration and may be the only agents for extensively resistant TBM (XDR, resistance to isoniazid, rifampin, fluoroquinolones, and either capreomycin, kanamycin, or amikacin), although they are not commonly used in pulmonary tuberculosis because of their high side-effect profile. Amikacin, kanamycin, and capreomycin are injectable agents with moderate antituberculosis activity. Moxifloxacin and levofloxacin are the preferred fluoroquinolones and are commonly used as second-line agents. Intrathecal therapy with amikacin and levofloxacin was successful in an HIV patient with multidrug-resistant TBM [52]. Drug monitoring, if feasible, is useful in the management of these patients.

Regimens should consist of at least four drugs with proven effectiveness and are based on the history of drugs taken by the patient. Occasionally, five to six drugs are needed simultaneously. The minimum length of treatment is usually 18 months. The WHO has published guidelines with recommendations on the management of these patients [53].

Prognosis

The level of consciousness at hospital admission and the timing of therapy initiation are two important prognostic markers in TBM. Patients initially classified as having stage 3 at admission and those in whom therapy is delayed show a poor prognosis [54]. Also, patients under the age of 3 or over 65, as well as those with associated miliary tuberculosis, may have a poorer outcome.

Verdon et al. carried out a study on adults admitted to the intensive care unit with tuberculous meningitis and found three variables that correlated with outcome: time to onset of treatment ≥3 days, coma, and a simplified acute physiology score of >11 [7]. Another study observed important neurological sequelae 1 year after disease onset in 78.5% of patients that included cognitive impairment in 55%, motor deficit in 40%, optic atrophy in 37%, and other cranial nerve palsy in 23%. Focal motor deficit at admission was the most important predictor of neurologic deficits at 1 year, whereas GCS score predicted the cognitive and motor sequelae [55].

Parenchymal CNS Disease: Tuberculomas and Tuberculous Abscesses

Tuberculous granulomas (*tuberculomas*) are composed of a central zone of caseation necrosis with few bacilli surrounded by a capsule of collagenous tissue and mononuclear inflammatory cells [56]. They are most commonly supratentorial in

adults (infratentorial in children) and are multiple in one-third of patients [57]. The clinical course is subacute or chronic, and the commonest presentation includes headache, intracranial hypertension, seizures, and papilledema [58]. The tuberculin skin test is positive in 85% of patients, and chest X-rays show tuberculous changes in 30–80% of patients. CSF findings are unremarkable, and microbiology is usually negative [59]. A retrospective review of 23 tuberculoma patients from high-risk countries found a laboratory-proven meningitis in 43.5% [58].

The diagnosis is made on the basis of neuroimaging findings, skin test, and response to empirical therapy. On CT scan, tuberculomas appear as solid-enhancing, ring-enhancing, or mixed lesions; on occasions, there is a central calcification surrounded by a hypodense area with peripheral ring enhancement (target sign) [60, 61], a pattern highly suggestive of tuberculosis, although occasionally present in metastatic adenocarcinoma [61]. Lesions are most often located at the corticomedullary junction and periventricular regions, consistent with hematogenous spread.

Magnetic resonance imaging (MRI) shows tuberculomas as isointense to gray matter on T1-weighted images, sometimes with a hyperintense rim [60] (Fig. 8.2). Noncaseating lesions are bright on T2-weighted images with nodular enhancement. Caseating tuberculomas vary from isointense to hypointense on T2-weighted images and also exhibit rim enhancement [62]. There is a variable degree of

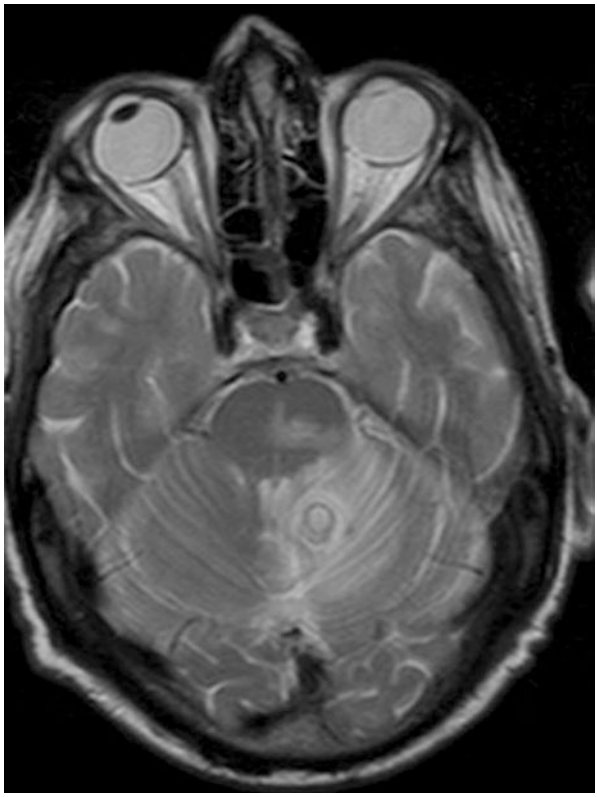

Fig. 8.2 Magnetic resonance imaging (T2-weighted sequence) showing a ring-shaped cerebellar tuberculoma surrounded by edema. Another smaller tuberculoma was present in the pons (observe the presence of pons edema). Both disappeared with a four-drug antituberculous therapy for 1 year

perilesional edema and mass effect. Normal diffusion-weighted MRI with normal apparent diffusion coefficient (ADC) values has been described in tuberculomas [63]. The differential diagnosis includes neoplasms and other granulomatous processes like sarcoidosis and parasitic diseases such as cysticercosis and toxoplasmosis. Magnetization transfer imaging analysis has proved helpful in differentiating tuberculomas and pyogenic abscess from brain tumors [64]. With therapy, tuberculomas usually decrease in size to complete resolution within 3 months although it may take longer (even years), sometimes leaving a residual calcification [65, 66]. Medical therapy alone is indicated initially, and surgery is required in the presence of intolerably increased intracranial pressure or of medical failures. Mortality with current chemotherapeutic regimens is <10%, while prior to the availability of antituberculous drugs, mortality after decompression and excision was 35–85% [67]. Some patients, however, develop intracranial tuberculomas or present a paradoxical enlargement of preexisting ones, during the first weeks or months of treatment for TBM [68]. Paradoxical deterioration in HIV-negative patients is frequently accompanied by an increase in peripheral blood lymphocyte count and an exaggerated tuberculin skin reaction [69]. Steroids seem to improve the general outcome, and dexamethasone is recommended for 4–8 weeks [70]. The review of the literature shows that surgery has been employed in approximately 60% of these patients [69].

When the caseous core of a tuberculoma liquefies, a *tuberculous abscess* will result. They are larger and much less frequent than tuberculomas, may be multiloculated, and often have greater mass effect and edema. In contrast to the solid caseation and few organisms seen in tuberculomas, the abscess is formed by pus, where many bacilli can be found [71]. Its wall is devoid of the granulomatous reaction that surrounds the tuberculoma, with its appearance resembling that of a typical pyogenic abscess (Fig. 8.3). They have a more accelerated clinical course

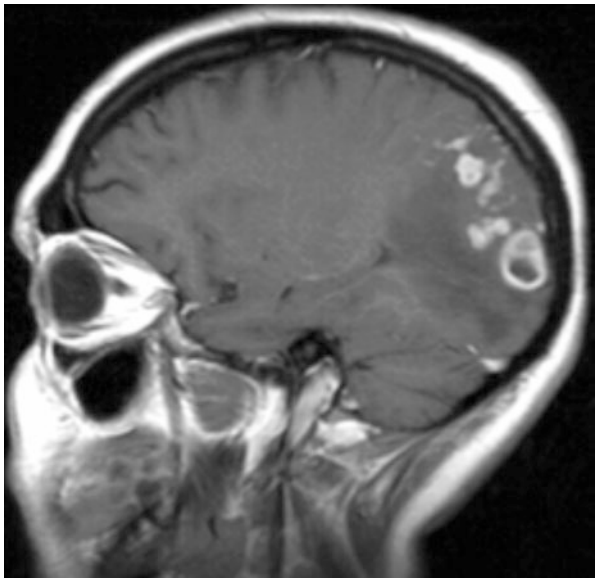

Fig. 8.3 Magnetic resonance imaging (T1-weighted sequences after gadolinium administration) showing an occipital tuberculous abscess in an HIV patient with disseminated tuberculosis and seizures. The lesion disappeared with antituberculous therapy

than tuberculomas, usually presenting acutely with fever, headache, and neurological focal signs, and are most commonly supratentorial [72]. On CT, abscesses are hypodense, with surrounding edema and mass effect, and peripheral enhancement, usually thin and uniform. On MRI, there is a central area of hyperintensity on T2-weighted images [60]. This pattern is not specific, and thus, they are difficult to differentiate from toxoplasmic, fungal, or pyogenic abscesses or even from lymphoma in AIDS patients. Localized areas of cerebritis with gyriform enhancement are less frequently observed. Appropriate therapy includes antituberculous chemotherapy and surgical excision or aspiration where needed. Ofloxacin proved successful in a patient with intracranial tuberculomas in whom first-line therapy failed [73].

Spinal Cord Involvement

Tuberculous myelitis or radiculomyelitis usually presents as an acute or subacute transverse myelitis with variable degree of radicular pain. Ischemic spinal cord infarction secondary to vasculitis may also occur [74]. CSF analysis reveals an increased protein content with lymphocytic pleocytosis; low glucose levels are observed in up to one-third of patients [75]. The thoracic cord is most commonly affected, followed by the lumbar and the cervical regions. MRI shows contrast-enhancing tissue that surrounds the spinal cord and the roots and obliterates the subarachnoid space with focal or diffuse increased intramedullary signal on T2-weighted images and variable degrees of edema and mass effect. Postcontrast T1-weighted images reveal leptomeningeal enhancement (Fig. 8.4). The nerve roots may be clumped and show contrast enhancement depending on the degree of involvement [76]. Corticosteroids seem to improve the prognosis [77]. Rarely, tuberculomas occur in the spinal cord, either as intramedullary lesions or located in the dural space [78], often requiring microsurgical resection and antituberculous chemotherapy. Infrequent cases of intramedullary tuberculous abscesses have been reported [79].

Tuberculous spondylitis most often involves the thoracolumbar region, with L1 being the most affected level and the cervical and sacral spine being only rarely involved [60]. The infection initially predominates in the anterior part of the vertebral body, usually involving more than one vertebral level, and disseminates to affect the disk and eventually extends along the anterior or posterior longitudinal ligaments or through the end plate. Vertebral collapse may occur, resulting in kyphosis. In the lumbar region, tuberculous spondylitis may result in a calcified psoas abscess, a finding very suggestive of tuberculosis. Neuroimaging discloses bone destruction and fragmentation with involvement of the disk space and calcified paravertebral mass. MRI seems the method of choice, with an accuracy of 94% in vertebral osteomyelitis [80]. It reveals hypointense T1-weighted areas in the vertebral bodies alternating with areas of hyperintense T2-weighted signal in the disk space and paravertebral soft tissue. Postgadolinium images show enhancement of the infected bone and disk.

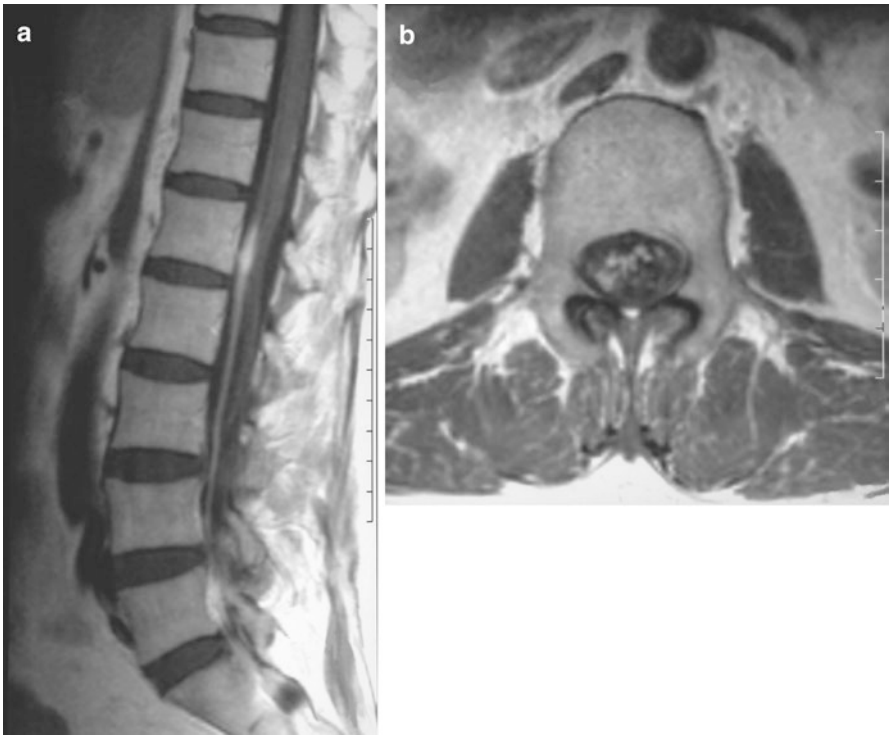

Fig. 8.4 Magnetic resonance imaging showing nodular thickening of the cauda equina roots in a patient with tuberculous meningitis and lumbosacral root involvement. Sagittal (**a**) and axial (**b**) T1-weighted sequences after gadolinium administration

Spondylitis can also complicate with an epidural abscess, resulting in different combinations of local and radicular pain, limb motor and sensory loss, and sphincter disturbances. Eventually, complete spinal cord compression with paraplegia, the most dreaded complication, may supervene.

Spinal cord disease is best treated with prolonged antituberculosis therapy and systemic steroids with the prognosis being better in those patients with recent onset disease and in whom prompt treatment is established. Surgery should be considered on an individualized basis depending on the extent and nature of the lesion and on the degree of neurologic deficit.

CNS Tuberculosis in the HIV Patient

Coinfection with HIV and tuberculosis has important implications, since the prognosis of tuberculosis is poorer due to the immunosuppression of these individuals and there is mounting evidence that the host immune response to

M. tuberculosis enhances HIV replication and might accelerate the natural progression of HIV infection. HIV testing is recommended for all patients with tuberculosis.

The clinical features and CSF profiles of tuberculous meningitis are not modified by HIV infection [32, 81]. HIV-infected patients show a lower percentage of tuberculin test positivity (30% with initial infection as compared with 50% in the immunocompetent adult), reflecting their cell-mediated immune deficiency. Anergy develops with advanced stages of immunosuppression.

Parenchymal disease seems more common in HIV patients and has been reported in 15–44% of patients with CNS tuberculosis [82].

When treating HIV-infected individuals, several facts should be considered. First, they usually have difficulty in controlling the infection due to the associated immune deficiencies. Second, rifamycins (rifampin, rifabutin, and rifapentine) reduce the activity of protease inhibitors due to induction of cytochrome CYP450 (all protease inhibitors are metabolized by CYP450). For this reason, rifabutin—which has substantially less activity as an inducer of cytochrome enzymes—is used instead of rifampin in these individuals, at a dose of 150 mg/day. Conversely, if protease inhibitors, particularly ritonavir or saquinavir, which are potent CYP450 inhibitors, are administered with rifabutin, blood concentrations of the latter increase markedly, and most likely rifabutin toxicity increases as well. Rifabutin is efficacious in nonresistant tuberculosis; its role in multiresistant cases is less clear [83]. Finally, HIV-infected patients can have malabsorption of antituberculous drugs [84] and are particularly prone to adverse drug reactions [85], which makes drug monitoring particularly important. Ideally, the management of tuberculosis among HIV-infected patients taking antiretroviral drugs should include directly observed therapy. It has to be taken into account that paradoxical reactions might occur during the course of tuberculosis treatment when antiretroviral therapy restores immune function [85].

Aside from classical regimens of long duration (see above), 6-month (isoniazid, rifabutin and pyrazinamide for 2 months and isoniazid and rifabutin for 4 additional months) and 9-month schedules (isoniazid, streptomycin, and pyrazinamide daily for 2 months and then 2–3 times/week for 7 months) are accepted regimens for HIV-infected patients [86].

Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is an important complication in HIV-infected tuberculosis patients who start combination antiretroviral treatment (ART). Neurological manifestations occur in more than 10% of TB-IRIS cases, mainly meningitis and tuberculomas [87].

CNS Infection by Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) are categorized into different groups based on characteristic colony morphology, growth rate, and pigmentation (the Runyon system of classification), although this system is being progressively replaced by

more efficient and rapid systems of molecular diagnosis. Growth rates in culture remain a practical means for grouping species and classify NTM into slow (>7 days)-, rapid (<7 days)-, and intermediate (7–10 days)-growing mycobacteria. The slow group includes the "*M. avium* complex" (MAC), constituted by *M. avium* and *M. intracellulare* (also known as MAI), *M. kansasii*, *M. scrofulaceum*, *M. xenopi*, and *M. genavense*, among others. Mycobacteria that grow at the intermediate rate include *M. gordonae* and *M. marinum*. Rapidly growing organisms include the *M. fortuitum* complex (*M. fortuitum* group and the *M. chelonei/abscessus* group). *M. avium* complex is responsible for most of the infections caused by NTM [88].

Currently, approximately 50 species of NTM are considered to be potential sources of disease. NTM are ubiquitous in the environment, including soil, water, and animals [88]. Most infections, including those that are hospital acquired, result from inhalation or direct inoculation from environmental sources. Ingestion may be the source of infection for children with NTM cervical adenopathy and for patients with the acquired immunodeficiency syndrome (AIDS) whose disseminated infection may begin in the gastrointestinal tract. Because person-to-person transmission is extremely rare, isolation of infected patients is not required.

NTM usually infect immunosuppressed individuals, primarily patients with AIDS and very low CD4 counts (<50 cells/μL) in whom prophylaxis with clarithromycin (500 mg twice daily) or azithromycin (1200 mg once weekly) is recommended. NTM produce a broad spectrum of disease, including chronic pulmonary disease in adults, lymphadenitis (mainly cervical) in children, skin and soft tissue disease, skeletal infection, catheter-related infections, and disseminated infection [88]. CNS infection is rare and occurs in the setting of disseminated disease.

The definite diagnosis is made by culture of the different samples depending on the organ involved and in cases of systemic infection by blood cultures, since they may be accompanied by high mycobacteremia. The diagnosis is also established if transbronchial, percutaneous, or open-lung biopsy tissue reveals mycobacterial histopathologic changes and yields the organism. Radiometric culture systems, DNA probes, and polymerase chain reaction assays have increased the speed and accuracy of laboratory diagnosis of pulmonary and extrapulmonary infections [89, 90]. Specific skin test antigens for NTM are not available.

Since NTMs are ubiquitous bacteria, their isolation from a clinical sample may represent a contamination. Thus, it is very important to consider the clinical features when evaluating a positive culture. In contrast, isolation from a sterile fluid such as CSF usually represents a genuine infection of the nervous system.

CNS infection by NTM is infrequent and usually consists of meningitis or meningoencephalitis [91]. *M. avium* is the most common etiologic agent of this group, especially in AIDS patients. Most of the patients had evidence of extensive disseminated disease. *M. kansasii* meningitis is similar to that of tuberculous meningitis but with a somber prognosis. *M. fortuitum* meningitis is related to prior CNS surgery and trauma, frequently associated with abscess and foreign bodies; prognosis in these cases can be more favorable if the concomitant abscess can be

successfully drained or the foreign body removed. Overall prognosis for NTM meningitis is poor, with a mortality rate close to 70% [91–93]. CSF examination in NTM meningitis shows mild lymphocytic pleocytosis, with glucose and protein levels close to normal [91].

Less frequently, these infections result in brain masses [94] or rhombencephalitis [95]. A case of chronic meningitis with a brain abscess in immunocompetent patients has also been described [96]. In a patient with Hodgkin's disease, the histopathological examination of the brain showed a perivascular infiltrate of lymphocytes and macrophages containing acid-fast resistant bacilli [97].

In a series of CSF cultures from 2083 AIDS patients with concomitant neurological manifestations, *M. tuberculosis* was the most commonly isolated microorganism (4.2%), followed by NTM (0.7%). Of 130 positive cultures, 89 (68.5%) corresponded to *M. tuberculosis* and 15 (11%) a NTM [98]. In another series, from Brazil, *Mycobacterium avium* was isolated in 11 of a total of 1273 (0.63%) AIDS patients [99].

A potential role has been suggested for bacteria of the *Mycobacterium avium* complex infection in contributing to AIDS peripheral neuropathy as a consequence of macrophage activation resulting in an increased macrophage-derived toxin production [100].

NTM have been implicated also in neurosarcoidosis after a positive hybridization with MAC by polymerase chain reaction assay on CSF from a patient with this disorder [101].

Therapy for disseminated NTM infections requires consultation with an expert and has been revised by the American Thoracic Society [102], although approaches to neurological infection are unclear due to their rarity. Decisions must weigh all potential drug toxicities and interactions as well as the results of susceptibility testing. Regimens usually include a macrolide (clarithromycin 500 mg twice daily or azithromycin 600 mg daily), ethambutol (15 mg/kg daily), and an additional third drug (rifampin 600 mg daily or rifabutin 150–300 mg daily, or ciprofloxacin). Optimal duration of therapy is unclear; immunocompetent patients should probably be treated for 18–24 months and AIDS patients for life.

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Parasitic Infections of the Central Nervous System

9

Oscar H. Del Brutto

Abstract

Parasitic infections of the CNS are a public health challenge to the developing world. During the past few decades, increased tourism, migratory movements, and the AIDS epidemic have facilitated the spread of formerly geographically restricted parasitic infections that now affect thousands of people living in developed countries. Parasites are classified into protozoa and helminths, and the latter are further divided into cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes). Parasitic infections are highly pleomorphic due to the unpredictable nature of the immunological reaction of the host against parasites as well as the many pathological lesions that these organisms may cause. Parasitic infections of the CNS may cause subacute or chronic meningitis, encephalitis, space-occupying brain lesions, stroke, and myelopathy. Diagnosis may be difficult due to nonspecificity of clinical manifestations and neuroimaging findings and the poor reliability of some of the most commonly used serologic tests. While the introduction of potent antiparasitic drugs has improved the prognosis in many patients, therapy still remains anecdotal for most of these conditions.

Keywords

Angiostrongyliasis • Baylisascariasis • Cerebral amebiasis • Cerebral malaria Chagas' disease • Coenurosis • Cysticercosis • Echinococcosis • Eosinophilic meningitis • Gnathostomiasis • Hydatid disease • Neurocysticercosis Paragonimiasis • Schistosomiasis • Sleeping sickness • Trypanosomiasis Sparganosis • Strongyloidiasis • Toxocariasis • Toxoplasmosis • Trichinellosis

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Protozoan Infections

Cerebral Amebiasis

Three genuses of free-living amoeba, *Naegleria*, *Acanthamoeba*, and *Balamuthia*, may invade the human CNS and cause disease. While *Naegleria fowleri* infections occur in healthy individuals, *Acanthamoeba* spp. and *Balamuthia mandrillaris* are opportunistic pathogens, typically affecting immunocompromised hosts. *N. fowleri* infection is most often acquired during swimming in warm freshwater; this parasite enters the nasal cavity and migrates through olfactory nerves to the CNS [1]. In contrast, *Acanthamoeba* spp. and *B. mandrillaris* enter the human body through the skin or the upper respiratory tract and secondarily invade the CNS by the hematogenous route [2].

N. fowleri causes a condition called "primary amoebic meningoencephalitis." This is a fulminant disease associated with hemorrhagic necrosis of the brain parenchyma that is more prominent around the olfactory bulbs and frontal lobes (as a reflection of the portal of entry of the microorganisms). Neuroimaging studies of nonspecific brain swelling and the diagnosis must be confirmed by the demonstration of mobile trophozoites in fresh cerebrospinal fluid (CSF) examination [3].

CNS infection with *Acanthamoeba* spp. and *B. mandrillaris* causes "granulomatous amoebic encephalitis," a subacute disease characterized by fever, focal neurological signs, seizures, increased intracranial pressure, and behavioral changes. These manifestations are related to the formation of hemorrhagic parenchymal brain abscesses that are seen on neuroimaging studies as multiple ring-enhancing lesions surrounded by edema. Invasion of the walls of intracranial arteries by trophozoites causes a necrotizing angiitis that may lead to ischemic strokes. As neuroimaging findings are nonspecific, diagnosis of this condition requires the demonstration of parasites in biopsy specimens [4]. Both *Acanthamoeba* spp. and *B. mandrillaris* may also cause disseminated disease with involvement of the lungs, skin, and kidneys.

Infections by free-living amoeba are highly fatal [5]. Amphotericin B, rifampin, and fluconazole may be used in *N. fowleri* infections, while surgery, pentamidine, and metronidazole are advised for *Acanthamoeba* spp. and *B. mandrillaris* brain abscesses.

Cerebral Malaria

It has traditionally been known that *Plasmodium falciparum* is the only one of the five species of human malaria parasites that invades the CNS and may cause cerebral malaria. However, there is some recent evidence suggesting that *P. vivax* infection may also be associated with this condition [6]. Human infection occurs when the sporozoite form of the parasite is inoculated through the skin during a blood

meal by a female *Anopheles* mosquito. Then, sporozoites are carried into the liver where they mature to schizonts that liberate merozoites which, in turn, enter the bloodstream, parasitize red blood cells, and transform in gametocytes. The life cycle of the *Plasmodium* is completed when the mosquito ingests infected human red blood cells and gametocytes transform into sporozoites [7].

The first clinical manifestation of cerebral malaria is fever. Then, seizures, dysconjugate gaze, cloudiness of consciousness, and extensor posturing occur. Some patients (particularly children) present with focal neurological signs related to the occurrence of a cerebral infarction or intracranial hemorrhage. Neuroimaging studies are often normal or may show brain swelling or small hemorrhages in severe cases. Cytochemical analysis of CSF is normal, but a spinal tap is mandatory to rule out other causes of encephalopathy. Diagnosis is confirmed by the finding of *P. falciparum* by examining thin and thick blood smears with Giemsa stain; repeated examinations may be needed since parasitemia is cyclical. The occurrence of the so-called malarial retinopathy, which is characterized by retinal whitening, flame hemorrhages, and papilledema, is highly reliable for confirming the diagnosis of cerebral malaria in children with parasitemia and coma [8].

In fatal cases, autopsy often reveals diffuse brain swelling and subcortical ring hemorrhages, which are the result of extravasation of erythrocytes due to endothelial damage. Of interest, erythrocytes that form the ring hemorrhages are not parasitized, suggesting that blood vessel damage may be related to the liberation of vasoactive substances (immune hypothesis). On the other hand, capillaries and venules are plugged by clumped, parasitized erythrocytes, suggesting that brain damage is caused by obstruction of the cerebral microvasculature (mechanical hypothesis). The brain of patients who survived the acute phase of the disease often develops granulomatous lesions, called Dürck nodules, at the site of ring hemorrhages.

Quinine is still considered as the drug of choice for cerebral malaria in most of the developing world. It has been shown that artemether (an artemisinin derivative) is as effective as quinine. However, its effect is short lasting, and artemether must be associated with mefloquine or amodiaquine [9]. Corticosteroids may be deleterious and must not be used. Due to chloroquine-resistant strains of *P. falciparum*, this drug should not be used in this setting. Hypoglycemia, pulmonary edema, renal failure, bleeding diathesis, and hepatic dysfunction may complicate the course of the disease, and up to 25% of patients die despite medical care. Permanent sequelae are more common in children and include mental retardation, recurrent seizures, blindness, and focal motor deficits.

Toxoplasmosis

Toxoplasmosis is the most common opportunistic infection of the CNS in AIDS patients and most often occurs as the result of the reactivation of a dormant infection that had been acquired several years ago [10]. The causal agent, *Toxoplasma*

gondii, is acquired by eating undercooked meat or by accidental ingestion of contaminated cat feces. While CNS invasion almost always occurs as an opportunistic infection, immunocompetent hosts may also suffer from CNS toxoplasmosis during acute infections, and the brain of fetuses may be affected due to placental transmission of tachyzoites from women who acquire the disease during pregnancy [11].

CNS invasion with *T. gondii* is associated with the development of necrotizing encephalitis related to perivascular inflammation. Focal lesions in the brain parenchyma consist of a necrotic center surrounded by tachyzoites and cysts, together with patchy areas of necrosis and perivascular cuffing of lymphocytes. The surrounding parenchyma usually shows glial nodules.

Cerebral toxoplasmosis in immunocompromised patients may present in the form of acute encephalitis or, more often, as a subacute disease characterized by fever, focal signs associated with seizures, increased intracranial pressure, and decreased level of consciousness. Those individuals may have absent or low serum antibody titers despite severe disease [12]. Neuroimaging studies usually show multiple ring-enhancing lesions surrounded by edema; lesions are most often located in the subcortical white matter, the basal ganglia, or the brainstem (Fig. 9.1). Abnormal enhancement of granulomas may be poor in severely immunosuppressed patients. These are not pathognomonic lesions, and definitive diagnosis theoretically requires histological demonstration of the parasite. However, initiation of empiric therapy followed by repeated neuroimaging studies 2 weeks later is an alternative to biopsy in these cases [13].

Combination therapy with pyrimethamine and sulfadiazine is the best option for CNS toxoplasmosis. Clindamycin, atovaquone, and trimethoprim/sulfamethoxazole are alternative drugs in patients allergic to sulfadiazine. CNS toxoplasmosis tends to recur after discontinuation of therapy; therefore, permanent maintenance therapy with pyrimethamine and sulfadiazine is advised to decrease the risk of relapses in immunosuppressed patients [11].

Trypanosomiasis

American Trypanosomiasis (Chagas' Disease)

Chagas' disease is caused by the protozoa *Trypanosoma cruzi*. Infection occurs when parasites enter the human body by direct inoculation through a bite of bugs of the genus *Triatoma* (the insect vector). Blood transfusions represent a common cause of *T. cruzi* infection in non-endemic areas [14]. Chagas' disease is a major public health problem in Latin America, where more than ten million people are infected with this parasite. The acute phase of the disease is often characterized by unilateral orbital edema (Romaña's sign) and mild constitutional symptoms. In some cases (particularly in infants and AIDS patients), early invasion of the CNS by trypanosomes may cause diffuse encephalitis [15]. In these cases, the brain shows multiple areas of hemorrhagic necrosis, glial proliferation, and perivascular infiltrates of inflammatory cells. During the chronic phase of the disease, neurological

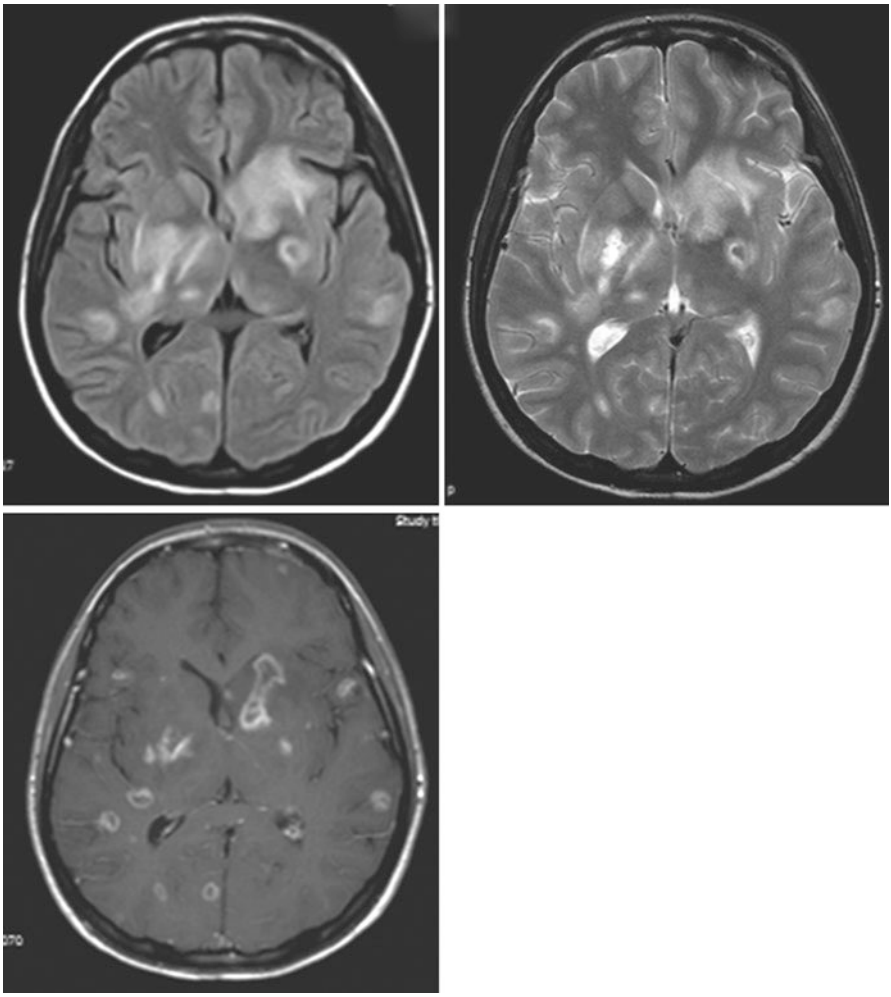

Fig. 9.1 FLAIR, T2-weighted, and contrast-enhanced T1-weighted MRIs of patient with AIDS and cerebral toxoplasmosis. Note multiplicity of lesions, predominance of involvement of the basal ganglia, and ring enhancement of most of them

complications are most often related to the occurrence of cardiogenic brain embolisms as the result of a chagasic dilated cardiomyopathy [16]. As expected, such strokes may be multiple and most often involving the territory of cortical branches of major intracranial arteries. However, some patients develop primary neurological complications due to direct damage of cerebral blood vessels.

Immunocompromised individuals may experience reactivation of chronic infections, resulting in a fatal meningoencephalitic syndrome similar to that observed in acute infections. During the acute phase of the disease (up to 12 weeks after

infection), diagnosis is possible by demonstration of *T. cruzi* in blood smears or CSF samples. Chronic disease must be confirmed by serologic testing since parasites are no longer detectable in blood smears. Nifurtimox and benznidazole may be used for patients during the acute phase of the disease, for those with acute reactivations of chronic disease, and for congenital infections. Chronic Chagas' disease has no specific treatment [17].

African Trypanosomiasis (Sleeping Sickness)

This condition may be caused by two subspecies of *Trypanosoma brucei*: *T. brucei gambiense* as the agent of West African trypanosomiasis and *T. brucei rhodesiense* as that of East African trypanosomiasis [18]. These protozoa enter the human body by direct inoculation through a bite of tsetse fly, the insect vector. In both forms of the disease, trypanosomes invade the CNS soon after inoculation and remain latent for long periods. Thereafter, the disease enters in a stage in which clinical manifestations ensue. These include fever, cervical lymphadenopathy (Winterbottom's sign), and hepatosplenomegaly, suggesting activation of the reticuloendothelial system. Then, somnolence, apathy, involuntary movements, and generalized rigidity appear. Neurological manifestations progress to severe cognitive impairment, coma, and death. The brain of fatal cases often shows diffuse gliosis, demyelination, and infiltrates of hypertrophied lymphocytes (Mott cells) involving the meninges, perivascular spaces, and brain parenchyma. Soon after infection, parasites may be isolated from the blood, CSF, and lymph nodes, and CSF examination may reveal moderate pleocytosis and the typical Mott cells. In contrast, chronic disease may only be diagnosed by immune tests performed in serum or CSF. Therapy of sleeping sickness depends on the subspecies involved and on the stage of the disease. For West African trypanosomiasis, pentamidine is recommended for early phases and eflornithine for late stages. For East African trypanosomiasis, suramin is the drug of choice for early stages and melarsoprol for late stages [18].

Nematode Infections

Eosinophilic Meningitis

While the term eosinophilic meningitis comprises all conditions causing meningitis associated with eosinophils in the CSF, it is commonly used to refer to the neurological complications related to infection with *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, and *Baylisascaris procyonis* [19]. Humans become accidental hosts of these tissue nematodes after eating raw snails (*A. cantonensis*), undercooked fish or poultry (*G. spinigerum*), or raccoon feces (*B. procyonis*). Once ingested, larvae of these parasites migrate to the tissues of the host, including the CNS.

CNS damage induced by tissue nematodes may be caused by mechanical injury or related to the immunological response of the host. The former mechanism explains the occurrence of hemorrhagic tracts in the brain parenchyma in cases of

G. spinigerum infection. In contrast, most neuropathologic findings in *A. cantonensis* infections are related to congestion and inflammation of leptomeninges [20].

Patients with angiostrongyliasis often present with a self-limited meningitis characterized by headache, neck stiffness, and cranial nerve palsies. Seizures, intracranial hypertension, somnolence, or coma may also occur. Neurological manifestations of gnathostomiasis include radicular pain, transverse myelitis, meningitis, encephalitis, and intracranial hemorrhages. Sudden blindness due to retinal detachment may occur as the result of migration of the parasite through the eye. Only a few cases of human baylisascariasis have been reported (particularly children). Some patients have developed a severe eosinophilic meningoencephalitis, while others have presented with spinal cord involvement or with neuroretinitis without major evidence of cerebral involvement [21].

As implicit in its name, the CSF of patients with eosinophilic meningitis usually reveals moderate pleocytosis with up to 70% eosinophils; protein contents may be increased, but glucose levels are normal. Neuroimaging studies may show abnormal meningeal enhancement, periventricular hyperintensities suggestive of demyelination, hydrocephalus, or, in patients with gnathostomiasis, hemorrhagic tracts in the brain parenchyma. While serologic tests may support the diagnosis in some cases, confirmation usually rests on identification of the larvae in tissues.

Since the course of angiostrongyliasis is usually benign, most patients improve in less than 1 month with symptomatic drugs. CSF drainage is effective for headache relief in patients who do not respond to common analgesics. A short course with corticosteroids may reduce the need of repeated spinal taps in these cases [22]. The management of *G. spinigerum*- and *B. procyonis*-related eosinophilic meningitis requires the use of intravenous dexamethasone to reduce the inflammation-mediated damage of intracranial blood vessels. Thiabendazole, mebendazole, albendazole, and ivermectin may be active against the tissue nematodes causing eosinophilic meningitis. However, the actual role of specific therapy for eosinophilic meningitis has not been settled.

Other Nematode Infections

Strongyloidiasis

Under normal conditions, *Strongyloides stercoralis* is confined to the human intestinal tract and does not invade the CNS. Disseminated disease may occur when the host's immune mechanisms fail to control the normal cycle of autoinfection (hyperinfection syndrome). Common predisposing factors include HTLV-1 infection, chronic corticosteroid therapy, transplant recipients, and chemotherapy administration [23]. Cerebral infarcts and brain abscesses may occur in such cases. Definitive diagnosis requires identification of the larvae in the CSF or tissue specimens. However, the disease should be suspected in immunosuppressed patients who develop meningitis, focal neurological signs, or acute encephalopathy. Mortality of disseminated strongyloidiasis is high, although ivermectin or thiabendazole may be of value in some patients.

Toxocariasis

This disease is caused by nematodes of the genus *Toxocara*. The infection is acquired when humans ingest soil contaminated with dog or cat feces containing *Toxocara* eggs. Eggs mature into larvae which migrate to the tissues of the host producing a disease called visceral larva migrans. Migration to the eye produces ocular larva migrans, in which the parasite is easily identified by fundoscopic examination (Fig. 9.2). CNS damage is related to migration of larvae through the brain parenchyma leaving necrotic tracks or to the inflammatory response that develops around inert larvae. Clinical manifestations include subacute encephalitis, parenchymal brain granulomas, or cerebral infarcts due to angiitis [24]. Diagnosis may be suspected in patients with positive serology, particularly if intrathecal synthesis of anti-*Toxocara* antibodies is documented. Neuroimaging studies may show multiple enhancing lesions in the brain parenchyma. Albendazole and diethylcarbamazine have been useful in some cases [25].

Trichinellosis

This disease occurs after ingestion of undercooked pork contaminated with larva of *Trichinella spiralis*. Larvae enter the bloodstream and encyst in the skeletal muscle. Trichinellosis is often asymptomatic; however, CNS involvement, characterized by meningoencephalitis or stroke, may occur. Stroke subtypes associated with trichinellosis include hemorrhagic infarcts related to venous thrombosis and subcortical infarcts caused by small-artery disease. It has been suggested that migrating larval emboli are responsible for occlusion of cerebral vessels. However, other studies suggest that hypereosinophilia is responsible for these vascular lesions. Eosinophils

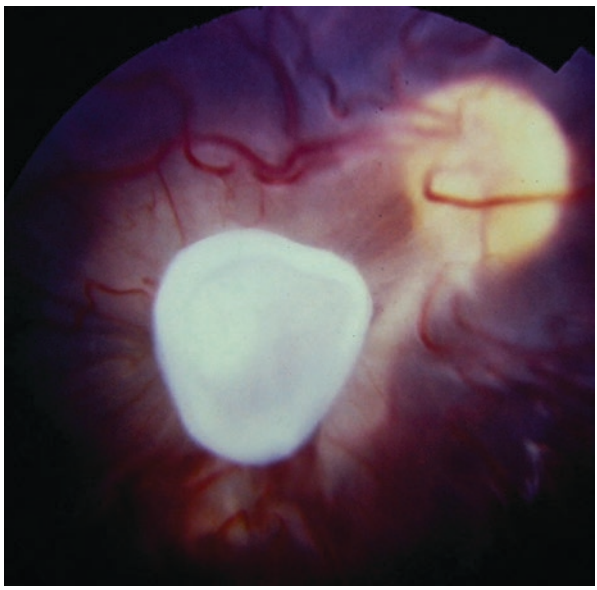

Fig. 9.2 Fundoscopic examination of a patient with ocular larva migrans (Courtesy of Dr. Nelson Matamoros, Guayaquil, Ecuador)

may directly induce vascular occlusion through a prothrombotic effect or may damage the vascular endothelium after being stimulated by cytokines produced in response to *T. spiralis* infection. Neurotrichinellosis should be suspected in patients who, besides a cerebral infarct, have fever, myalgia, periorbital edema, and peripheral eosinophilia. Cytochemical analysis of the CSF is most often normal, and neuroimaging may show nonspecific patchy hyperintensities in the subcortical white matter. Support for the diagnosis is provided by the presence of anti-*Trichinella* antibodies or by the identification of the parasite in the muscle tissue. Corticosteroids suppress the eosinophilic-induced vascular damage and reduce mortality in severe cases [26].

Trematode Infections

Paragonimiasis

Paragonimiasis is caused by trematodes of the genus *Paragonimus* (lung flukes). Humans acquire the disease by ingesting undercooked crustaceans infected with larvae of these parasites. Then, larvae cross the intestinal wall, enter the peritoneal cavity, and migrate to the lungs. Further migration of the worms through the foramina of the skull base to the CNS may occur. Neurological syndromes occurring in the course of cerebral paragonimiasis include meningitis, granulomatous or calcified parenchymal brain lesions, and intracranial hemorrhages. *Paragonimus* meningitis may be associated with cerebral infarctions due to endarteritis. Parenchymal brain lesions may be associated with seizures, focal signs, and intracranial hypertension. Cerebral hemorrhages may occur along tracts of larva's migration or as the result of the necrotizing vasculitis that develops during early granuloma formation [27]. Diagnosis is suggested by the presence of specific antibodies in the CSF or by neuroimaging findings of confluent calcifications located in the temporal and occipital lobes that resemble "soap bubbles." Lesions may also be located at the spinal intradural space [28]. Support for the diagnosis is provided by demonstration of *Paragonimus* eggs in sputum. Therapy includes praziquantel and corticosteroids.

Schistosomiasis

Schistosomiasis occurs when humans become definitive hosts in the life cycle of trematodes of the species *Schistosoma* (*S. japonicum*, *S. mansoni*, *S. haematobium*) [29]. These parasites enter the body through the skin following aquatic exposure with their larval forms. Larvae migrate, transform into adult worms, and settle in the mesenteric veins. Larvae may also migrate to the spinal cord or the cerebral vasculature. The spectrum of neurological manifestations is related to the *Schistosoma* species and the location of parasites; *S. japonicum* almost always affects the brain. In contrast, the other two species most often affect the spinal cord and only eventually the brain [30].

Acute infection with *S. japonicum* produces meningoencephalitis—a disease called "Katayama fever"—associated with fever, seizures, visual loss, neck stiffness, disorientation and stupor, and focal neurological deficits. The chronic phase of the disease is characterized by seizures, focal signs, and intracranial hypertension related to the development of single or multiple parenchymal brain granulomas. Intracranial hemorrhages may occur; they are related to segmental damage of small leptomeningeal or parenchymal blood vessels induced by the parasites [31].

Infections with *S. mansoni* and *S. haematobium* are often associated with transverse myelitis related to inflammatory necrosis of the spinal cord. Myelitis usually affects the lower segments of the spinal cord and is characterized by flaccid paraplegia associated with sphincter dysfunction and sensory loss. In addition, granulomatous masses may involve the conus medullaris and cauda equina, causing low back pain, saddle anesthesia, sphincter dysfunction, and weakness in the lower limbs. Acute paraplegia has resulted from occlusion of the anterior spinal artery by the parasite.

Cytochemical analysis of the CSF may be normal or may show a nonspecific mononuclear pleocytosis and increased protein contents. Neuroimaging studies may show discrete hemorrhagic or enhancing lesions in patients with *S. japonicum* schistosomiasis and enlargement of the lower spinal cord in some patients with spinal schistosomiasis (Fig. 9.3). Most patients with spinal cord involvement have specific antibodies detected by ELISA. The absence of schistosomal eggs in stool and urine does not exclude the diagnosis. Praziquantel associated with corticosteroids is effective for some patients with brain or spinal cord involvement. Surgical decompression of the spinal canal is still an option in some cases [30].

Cestode Infections

Cysticercosis

Cysticercosis is the most common helminthic infection of the CNS. It is caused by the larval stage of *Taenia solium*, a cestode with a complex life cycle involving humans as definitive hosts and either pigs or humans as intermediate hosts. Cysticercosis in humans occurs after the ingestion of *Taenia* eggs through direct or indirect contact with feces of a *T. solium* carrier. Cysticerci may invade almost every organ; however, relevant clinical manifestations are almost always related to CNS involvement [32].

Cysticerci are liquid-filled vesicles including an invaginated scolex that has a similar appearance than the adult *T. solium*. These cysts may be located anywhere within the CNS. Parenchymal brain cysticerci are mainly located in the cerebral cortex or the basal ganglia. In contrast, subarachnoid and ventricular cysticerci may attain a large size due to a mechanism of hydropic degeneration by which the CSF enters through the parasitic membrane and causes enlargement of the vesicle. Spinal cysticerci may be found at either the cord parenchyma or the subarachnoid space. Individual variations in the location of parasites and in the severity of the

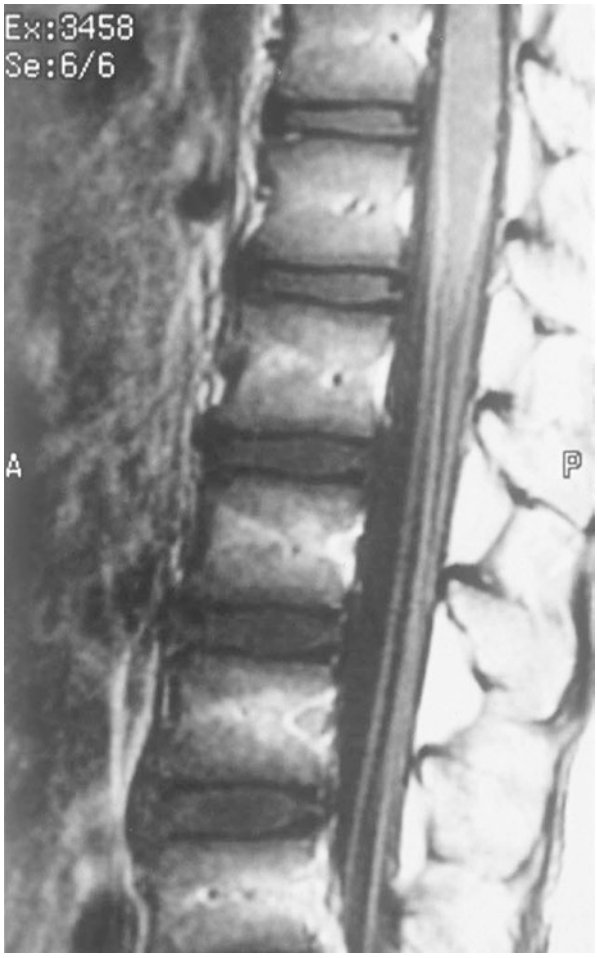

Fig. 9.3 Contrast-enhanced MRI showing enlargement of the conus medullaris in patient with *Schistosoma mansoni* schistosomiasis (Courtesy of Dr. Francisco X. Carod-Artal, Barcelona, Spain)

inflammatory reaction against cysticerci explain the vast clinical pleomorphism of the disease. Some parasites escape the host's immune detection, while others evoke an intense immune response causing both destruction of cysticerci and damage of the surrounding tissues. Common pathological lesions in the latter include astrocytic gliosis, brain swelling, arachnoiditis, hydrocephalus, and angiitis of small- and medium-sized intracranial arteries [33].

Seizures (particularly late-onset seizures) are the most common clinical manifestation of neurocysticercosis. They often occur in patients with parenchymal brain cysts or calcifications. Focal neurological signs usually follow a subacute or chronic course, although they may occur abruptly in patients who develop a cerebral infarct as a complication of angiitis. Increased intracranial pressure is the result of hydrocephalus, ventricular cysts, or cysticercotic encephalitis. The latter is a severe form of the disease that occurs in patients who develop a severe immune response against

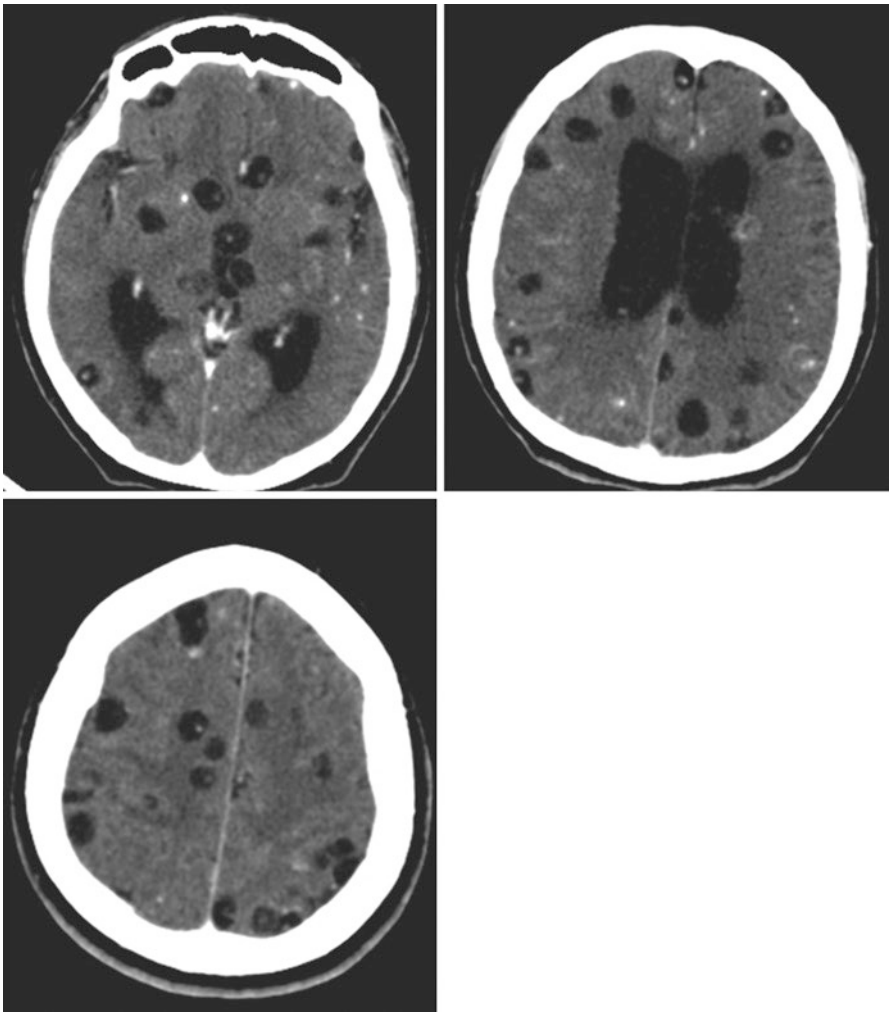

Fig. 9.4 Contrast-enhanced CT of patient with heavy non-encephalitic cysticercosis. Cysts appear as well-defined hypodense lesions with no edema and no abnormal enhancement. The scolex can be visualized in the interior of some of these lesions as a brilliant dot

massive cysticerci infection of the brain parenchyma. Clinical manifestations of spinal neurocysticercosis are also nonspecific [34]; spinal arachnoiditis is characterized by root pain and weakness of subacute onset, and cysts in the cord parenchyma are associated with motor and sensory deficits that vary according to the level of the lesion.

Neuroimaging studies provide proper localization of cysticerci and reveal the activity of the disease. Cystic lesions showing the scolex (Fig. 9.4) and parenchymal brain calcifications (Fig. 9.5) are the most characteristic findings of

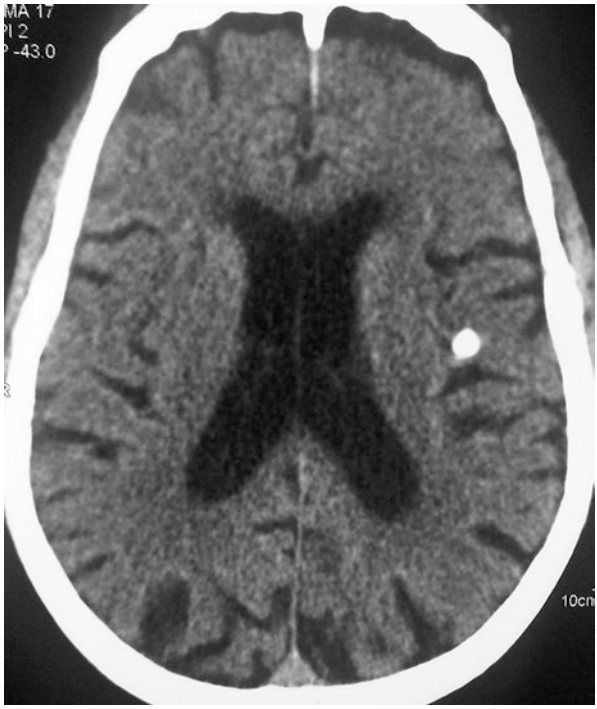

Fig. 9.5 Plain CT showing a single parenchymal brain calcification. This is the most common—though nonspecific—neuroimaging finding in neurocysticercosis

neurocysticercosis. Ring-enhancing lesions, hydrocephalus, and abnormal enhancement of the leptomeninges are non-pathognomonic and represent a diagnostic challenge. Immune diagnostic tests should never be used by themselves to exclude or confirm the disease. The most effective is the serum immunoblot; however, some disappointing results have been reported in patients with a single brain lesion. A set of diagnostic criteria based on objective clinical, radiological, immunological, and epidemiological information has been proposed to allow physicians to diagnose neurocysticercosis [35]. Four categories of criteria—absolute, major, minor, and epidemiological—are stratified according to their individual diagnostic strength and allow two categories of diagnostic certainty for NCC, definitive and probable.

Patients with parenchymal brain or subarachnoid cysts must be treated with cysticidal drugs (albendazole or praziquantel). These drugs result in disappearance of most cysts as well as in better control of seizures and improvement in focal neurological deficits. Patients with calcifications alone should only receive symptomatic treatment. Ventricular cysts should be better resected by neuroendoscopy to avoid risks related to enlargement of those cysts as the result of cysticidal drug therapy. Also, medical treatment may favor the occlusion of a blood vessel in patients with subarachnoid cysts or may worsen the brain edema accompanying cysticercotic encephalitis; corticosteroids are advised for the prevention of such complications. Therapeutic priorities, i.e., ventricular shunt for hydrocephalus, must be considered before the use of cysticidal drugs in patients with mixed forms of the disease [36].

Echinococcosis (Hydatid Disease)

There are two main forms of hydatid disease: cystic hydatid disease, caused by the larval stage of *E. granulosus*, and alveolar hydatid disease, caused by the larval stage of *E. multilocularis*. In addition, some cases of cystic hydatid disease have been recently attributed to *E. vogeli* infections [37]. Canids are definitive hosts for *Echinococcus* spp., and sheep or rodents are intermediate hosts. Humans may become accidental intermediate hosts after the ingestion of food contaminated with eggs of these cestodes. Echinococcal cysts grow in the liver, the lungs, the heart, and the CNS. In the latter, the cysts may grow primarily or secondarily from metastatic dissemination of a visceral cyst.

E. granulosus cysts are single, spherical, and well demarcated from the surrounding tissues. In contrast, *E. multilocularis* cysts tend to group in clusters, expand rapidly, elicit a severe immune reaction from the host, and metastasize. In both species the larva may be found within the cysts. Both forms of hydatid disease may course with seizures and intracranial hypertension; however, clinical manifestations are more severe in patients with alveolar hydatid disease. Patients with cystic hydatid disease of the orbit develop unilateral proptosis and diplopia. Spinal cord involvement may be observed in both forms of the disease; usual manifestations include root pain and motor or sensory deficits. Primary hydatid cysts of the heart may embolize and occlude an intracranial artery with the subsequent development of a brain infarct.

Cystic hydatid disease is seen on neuroimaging studies as a large, spherical, non-enhancing, liquid-filled vesicle, which is well demarcated from the surrounding brain parenchyma. Cysts are most often located within the brain parenchyma although extradural cysts with bone erosion may occur. In contrast, alveolar hydatid disease is associated with multiple and confluent lesions that show abnormal contrast enhancement. Diagnosis by ELISA or immunoblot is not accurate due to cross-reactions with other parasites [38].

Hydatid cysts have been traditionally resected by surgery using the Dowling's technique. However, albendazole may destroy these cysts, obviating the hazards of trans-operative cyst rupture. Albendazole is effective against both *E. granulosus* and *E. multilocularis* and may be used in patients who are not candidates for surgical resection of lesions, as prophylactic therapy for those who have a perioperative risk of accidental rupture of the cysts, or to treat recurrent cystic hydatid disease after surgery [38]. Praziquantel has protoscolicidal activity and may have a role in the prevention of secondary reactions related to accidental spillage of protoscolices during surgery.

Other Cestodes

Coenurosis

This disease is caused by *Coenurus cerebralis*, the larval stage of *Taenia multiceps*. The definitive host is often a canid, and sheep or other herbivorous mammals

are the natural intermediate hosts. Humans become accidentally infected after ingestion of dogs' feces contaminated with *T. multiceps* eggs. *C. cerebralis* is a cystic vesicle that includes multiple scolices. Cysts may lodge in subcutaneous tissues, skeletal muscles, and the CNS. In the latter, they are most often located at the base of the skull where they induce arachnoiditis with obstructive hydrocephalus. Parenchymal brain involvement may also occur; seizures and focal signs occur in these cases. Neuroimaging studies show hydrocephalus and cystic or ring-enhancing lesions in the brain parenchyma or CSF cisterns. Diagnosis is done by biopsy of a brain lesion. There is no known medical therapy for cerebral coenurosis [39].

Sparganosis

This disease is caused by the second-stage larva of cestodes of the genus *Spirometra*. Dogs and cats are definitive hosts, cyclops are the first intermediate hosts, and frogs and snakes are the second intermediate hosts. Humans acquire the infection by drinking water contaminated with cyclops harboring the larva or by eating infected frog or snake. The sparganum migrates to skeletal muscles or subcutaneous tissue where it further develops into granulomas. Further migration through the foramina of the skull base and vertebral column is associated with involvement of the CNS, including the brain parenchyma, the subarachnoid space, and the spinal canal. Inflammatory changes and focal necrosis along the tracks of migration of these larvae are common findings. Patients with parenchymal brain sparganosis present with seizures or focal neurological signs. Neuroimaging findings are usually confined to one cerebral hemisphere and include multifocal areas of low density within the subcortical white matter, focal cortical atrophy, ipsilateral ventricular enlargement, spotty calcifications, and enhancing nodules that may change in location on sequential scans. Definitive diagnosis depends on the visualization of the parasite from a brain biopsy. Surgical resection of the parasite is the treatment of choice [39].

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Infections of the Spinal Cord

10

Francisco Javier Carod-Artal

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 D68 and 71 have been identified as the etiologic agent of a poliomyelitis-like syndrome. The *Flaviviridae* family includes some mosquito-borne virus such as dengue, chikungunya, Zika, 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's 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 schistosomal spinal syndromes. Other parasitary diseases that may affect the spinal cord are gnathostomiasis, cysticercosis, hydatid disease, and paragonimiasis. Invasive fungus may provoke a spinal cord compression syndrome from osteomyelitis, epidural abscess, or paravertebral lesions.

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Introduction

Infectious myelopathies can be caused by viral, bacterial, fungal, and parasitic agents. 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 neurological 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 is very helpful 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 is called parainfectious transverse myelitis, and its diagnostic criteria are summarized in Table 10.1. Probable pathogenic mechanisms are 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.

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

Viral Myelitis

Although viral infections may cause a parainfectious acute transverse myelitis, some viruses are indeed neuroinvasive 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 neurotropic 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, 5]. Pathogenic mechanisms of acute transverse myelitis in HIV patients are 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 [6].

CD8 T-cell neurological disorders have been recently recognized as a new inflammatory HIV-driven condition. This immune-mediated syndrome may be triggered by a concomitant minor infection or by the interruption of combined antiretroviral therapy. Encephalitis and recently CD8 T-cell transverse myelitis have been described. CSF analysis may reveal a lymphocytic pleocytosis with predominance of CD8 T cells, and the MRI of the spine shows multiple intramedullary lesions displaying patchy gadolinium enhancement [7].

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 [8]. 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. Since the 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. HIV 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. Other causes of HIV-associated vacuolar myelopathy should be excluded. Differential diagnosis includes opportunistic infections such as viral (herpes, cytomegalovirus, HTLV-1), bacterial (*Treponema pallidum*, *Mycobacterium tuberculosis*), fungal (*Cryptococcus neoformans*), and parasitic diseases (*Toxoplasma gondii*) and vascular, neoplastic, inflammatory, and other disorders such as cobalamin deficiency [9, 10].

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-2, a related type C retrovirus, affects predominantly American Indians and parenteral drug abusers [11].

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), transplantation, and sharing of needles and syringes [12]. Intravenous exposure to blood is the most efficient mode of HTLV-1 transmission [13].

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 [11].

Classical TSP/HAM is characterized by a slowly and progressive spastic paraparesis with lower limb weakness and sensory symptoms, back pain, sphincter 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 [14]. On neurological exploration, symmetric and proximal weakness of the legs, hypesthesia, 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 [14]. A list of systemic and neurological complications associated with 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

Table 10.2 Neurological and systemic conditions associated with 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 polyarthralgias
Periodontal disease
Bronchoalveolitis
Infective dermatitis
Predisposition to helminthic and bacterial infections
Strongyloides stercoralis coinfection

interaction between the virus and the host's immune system. HTLV-1 proviral DNA and mRNA load are significantly raised in TSP/HAM patients compared to asymptomatic carriers. This antigenic load activates T-cell CD8+ specific for Tax protein, which upregulate pro-inflammatory cytokines [15].

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 neuroinflammation 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; pyramidal, spinocerebellar, and spinothalamic tract damage; axonal and myelin degeneration; and spinal cord atrophy predominate [11].

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. Atypical lymphocytes and high HTLV-1 proviral load in peripheral blood mononuclear cells can be observed. Polymerase chain reaction (PCR) allows for distinction between HTLV-1 and 2 and permits the quantification of proviral load. High HTLV-1 proviral load may be a good predictor of developing TSP/HAM [16].

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 [14].

Repeated courses of steroids (intravenous methylprednisolone) are used to treat symptoms at initial presentation. Alpha interferon, plasma exchange, intravenous immunoglobulins, danazol, pentoxifylline, zidovudine, lamivudine, daclizumab, valproic acid, prosultiamine (a vitamin B1 derivative), and pentosan polysulfate sodium (a heparinoid with hemorheological properties) have been used in open trials in a small number of patients [16]. Although alpha interferon may cause a reduction in HTLV-1 proviral load, its 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 and anticholinergic drugs. Constipation, neurogenic pain, and spasticity are other relevant issues that should be treated in the chronic stage of the disease [15].

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

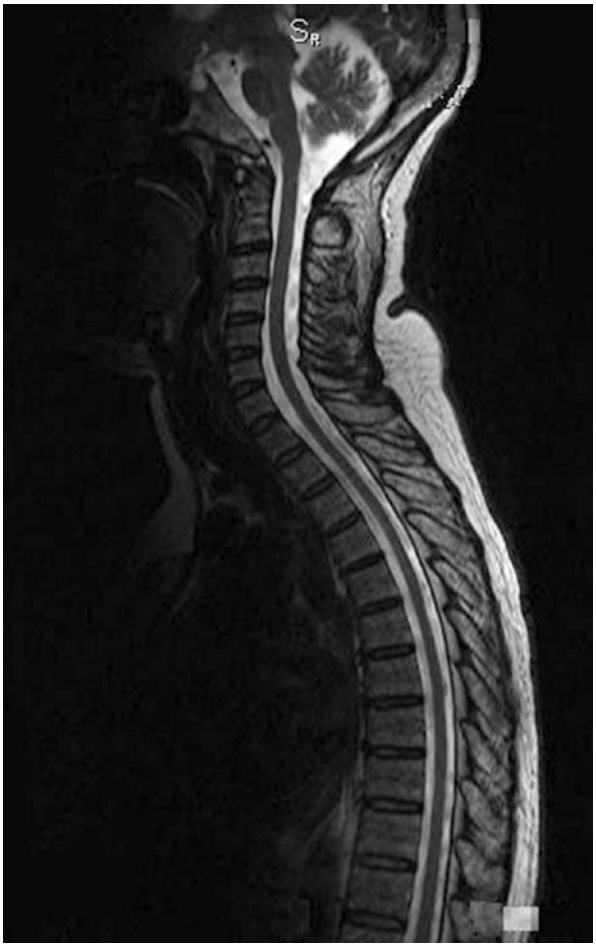

Fig. 10.1 Spinal cord MRI, T2-weighted imaging of a patient affected by HTLV-1 tropical spastic paraparesis. Atrophy of the thoracic spinal cord

upper respiratory tracts [17]. Most enteroviral infections are asymptomatic, but some of them may cause herpangina, myocarditis, pericarditis, and hand-foot-and-mouth disease. Enteroviruses are the most common cause of viral meningitis and can also provoke an acute myelitis affecting the anterior horn of the spinal cord.

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 1000 cases in 2010 [18]. 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. Polio outbreaks attributed to circulating vaccine-derived poliovirus have also been described. Vaccine-derived polioviruses causing paralytic disease have undergone recombination with human enterovirus C species [19, 20].

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 [18].

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 [17].

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 lower motor neuron involvement and exclusion of other disorders as cause of the new symptoms. It has been hypothesized that the muscle-related effects of post-polio syndrome are 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 syndrome patients should be advised to avoid both inactivity and overuse of weak muscles [21].

Enterovirus 71

Enterovirus 71 (EV71) was 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 occurred 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, and increased vascular permeability; and neurological involvement [23].

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 ventral roots of the cervical spinal cord [24, 25]. In a Chinese retrospective study of 134 children who had EV71 infection, the most common neurologic complications were aseptic meningitis ($n = 74$), brainstem encephalitis ($n = 24$), acute flaccid paralysis ($n = 20$), acute panencephalitis ($n = 12$), and encephalomyelitis ($n = 4$) [26].

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/μL) is usually found in 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 sometimes in the ventral cervical roots [27]. Bilateral T2-sequence 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 were identified as independent risk factors for neurological involvement as evidenced by CSF pleocytosis [22]. There is no effective therapy for EV71 myelitis; the antiviral drug pleconaril has been used in some cases with modest effects against this virus.

Enterovirus D68

Enterovirus D68 (EV-D68) is another emerging picornavirus that causes severe respiratory disease in children. The largest and most widespread EV-D68 outbreak in North America was reported in 2014 [28]. Approximately 1100 cases of respiratory EV-D68 infections in children were reported, and many of them required intensive care unit support. An association between EV-D68 infection and cases of acute flaccid paralysis/myelitis was observed during the outbreak, and 120 cases of acute flaccid myelitis were recorded [28–30]. In Europe, an increase in the number of EV-D68 infections and occasional acute flaccid myelitis cases were also reported, and phylogenetic analysis showed that most of sequences obtained belonged to clade B3 [31]. The MRI may detect hyperintense non-enhancing gray matter lesions in the brainstem and spinal cord in the affected children [30].

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 viruses such as dengue virus, Zika virus, chikungunya virus, Japanese encephalitis virus, yellow fever virus, West Nile virus (WNV), and Murray Valley encephalitis virus, and tick-borne virus. Flaviviruses are a cause of encephalitis in the tropics, but they

have been associated with a flaccid poliomyelitis-like syndrome [32, 33]. Acute transverse myelitis following Japanese encephalitis virus infection and myeloradiculopathy associated with chikungunya virus infection have also been described [34, 35].

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-related polio-like syndrome. MRI of the spinal cord may show marked contrast enhancement of the affected nerve roots in flavivirus polyradiculitis [36]. 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 [32].

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 [37]. 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 [38].

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 [37].

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 immunoglobulin M (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 [39], 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 [40]. 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 [41].

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, and 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 [42].

Spinal cord involvement following DENV infection has been reported during the infectious and post-infectious stages [43–46]. Direct virus invasion and immune-mediated factors are pathogenic mechanisms involved in each one of these stages, respectively [47]. Post-dengue acute transverse myelitis may present as acute weakness and numbness of the lower limbs and urinary retention. Longitudinally extensive transverse myelitis associated with dengue fever has also been reported [48].

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 has been detected in dengue myelitis patients [49]. Spinal cord MRI may be normal or show high signal areas in T2-weighted imaging. Therapy is supportive.

Zika virus

Zika virus is a new emerging virus that has spread in the Americas since 2015. The World Health Organization declared the recent clusters of microcephaly, Guillain-Barré syndrome (GBS) and other neurological complications, a Public Health Emergency of International concern. Cases of meningoencephalitis, myelitis, and acute disseminated encephalomyelitis have been reported in patients with Zika virus infection [50, 51].

GBS may mimic a transverse myelitis, and most patients present with rapidly progressive weakness and areflexia of lower limbs. The presence of cytoalbuminologic dissociation on CSF and the absence of cutoff sensory level on clinical examination support the diagnosis of GBS. A case-control study performed in French Polynesia during the 2013–2014 outbreak showed a strong association between Zika virus infection and GBS [52]. Similar findings were reported in the 2016 outbreak in Colombia and other South American countries [53].

The first case of acute myelitis due to Zika virus infection was described in a 15-year-old girl in Guadeloupe [54]. The patient presented with back pain, paresthesias, and weakness in the absence of fever or meningism. Reverse real-time PCR

(rRT-PCR) detected Zika virus particles in serum, urine, and CSF 9 days after symptom onset. The MRI of the brain was normal, and the spine MRI showed enlargement of the cervical spinal cord and areas of hyperintensity in cervical and thoracic spine.

Diagnosis of Zika virus infection can be done in those patients presenting with a suggestive clinical picture (fever, itchy rash, conjunctivitis, muscle or joint pain) and a positive rRT-PCR, either in serum or urine. However, a negative rRT-PCR in blood does not rule out Zika virus infection, mainly when it is performed 2 weeks after the initial infection. In these cases, urine PCR or serological tests may be needed to determine evidence of Zika virus infection. Cross-reactivity between dengue, Zika, and chikungunya viruses has been described, and paired plaque reduction neutralization test on serum may be helpful to distinguish Zika virus from another recent flavivirus infection [55].

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 [56].

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 and young adults [56]. Recently, a case of a 18-year-old male who presented with upper limb weakness and rapidly evolving to quadriplegia has been reported. The MRI of the spine showed diffuse edema and myelitis affecting the cervical spinal cord, and the PCR for HSV1 was positive in CSF [57]. Follow-up MRI confirmed a cystic myelomalacia.

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 [58, 59]. 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 [60]. 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 [58].

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 [61].

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 [62, 63].

VZV infections of the CNS have been increasingly reported in highly active multiple sclerosis patients treated with the new modern drugs used as second-line therapy for the prevention of relapses such as fingolimod and natalizumab. Cases of VZV myelitis in multiple sclerosis patients treated with the monoclonal antibody natalizumab [64] have been published. The more severe cases [65] presented with longitudinally extensive myelitis that resembled the appearances observed in neuromyelitis optica.

Rare cases of VZV myelitis of the cervical spinal cord in immunocompetent patients have also been reported [66]. Varicella myelitis is very rarely observed in healthy adults [67].

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 [68].

Cytomegalovirus

Cytomegalovirus is an opportunistic infection that 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/μL [69]. CMV polyradiculopathy has also been reported in solid-organ transplant recipients [70]. Less frequently, a necrotizing myelitis in the absence of radiculitis may occur. Patients present with acute ascending flaccid paralysis of the lower limbs and sphincter dysfunction. The MRI detects clumping and thickening of the cauda equina with areas of enhancement. [71]. Nodular leptomeningeal enhancement from lower thoracic cord, extending along the conus medullaris and lumbosacral nerve roots, has also been observed on MRI [72].

Cytomegalovirus can reactivate in the CNS in immunosupressed patients such as organ transplant recipients. CMV transverse myelitis, although rare, has been reported, and in a review of nine cases, the cervical and thoracic spinal cord were frequently affected [73]. Rare cases have also been described in immunocompetent patients [74, 75]. CMV transverse myelitis may be followed by immune-mediated disseminated encephalomyelitis [76].

Pleocytosis and elevated protein concentration can be seen on CSF [75, 77]. PCR has been found to be the most reliable method for the diagnosis of CMV myelitis. Spinal cord MRI usually shows high T2 signal in the central portion of the spine, spinal cord and root 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 [78–80]. Primary Epstein-Barr virus infection presenting with polyradiculitis has also been described in immunocompetent adults [81].

CSF is usually inflammatory, with mononuclear pleocytosis in 80% of cases, and 70% have abnormal MRI findings [82]. 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 [83].

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 [84].

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 [85]. 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 [86].

Tuberculous myelopathy may develop as a secondary extension of vertebral body tuberculosis (Pott's 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 [87].

Pott's 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 cord involvement in tuberculous meningitis is common. In a prospective study of 71 consecutive tuberculous meningitis cases, 46.4% had signs and symptoms of spinal cord and nerve root involvement. Paraparesis was present in one third of cases. Meningeal enhancement on spinal MRI was detected in more than half of patients, and in one third enhancement was present in the lumbosacral region. Raised CSF protein >250 mg/dl was a significant predictor associated with myeloradiculopathy [88].

Spinal forms associated with 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 [89, 90]. Longitudinal extensive transverse myelitis due to tuberculosis has also been reported [91].

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 [92]. 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's 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 [87].

Early diagnosis and treatment are 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 [93].

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 [94].

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* [95].

Other less common spinal cord neurosyphilitic syndromes are hypertrophic pachymeningitis, motor neuron disease associated with 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 (FTA-ABS) test, are used to exclude the diagnosis of neurosyphilis. FTA-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 [96].

Tabes dorsalis should be treated with intravenous aqueous penicillin (four 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 the 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 [96, 97].

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 [98]. Data from a 10-year clinical experience at a tertiary center showed that incidence increased from 2.5 to 8.0 per 10,000 admission, a 3.3-fold change from 2005 to 2015 [99]. 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% [98]. 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 [100].

Risk factors associated with epidural abscess include spinal abnormality, spinal trauma, spinal surgery or procedure, immunosuppression, diabetes mellitus, alcoholism, hemodialysis [101], 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 [102].

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.

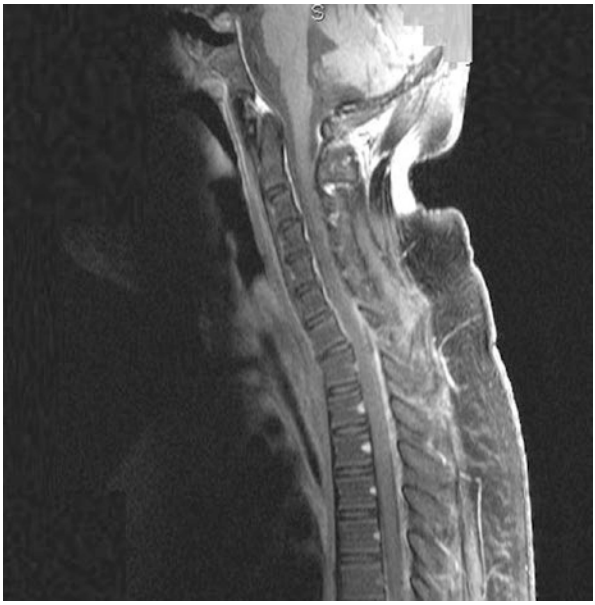

Fig. 10.2 Spinal cord MRI, T1-enhanced weighted imaging. Epidural cervical abscess with diffuse enhancement of contrast

Once diagnosed, patient should perform emergent surgical drainage and debridement, spinal decompression, and prolonged antibiotic therapy for 6–8 weeks. 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 [100].

Other Pyogenic Infections of the Spine: Brucellosis

Brucellosis is an infection caused by *Brucella melitensis* that is endemic in the Mediterranean area and Middle East countries. Brucellosis can be transmitted by contact with blood and secretions of infected animals or consumption of cheese and unpausterized milk. 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 [103, 104]. Clinical symptoms are unspecific and include night sweats, fever, and lumbar back pain [105]. Brucella infection of the thoracic vertebral arch presenting with an epidural abscess has also been described [106]. 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 [107].

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 perforates the skin of human beings and through lymphatic and hematogenous spread settles 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*) [108].

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 [109]. 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 schistosomiasis (Fig. 10.3). *S. mansoni* and *S. haematobium* eggs are larger than

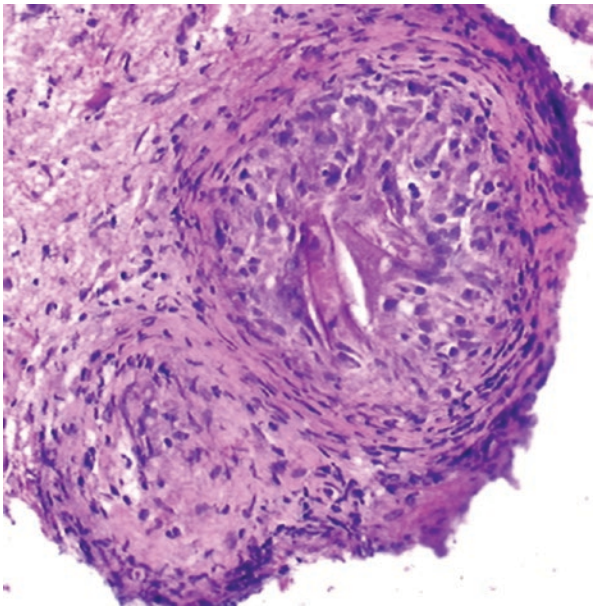

Fig. 10.3 Spinal cord biopsy of a patient with schistosomal myelopathy showing several granulomas around *S. mansoni* eggs

the *S. japonicum* ones and are retained much more frequently in the spinal cord. The higher size of *S. mansoni* ova, 60 μm in width by 150 μm in length, and its lateral spine may limit their progress along the vertebral venous plexus to the brain [108].

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 [108].

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 [109, 110].

Cauda equina 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 [110].

Less frequent clinical pictures are painful radiculopathy, chronic asymmetric myeloradiculopathy, cervical intramedullary schistosomiasis, and spinal cord compression due to extra-axial granulomas [108].

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 [111] (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 [112].

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.

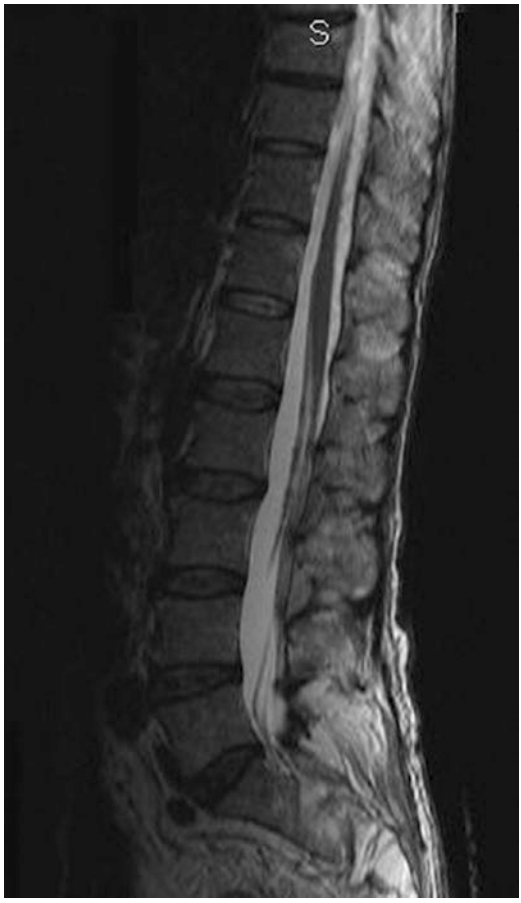

Fig. 10.4 Lumbosacral MRI of a patient affected by a schistosomal myeloradiculopathy showing arachnoiditis and adherence of the lumbar and sacral roots

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 equina 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 the 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

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 [107]. 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 [109].

Combined therapy with steroids and praziquantel is used to treat acute schistosomal myelopathy [113]. 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 tumorlike 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 [114]. 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 (500–2000 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 [115].

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 [116]. Many of these patients may have an already known intracranial neurocysticercosis in which a migration of subarachnoid cyst from the basilar cisterns has occurred. Intradural extramedullary primary spinal cysticercosis may mimic an arachnoid cyst [117].

Intramedullary cysts are much less common [1], and isolated intramedullary spinal neurocysticercosis is very rare [118, 119]. 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 throughout Adamkiewicz's artery [120].

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 of the subarachnoid space 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 [116].

CSF may show eosinophilia and increased protein concentration. MRI in intramedullary neurocysticercosis may show a ring-enhancing cystic lesion surrounded by edema [120]. Spinal cysticercosis should be treated with steroids and albendazole, although decompressive surgery may be needed to treat compressive arachnoiditis [121].

Hydatid Disease

Hydatidosis, the cystic infection caused by the cestode *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 mostly the extradural extramedullary space; intradural and intramedullary echinococcoses are even rarer [122]. 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 hydatid intervertebral cysts with a bunch of grape appearance, expansion and destruction of bony elements, and extension into the extradural space and paravertebral soft tissues [122]. Serological analysis may confirm the diagnosis. Prognosis is poor due to high recurrence index, and treatment is based on albendazole plus spinal decompressive surgery [123].

Other Parasitary Diseases

In China, paragonimiasis can cause myelopathy due to extradural compression or less frequently due to intramedullary granulomas [124]. 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 [125]. Toxoplasmosis of spinal cord has been described in AIDS patients presenting as paraparesis [126]. The MRI may show T1-isointense intramedullary lesions that enhance gadolinium on post-contrast sequences [127]. Acute

disseminated encephalomyelitis associated with acute *Toxoplasma gondii* infection has also been reported in immunocompetent children [128].

Visceral *larva migrans* syndrome due to *Toxocara canis* or *Ascaris suum* infection has been reported to cause myelitis in Japan [129–131].

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 and lymphoma, hematopoietic stem cell transplant recipients, and those suffering from AIDS and 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 [132].

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 have 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 [133]. Invasive aspergillosis may provoke a meningovascular infiltration and a necrotic endarteritis with thrombosis and ischemia leading to vessel occlusion and spinal cord infarctions. Aspergillus angioinvasive nature usually results in vascular occlusion or vasculitis [134]. Aspergillus vertebral osteomyelitis may cause intramedullary abscess [135].

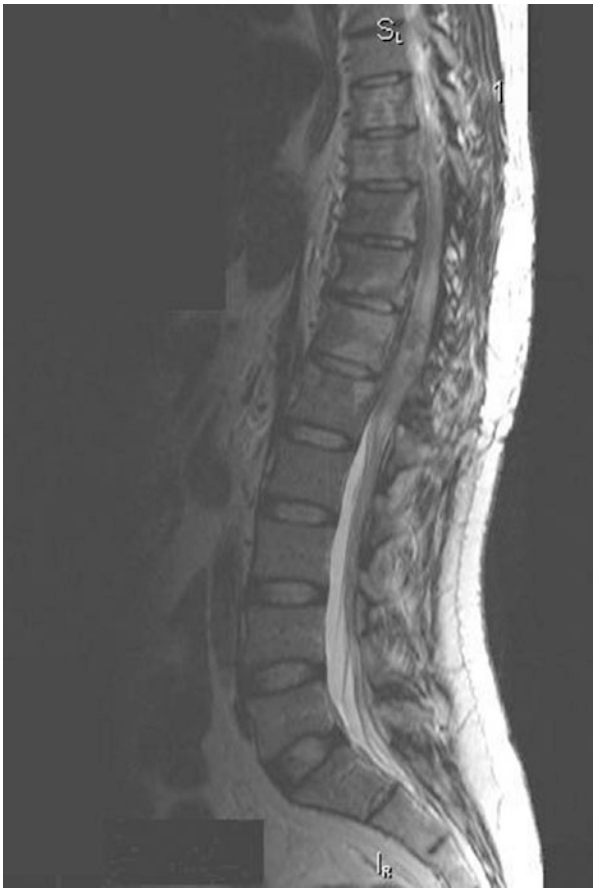

Fig. 10.5 Spinal cord MRI, T2-weighted imaging of a patient affected by chronic fungal spinal infection due to *Scedosporium prolificans*

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 [136].

Candida albicans can also provoke intramedullary, vertebral, and paravertebral abscesses. Epidural abscess caused by *Candida albicans* has been reported in chronic renal failure patients [137]. However, *Candida albicans* spondylodiscitis and subdural spinal granuloma may occur in healthy people [138–140].

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 [141]. Intramedullary cryptococcomas of the spinal cord may resemble a spinal tumor [142]. Cryptococcus myeloradiculitis has also been reported in HIV-infected patients.

Blastomycosis can also imitate vertebral tuberculosis, provoking osteolytic injuries, abscesses, granulomas, and compressive meningitis of the spinal cord [143]. Intramedullary blastomycosis has also been described in children [144]. *Coccidioides immitis* is a dimorphic fungus common in Central and South America. Coccidioides infection can provoke chronic meningitis, tumorlike lesions, hydrocephalus, and spinal arachnoiditis. Coccidioidomycosis can provoke destructive lesions of the vertebral bodies and formation of paraspinal granulomatous masses [145].

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. New diseases such as enterovirus D68 and Zika virus infections have appeared recently. Teaching programs in neuro-infection and tropical neurology are needed, and they should cover this particular topic.

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The Human Borreliosis: Lyme Neuroborreliosis and Relapsing Fever

11

John J. Halperin and Juan Carlos García-Moncó

Abstract

Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi*, infects the nervous system in up to 15% of patients. Involvement can include the peripheral nervous system, with a mononeuropathy multiplex manifest as a radiculopathy, cranial neuropathy, plexopathy, or confluent mononeuropathy multiplex. In most instances, central nervous system involvement is limited to meningitis; rarely the spinal cord or brain parenchyma can be involved. Recent work has shed light on the pathophysiologic sequence that results in neuroborreliosis, including early CNS invasion, CXCL13-stimulated B cell entry into and proliferation within the CNS, and then a prominent immune response that requires ongoing presence of organisms. Pathophysiology of peripheral nerve involvement is not well established although it similarly requires the presence of viable organisms. Future work should focus on the mechanisms of tissue injury. Regardless of the presentation, infection is highly responsive to antimicrobial therapy.

Relapsing fever is another human borreliosis caused by a variety of *Borrelia* species and transmitted by lice (epidemic form) or ticks (endemic form). Both are characterized by recurrent spirochetemia and can cause neurological complications similar to Lyme neuroborreliosis. Diagnosis is made by the direct observation of the spirochetes in peripheral blood during febrile episodes and by PCR. Tetracycline therapy is used.

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Introduction

Much like syphilis—and neurosyphilis—which achieved near mythological status during the centuries it ran rampant in Europe, Lyme disease is often thought to be an undiagnosable, incurable illness that will inexorably reduce its unfortunate victims to cognitive cripples. With syphilis, this misperception could be explained by the then very limited understanding of pathophysiology, particularly as it pertained to nervous system diseases. Until the advent of reaginic tests and antibiotics, syphilis was indeed often very difficult to diagnose and virtually impossible to treat. How is it then that in this age of molecular diagnosis and effective antimicrobial therapy so many misperceptions persist concerning Lyme disease—among patients and even many physicians?

To understand Lyme disease—the multisystem infection caused by the tick-borne spirochete *Borrelia burgdorferi*—and its nervous system manifestations, it is important to appreciate not only what has been learned about the illness and its pathogenesis but also the historical context that has resulted in current misperceptions.

History

The term "Lyme disease" was coined to describe what appeared to be an outbreak of juvenile rheumatoid arthritis in Lyme and Old Lyme, Connecticut [1]. Importantly from a historical perspective, the unusual nature of this outbreak was initially recognized not by an astute epidemiologist or physician but by the parents of affected children, who declined to accept their physicians' diagnoses and appealed to both the Yale School of Medicine and the Centers for Disease Control. This then triggered a series of epidemiologic, entomologic, and clinical studies leading to the recognition that the arthritis was associated both with bites by hard-shelled *Ixodes* ticks and the development of an unusual rash. Further studies led to the observation that the same tick bites and rashes could be associated with a neurologic triad [2] and occasionally with heart block. Ultimately this led to the isolation and identification of *B. burgdorferi* as the causative agent [3–5].

Several years before these investigations began, a Wisconsin dermatologist identified the same rash in a patient bitten by a wood tick; recognized the rash as erythema migrans (EM), long described in the European literature; and treated the patient successfully with penicillin [6] as had been customarily done in Europe since the 1950s [7].

The European history of this infection actually goes back to early in the twentieth century, with early characterizations of EM—ironically, perhaps, in a journal of dermatology and syphilology [8]. Of historical importance, the first extracutaneous manifestations recognized were neurological, with the description of a patient with painful radiculitis, meningitis, and EM following a tick bite [9]. The patient had a slightly positive reaginic test for syphilis; the authors conjectured that this was a tick-borne spirochetal infection and treated him successfully with neoarsphenamine. The syndrome was ultimately expanded to include both cranial neuropathies and joint symptoms. The perception from this 1922 report onward was that this was primarily a neurologic disorder.

It was only in the 1980s that the responsible microorganisms were identified as *Borrelia* spirochetes—*B. burgdorferi* sensu stricto in the USA; this species as well as *B. garinii* and *B. afzelii* in Europe (as well as several less commonly seen species) [10].

Disease manifestations appear to differ somewhat depending on the specific *Borrelia* species—although to some extent, this perception may be colored by an ascertainment bias since historically Lyme disease has been perceived to be a rheumatologic disease in the USA, while Garin–Bujadoux–Bannwarth syndrome is felt to be a neurologic one in Europe.

Diagnosis

Like syphilis, and unlike most other bacterial infections, diagnosis generally relies on demonstration of an antibody response to the causative organism, as direct microbiologic diagnostics are of limited sensitivity and availability. EM, and occasionally elements of Garin–Bujadoux–Bannwarth syndrome, can occur before a measurable antibody response has developed. In the case of EM, the appearance—in the appropriate context—is sufficiently characteristic that treatment should be initiated without even trying to obtain serologic results—particularly since the latter will be negative in over 50% of such patients [11]. This seronegativity should not be interpreted as a unique flaw in the laboratory tools available in Lyme disease but rather as the perfectly normal lag between antigen exposure and development of a detectable antibody response.

A number of misconceptions about serologic testing are common and contribute greatly to the "controversy" surrounding this infection. First, with the exception of the normal, very early seronegativity just described, "seronegative Lyme disease" occurs rarely if ever. Early reports of this [12] probably reflected shortcomings of the then available technology. Virtually all patients with symptoms attributable to Lyme disease, who have been ill for more than 4–6 weeks, should have positive serologic results.

Once a patient has developed an antibody response, this will usually continue to be evident for quite some time—reflecting the normal function of the humoral immune response. There is no reason to expect the antibody response to disappear at the end of curative treatment. Hence, the serology cannot be used as a measure of

treatment efficacy, and treating until the serology becomes negative is illogical. For the same reason, the presence of a positive serology can only be considered evidence of infection at some time in the past and not necessarily current infection. Taking antibiotics at the time the serum sample is obtained has no effect on the test results.

Recommended serologic testing involves a two-tier approach [13]. An initial screening test—typically an enzyme-linked immunosorbent assay (ELISA), but occasionally an immunofluorescent assay (IFA)—is used to measure total *B. burgdorferi-reacting* antibody, comparing this immunoreactivity to normal controls. This sensitive screening method can lack specificity. ELISAs to a specific antigen known as C6 have been proposed as an alternative initial test, particularly since the antigen is present in both North American and European *B. burgdorferi* strains [14]. Although the specificity of this as a single test remains unclear, a recent study suggests it may be more useful as a secondary confirmatory test in individuals whose conventional ELISA is borderline or positive [15].

Until this finding is confirmed, though, Western blots—to determine the specific antigens that result in ELISA positivity—remain the recommended confirmatory assay in such individuals. Western blots are rarely informative in patients whose ELISAs are negative—the signal to noise ratio of the background reactivity makes it very difficult to judge the significance of any bands that might be present in such a situation. The criteria for interpretation of Western blots (Table 11.1) are based on statistical analyses of large numbers of samples, to determine which combinations of bands have the greatest positive predictive value for a correct diagnosis. Interpretation is not based on the presence of any single unique bands that in and of themselves make the diagnosis likely.

Western blots are performed separately for IgG and IgM antibodies. Studies have demonstrated that patients with five or more of ten selected IgG bands (Table 11.1) almost certainly have been infected with *B. burgdorferi*. Such IgG bands should be demonstrable in essentially all patients with more than 4–6 weeks of symptomatic infection. IgM blots, interpreted based on the presence of two of three selected bands (Table 11.1), are only meaningful in the first 4–6 weeks, before the serologic response has evolved to produce IgG. IgM generally is far more cross-reactive than IgG. With a requirement of just two bands, there is considerable risk of false positives, particularly in patients with hypergammaglobulinemia due to any inflammatory state. Isolated IgM blot positivity in a patient with many months of symptoms should never be interpreted as evidence of ongoing *B. burgdorferi* infection.

Table 11.1 Western blot criteria for the serologic diagnosis of Lyme disease, applicable only if ELISA (or IFA) positive or borderline [13]

	IgM	IgG
Bands tested (kD MW)	24, 39, 41	18, 21, 28, 30, 39, 41, 45, 58, 66, 93
# needed for Dx	Any 2 of 3	Any 5 of 10
Applicability	Only in first 4–6 weeks of disease	Required if symptoms > 4–6 weeks duration

Intrathecal Antibody Production

Although the innate, humoral, and cell-mediated arms of the immune system all play important roles in the host response to this infection, the humoral response is quite prominent. This is particularly apparent when infection involves the central nervous system (CNS). Since normally only a small amount of peripheral blood immunoglobulin enters the CNS, and since the CNS behaves as an immunologically distinct compartment, to which antigen-specific B cells migrate and then proliferate, measurement of CSF antibodies can be quite informative. The prominent intrathecal humoral response often results in an increase in total CSF IgG concentration, reflected in an increased IgG synthesis rate or IgG index. Because this increased synthesis is directed at a small number of antigens, oligoclonal bands may be evident, a finding reported more frequently in patients infected with European strains. This added production of antibodies specific to the antigens of the infecting organisms allows a particularly helpful diagnostic tool. In many patients with CNS infection, the proportion of CSF IgG specific to *B. burgdorferi* exceeds that in serum, allowing a calculation of intrathecal production of specific antibody by comparing CSF and serum immunoreactivity [16–18]. This measure of intrathecal antibody production (ITAb) has high specificity for CNS Lyme disease infection. False positives occur with neurosyphilis, but this can usually be distinguished by measuring CSF reaginic antibodies, such as the VDRL or RPR, which occur rarely if ever in neuroborreliosis. In theory, relapsing fever, another *Borrelia* infection, could produce cross-reactions, but there is so little geographic overlap between these infections that this is rarely an issue. The one problematic "false positive" is that apparent ITAb may persist for years after successful eradication of the CNS infection [19], presumably as antibody production in the CNS and the periphery gradually decline in parallel.

The greater concern with this measure is with its sensitivity. European studies, which historically required the presence of ITAb to confirm the diagnosis of CNS neuroborreliosis, not surprisingly find sensitivity to be nearly 100%. A recent European study found intrathecal production of IgG antibody in 89% of patients with neuroborreliosis [20], similar to the finding of an older small US study of acute neuroborreliosis [21]; however in more chronic syndromes estimates have been closer to 50% [22]. One of the challenges in defining sensitivity is the absence of an alternative, more definitive diagnostic test for CNS neuroborreliosis. As a result, some patients included in these studies may not have actually had CNS infection. Since there is no reason to think ITAb would need to be present in patients with peripheral nerve involvement, or in those with an infection-related encephalopathy, the implications of these observations are unclear.

Clinical Phenomenology

Both EM and the neurologic triad of meningitis, cranial neuritis, and radiculoneuropathy occur commonly in both European and US patients. EM, which occurs in

up to 90% of infected children [23], typically consists of a single erythroderm arising at the site of a tick bite. Unlike an acute allergic reaction to tick saliva, which appears almost immediately, EM appears days to at most a month after the bite. Its hallmark is its slow expansion, day by day, ultimately becoming many inches in diameter (minimum of 2 in. for CDC diagnostic criteria). The rash, which results from spirochetes slowly migrating centrifugally from the initial site of inoculation, can be remarkably asymptomatic. If not in a readily visualized location, it may go unnoticed. In some patients spirochetes disseminate hematogenously from the initial locus, seeding remote cutaneous sites where secondary EMs can develop. This occurs in about a fourth of US patients, a smaller proportion in Europe.

B. afzelii causes an unusual late cutaneous manifestation in European patients, known as acrodermatitis atrophicans, in which the skin, typically of a distal extremity, becomes tissue paper thin and discolored. This disorder has not been recognized in patients infected in the USA. Even though Bannwarth's paper on the neurologic disorder that bears his name included the term "rheumatism" in its title [24], joint involvement has been considered the hallmark of US Lyme disease, felt to occur in up to 85% of patients not treated early in the infection. This arthritis is distinctive in that it preferentially affects single large joints, which spontaneously become red and swollen and then gradually improve. Over the course of the illness, different joints are affected, seemingly at random.

Cardiac involvement, which generally occurs quite early in infection, typically consists of conduction abnormalities. In severe cases it can include complete heart block, requiring a temporary pacemaker. This almost invariably resolves with antibiotic treatment. Occurring in about 5% of patients in early US series, this is now felt to occur even less commonly.

Neurologic Manifestations

Overall, CNS or peripheral nervous system (PNS) involvement occurs in 10–15% of infected patients [25]—a number that appears to be similar in both Europe and the USA. The classic three manifestations—meningitis, cranial neuritis, and radiculoneuritis—typically occur quite early in infection [26]. Since ticks feed from spring through fall, this is when these are most likely to present. Each element of the triad presents its own diagnostic challenges. Meningitis, which may occur in isolation or in association with either or both of the other two elements, varies widely in its symptomatology. Some patients have severe headache, photosensitivity, and neck stiffness—with or without inflammation in the cerebrospinal fluid (CSF). Other patients with cranial neuritis may have a substantial CSF pleocytosis with no meningeal symptoms. When abnormal, the CSF typically shows a modest lymphocyte-predominant pleocytosis (up to several 100 WBCs/mm^3), mildly increased protein, and normal glucose. There may be evidence of local production of anti-*B. burgdorferi* antibodies within the CNS—i.e., disproportionately increased *Borrelia*-specific antibodies (ITAb). In patients in whom CNS inflammation has been present for a

longer period of time, particularly with European strains of *Borrelia*, there may be sufficient overproduction of immunoglobulins that patients have both increased total IgG in the CSF (increased IgG synthesis rate or IgG index) and even oligoclonal bands.

Since Lyme meningitis and enteroviral meningitis often occur in similar locations at similar times of year, several algorithms have been proposed to try to differentiate between these entities. The common thread is that Lyme meningitis tends to have a more indolent evolution and a more strongly mononuclear cell pleocytosis [27–29]. The most compelling differentiating element is the presence of an associated VII nerve palsy, which virtually never occurs in viral meningitis. Unfortunately, the other criteria overlap so extensively that they are not terribly helpful.

Cranial neuropathies are probably the most common presenting neurologic sign (as meningitis may be asymptomatic). The facial nerve is the most commonly involved; Lyme disease is one of the few disorders associated with bilateral facial nerve palsies (others including sarcoidosis, HIV, other basilar meningitides, Guillain–Barré syndrome). In endemic areas, Lyme disease-associated facial nerve palsy (LAFP) may be the cause of about a quarter of cases of facial nerve palsy [30]. As with meningitis, a number of authors have attempted to develop algorithms to differentiate between LAFP and Bell's palsy; these have emphasized the greater likelihood of a CSF pleocytosis with LAFP [31] and the more frequent co-occurrence of other neurologic signs or symptoms, elements which may be helpful but are not sufficiently compelling to obviate the need for laboratory support for the diagnosis.

Other cranial nerves can be involved in neuroborreliosis, but substantially less commonly. Nerves III, IV, and VI are involved occasionally, as are V and VIII, each causing the expected symptoms. Optic nerve involvement has been reported, but most case reports are not compelling [32]. Involvement of nerves IX–XII is reported rarely.

Peripheral nerve involvement occurs with some frequency. As described by Garin and Bujadoux, this can involve striking radicular pain, mimicking a mechanical radiculopathy, typically involving one or a few dermatomes. Weakness and atrophy can be far more impressive than sensory loss. The frequency of this disorder is difficult to estimate as symptoms are probably frequently misdiagnosed as mechanical in origin and testing not performed. Patients may present as plexopathies, mononeuropathies, mononeuropathy multiplex, or even as an apparent diffuse polyneuropathy. Notably, all—including most cranial neuropathies—probably represent varying manifestations of a mononeuropathy multiplex [33, 34]. Biopsies consistently demonstrate perivascular inflammatory infiltrates with neither vessel wall necrosis nor unambiguous evidence of spirochetes or their antigens [35–39].

Parenchymal CNS involvement occurs rarely and has been reported primarily in patients infected with European strains. Least rare is involvement of the spinal cord at the affected segmental level in Garin–Bujadoux–Bannwarth radiculitis. More rarely patients develop parenchymal brain involvement, presenting with focal

symptoms and findings consistent with the location [40, 41]. This disorder appears to affect white matter more often than gray, rarely causes seizures, and can occasionally cause MRI abnormalities similar in character to those seen in demyelinating disease, but without the same anatomic predilection [16].

In the past several years, two additional *Borrelia* pathogens have been identified. *B. miyamotoi* causes a relapsing fever like illness and has been identified in patients and ticks in the USA [42] and Europe [43]. A single immunocompromised patient from Germany apparently developed *B. miyamotoi* meningitis. *B.mayonii* has been isolated from a small number of patients thought to have been infected in Minnesota or Wisconsin [44]. Five of the six reported patients had an acute febrile illness, four with rash. One was afebrile with knee arthritis; to date none has had any neurologic maniferations.

Lyme Encephalopathy

Probably the disorder responsible for more of the confusion and controversy related to Lyme disease than any other is the phenomenon usually referred to as Lyme encephalopathy. Originally described in patients with other clear evidence of Lyme disease, e.g., arthritis, cardiac conduction abnormalities, and acute neuroborreliosis, the earliest studies indicated that this was probably not caused by CNS infection but rather was analogous to the "toxic metabolic" encephalopathy occurring in most other infections and inflammatory states—from urinary tract infections and pneumonia to acute flares of rheumatoid arthritis [16, 45, 46]. However, three incorrect assumptions rapidly entered the discussion and have been virtually impossible to eradicate. First was that this disorder—consisting of difficulty with mental processing, memory and other cognitive functions—was indicative of a CNS infection. Second was the sense that this was in some way specific to Lyme disease. Third was the notion that it was sufficiently specific for Lyme disease that these symptoms, in and of themselves, were evidence of active neuroborreliosis in need of treatment, regardless of any other clinical, laboratory, or epidemiologic considerations. The last has, in turn, resulted in the notion of post-Lyme disease syndrome, patients who have fatigue and cognitive symptoms following what should be microbiologically curative treatment for Lyme disease.

Numerous studies of "Lyme encephalopathy" have shown that intrathecal antibody production or even other, less specific markers of CNS infection such as a CSF pleocytosis are neither necessary nor sufficient for this diagnosis [47]. Unfortunately, the observed lack of ITAb in these patients, coupled with the misperception that this state is necessarily due to CNS infection, probably contributed to the conclusion that ITAb is an insensitive measure of CNS infection. No studies have identified unique biologic or neuropsychologic markers that differentiate between Lyme encephalopathy and other toxic metabolic encephalopathies.

Finally, the notion of post-Lyme disease syndrome (or encephalopathy) is itself suspect. First and foremost, it does not appear to be associated with neuroborreliosis

[48]. Uncontrolled trials have emphasized that these symptoms persist in about 40% of treated patients [49, 50], a number confirmed in some trials that include control groups. However, the latter studies have found a comparable frequency of symptoms in controls—both in children [51] and in adults [52]. Other controlled trials have found a similar rate of subjective symptoms among patients previously treated for Lyme disease [53], a rate higher than that in the included control group, but no difference in objective abnormalities when these individuals are compared to controls. Others have found lower rates of subjective symptoms in treated patients, with these lower rates indistinguishable from that in controls [54]. Since it is clear that these symptoms occur in large numbers of otherwise healthy individuals [55] and since the popular perception that these symptoms persist following Lyme disease is so ubiquitous, leading patients and others to assume a causal relationship, it seems quite plausible that "post-Lyme disease syndrome" is primarily due to anchoring bias and is not a real entity.

Pathophysiology

Much has been learned about the pathophysiology of neuroborreliosis in recent years. It has long been clear that *B. burgdorferi* can cross the blood–brain barrier very early in infection [56–58]. *B. burgdorferi* bind to brain microvascular endothelial cells [59] and then cross the blood–brain barrier in a process that requires metalloproteinases and plasmin [60]. Strains of *B. burgdorferi* vary in their ability to accomplish this [60]. Once inside the CNS, *B. burgdorferi* appear to trigger the production of CXCL13 in endothelial cells and microglia. This cytokine then induces B cell in-migration and proliferation [61].

One of the conceptual challenges has always been the great difficulty in finding evidence of spirochetes in CSF or tissue from patients with known CNS *B. burgdorferi* infection. Even polymerase chain reaction (PCR)-based techniques only detect spirochetes in a small percentage of CSF samples from patients with known Lyme meningitis [56, 62]. Yet the consistent improvement in symptoms with antibiotic treatment seems to provide compelling if indirect evidence of the requirement for viable organisms in disease pathogenesis. The alternative hypothesis that disease might be due to immune cross reactivity between *B. burgdorferi* and neural antigens [63, 64] has seemed less plausible based both on this rapid improvement with treatment and the corollary observation that patients recover from nervous system disease despite the persistence of most anti-*B. burgdorferi* antibodies. Although some studies have found evidence of *B. burgdorferi* in brain samples of experimentally infected animals [65], these studies have been unconvincing due to the possibility of CSF contamination. More recent work demonstrating organisms in dorsal root ganglia is perhaps the most suggestive evidence to date [66]. Other studies showing that microglia stimulated by *B. burgdorferi* might trigger oligodendroglia apoptosis [67] are intriguing, but the implication of this observation in neuroborreliosis is unclear, given the extreme rarity of CNS parenchymal infection.

Table 11.2 Treatment recommendations [70]

	Adult	Pediatric[a]
Medication, duration		
Parenteral (2–4 weeks)		
Ceftriaxone[b]	2 g/day IV	50–75 mg/kg/day
Cefotaxime	2 g q8/IV	150–200 mg/kg/day in 3–4 divided doses
Penicillin	20–24 million units IV/day	300,000 units/kg/day divided, every 4 h
Oral (3, possibly 4 weeks)		
Doxycycline[c]	100 mg PO b.i.d. To q.i.d.	4 mg/kg/day in 2 divided doses
Limited data but probably effective		
Amoxicillin	500 mg PO t.i.d.	50 mg/kg/day in 3 divided doses
Cefuroxime axetil	500 mg PO b.i.d	30 mg/kg/day in 2 divided doses

[a]Pediatric weight-based doses should never exceed the recommended adult dose
[b]Ceftriaxone should not be used late in pregnancy
[c]Doxycycline should not be used in pregnant women or children under the age of 8 years

Treatment

Fortunately, *B. burgdorferi* remains highly sensitive to widely available antimicrobials. Recommended treatment for cutaneous and other nonnervous system infections consists of oral amoxicillin, cefuroxime axetil, or doxycycline (Table 11.2). Although for many years parenteral penicillin, ceftriaxone, and cefotaxime have been recommended for nervous system infection, numerous European studies support the use of oral doxycycline for Lyme meningitis, cranial neuritis, and radiculoneuritis, with efficacy shown to be comparable to parenteral treatment in multiple controlled trials [68]. Although these studies have not, to date, been replicated in the USA, similar antibiotic sensitivities would strongly suggest efficacy of such regimens in US patients. No studies have addressed treatment specifically in those very rare individuals with parenchymal CNS infections, but by analogy to other brain infections, parenteral treatment would seem the most reasonable. Multiple studies have consistently shown that prolonged treatment—for more than 4 weeks—is rarely needed but carries significant potential for side effects [14, 69–71].

Relapsing Fever

Relapsing fever (RF) is a multisystemic borreliosis that occurs in epidemic (louse-borne) and endemic (tick-borne) forms and is caused by a variety of *Borrelia* species. The former is caused by *Borrelia recurrentis* and is transmitted by the human body louse *Pediculus humanus*, while the endemic form is transmitted by soft-bodied ticks, mostly of the genus Ornithodoros and caused by several different Old and New World *Borrelia* species. RF is found in Africa, Asia, Central and South America, southwestern North America, and the Mediterranean basin. Humans are

the main reservoir for the epidemic form, while several species of rodents are the reservoirs for the endemic species. With the current migrant crisis of nearly worldwide proportions, East African patients with relapsing fever have been increasingly recognized in parts of Europe [72, 73].

Neurological Manifestations of RF

In contrast to Lyme disease, where spirochetes in the blood are difficult to detect, RF is characterized by a recurrent spirochetemia that coincides with episodes of high fever and constitutional symptoms, such as headache, malaise, and myalgia. In time, the relapses of spirochetemia become shorter and less frequent. The recurrent nature of these borrelioses is due to a complex interplay of antigenic variation of the organisms and the immune system, notably, the antibody response [74].

The pattern of neurological and ocular manifestations of the relapsing fevers closely parallels and resembles those of Lyme disease [26, 75].

Studies of outbreaks of tick-borne RF have repeatedly shown that the neurological complications dominate the clinical picture. This clinical feature of relapsing fever has been known since the early twentieth century, when studies demonstrated that spirochetes were found in the cerebrospinal fluid of patients, thus providing definitive evidence of nervous system invasion.

The most common neurological manifestations of RF are meningitis and peripheral facial nerve palsy, followed by radiculitis, encephalitis, and psychiatric disturbances [75].

Neurological abnormalities are more common in tick-borne RF than in the epidemic form, with frequencies that greatly vary from one clinical series to another. Almost half of the patients affected by RF caused by *B. dutonii* in Africa presented meningismus [76], as compared with only 9% in another series [77]. Likewise, a variable degree of pleocytosis was present in the cerebrospinal fluid of 50–100% of patients with this type of neuroborreliosis [76], further underscoring the variable presentation of the relapsing fevers.

Encephalitis occurs occasionally in RF, sometimes accompanied by seizures and intense somnolence. Focal signs of central nervous system involvement such as hemiplegia and aphasia have been infrequently reported. Cranial nerve palsy, particularly of the seventh nerve, is common in tick-borne RF, usually appearing after the second febrile episode. Cranial palsies usually resolve spontaneously in several weeks, and this feature closely resembles the findings in Lyme disease. Little information is available about the cerebrospinal fluid findings in cranial palsy patients, but increased proteins have been noted. Radicular and spinal cord involvement may also appear, resulting in sciatic pain and sometimes paraplegia. Psychiatric problems include delirium and hallucinations in a variable degree of intensity [75].

Neuro-ophthalmological problems may also occur in tick-borne infections and include optic neuritis and uveitis. Eye involvement may be bilateral and almost always appears after several febrile episodes [78]. Sometimes it follows a relapsing course and may result in residual visual loss.

Diagnosis

The definitive diagnosis of relapsing fever is established by demonstrating the presence of Borrelias in the peripheral blood of febrile patients, in whom spirochetes are found in approximately 70% of cases by dark field microscopy or in Giemsa- or Wright-stained thick and thin smears [79]. Due to the high rate of antigenic variation of these organisms, serological assays based on antibody production are initially unreliable.

The polymerase chain reaction (PCR) is useful for the diagnosis of relapsing fever. It can be performed on blood samples or culture medium that is growing *Borrelia* species [80].

Treatment

Antibiotic therapy is employed in RF patients, not only to treat the neurological manifestations of RF but to prevent further febrile episodes. Systemic *louse-borne RF* fever is best treated with a single oral dose of 500 mg of tetracycline or 200 mg of doxycycline. A single oral dose of erythromycin (500 mg) is also effective and is indicated in pregnant women and children, in whom tetracycline should be avoided.

Intramuscular penicillin G procaine is an alternative (400,000–800,000 units). The recurrence rate after antibiotics is less than 5%.

Tick-borne RF fever is treated with oral tetracycline (500 mg every 6 h) or doxycycline (100 mg twice daily) for 10 days, since the relapse rate is higher (20%) and treatment failures are more common.

Erythromycin is an alternative in intolerant or allergic individuals, at a dose of 500 mg every 6 h for the same period.

When neurological manifestations are present, intravenous antibiotics are indicated, such as penicillin G (three million units every 4 h) or ceftriaxone (2 g once daily or 1 g twice daily) for at least 2 weeks or longer depending on the patient's response.

Rapid removal of large numbers of spirochetes from the circulation after antibiotic treatment requires that patients under therapy be monitored for the frequent appearance of Jarisch–Herxheimer reactions, which occur within 2 h of antibiotic administration and present with fever, shivering, and hypotension.

Pathophysiology

The laboratory mouse has been used to reproduce the neuroborreliosis of relapsing fever experimentally for many years. The presence of large numbers of motile spirochetes in the circulation could be a factor in the breakdown of the blood–brain barrier through waste products or mediators of inflammation so that penetration into

the CNS could be achieved more easily. Immunocompetent and immunodeficient mice have been infected successfully with both old and new world species of relapsing fever Borrelia. Infection of mice with subsequent neurological manifestations can be achieved through cutaneous inoculation, the route that reproduces transmission by ticks [81].

The most common neurologic manifestation in mice is meningitis with spirochetes detectable infrequently in the leptomeninges and in the cerebrospinal fluid. Despite the paucity of spirochetes in the brain, there is cerebral microgliosis that is more severe in immunodeficient mice. This finding emphasizes the role of the immune response in the development and severity of relapsing fever. Of note is the vestibular dysfunction of mice infected with relapsing fever Borrelia. While spirochetes have been observed in cranial and peripheral nerves, there are no studies documenting peripheral nerve disease in mice [5].

RF Borrelias are best known for the phenomenon of antigenic variation, which allows them to spontaneously change their serotype by switching the expression of variable major proteins (VMPs) of two sizes, large (Vlp) and small (Vsp). A switch in VMP allows RF Borrelias to escape killing by the host's serotype-specific antibody response. RF Borrelias persist in the brain after they disappear from the blood, a phenomenon known as residual brain infection (RBI) [82].

Borrelia Miyamotoi and Meningoencephalitis

Borrelia miyamotoi is another spirochete belonging to the RF taxonomic group and transmitted by ixodid ticks and hence potentially concurrent with the Lyme disease agent. This spirochete was responsible for a meningoencephalitis in an 80-year-old patient immunosuppressed as a result of non-Hodgkin's lymphoma who presented with progressive cognitive decline and weight loss [83]. He had had a previously treated erythema migrans and was resident in an endemic area for Lyme disease. Brain magnetic resonance imaging was normal, but his cerebrospinal fluid examination disclosed pleocytosis and increased proteins, and staining showed the presence of several spirochetes that were identified as *B. miyamotoi* by real-time polymerase chain reaction. Treated with intravenous penicillin, his status improved to normal. The authors concluded that the patient's illness was caused by *B. miyamotoi*. Since that case was reported, *B. miyamotoi* has been reported in association with meningoencephalitis [43, 84]. Additional patient series, however, did not show a prominent component of neurologic disease for infection with *B. miyamotoi* [85, 86]. However, both studies reported marked headache as a main symptom for their patients.

For many years, the relapsing fever Borrelias were thought to be transmitted exclusively by soft ticks, whereas the Lyme Borrelias were transmitted by hard ticks. *B. miyamotoi*, a relapsing fever Borrelia transmitted by a hard tick, suggests that these differences are not as clear-cut as once thought, particularly in areas where RF and Lyme Borrelia coexist [87].

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Neurosyphilis

12

Juan Carlos Salazar and Donald P. Rice Jr

Abstract

Syphilis is a sexually transmitted infection caused by the spirochetal bacterium *Treponema pallidum*, subspecies *pallidum*. During early syphilis, the spirochete has the ability to disseminate into the central nervous system and cause both symptomatic and asymptomatic meningitis and in more severe cases vasculitis leading to thrombosis, ischemia, and even death. During tertiary syphilis, the chronic inflammatory responses to the spirochete can severely compromise the brain parenchyma and the spinal cord, leading to paresis and tabes dorsalis. In this chapter we will review the clinical presentation, diagnostic criteria, and treatment modalities for neurosyphilis.

Keywords

Treponema pallidum • Neurosyphilis • Meningitis • Meningovascular syphilis Gumma • Paresis • Tabes dorsalis

Introduction

Syphilis is a sexually transmitted infection caused by the spirochetal bacterium *Treponema pallidum*, subspecies *pallidum* [1, 2]. Despite the existence of inexpensive and effective antibiotic treatment regimens, roughly 10.5 million new syphilis

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cases are estimated to occur yearly throughout the world [3]. The multistage clinical syndrome, generally associated with untreated syphilis, reflects the propensity of *T. pallidum* to disseminate systemically and to induce chronic inflammation in the skin, meninges, and various organ tissues [1]. Infection begins soon after the bacterium comes into contact with the skin or mucous membranes, multiplying locally over several days while simultaneously disseminating through blood and lymphatic vessels. The distinctive painless ulcer (chancre) of primary syphilis typically only appears 2–4 weeks after the initial infection. By this time, organisms have disseminated from the primary site of infection and invaded various organ tissues, most notably the skin, setting the stage for what is classically known as secondary syphilis. This period of the disease characteristically presents with a variety of dermal manifestations as well as a series of systemic signs and symptoms, appearing within 4–10 weeks of the initial infection and in some cases affecting the central nervous system (CNS). Despite the robust nature of the cellular and humoral immune responses typically associated with this stage of the disease, which include the appearance of high titers of anti-*T. pallidum* antibodies with opsonizing activity and robust mixed cellular infiltrate in skin lesions, several weeks to months may elapse before the host can gain control of the invading bacterial pathogen [4]. The period that follows is generally asymptomatic and referred to as latent syphilis. Classic studies demonstrate that up to 30% of latent syphilis patients will develop recrudescent and more complex forms of the disease, which are collectively referred to as tertiary syphilis [5]. The tertiary stage may involve any organ system but primarily affects the central nervous system (neurosyphilis) [6], the heart and vascular structures (aortitis/aneurysms) [7], and the skin and bones (gummatous syphilis) [7]. These complications can ultimately lead to death. In this chapter we will review the neurologic syndromes associated with both early and late venereal syphilis.

Causative Agent

T. pallidum belongs to one of five genera within the order *Spirochaetales*. The genera that are pathogenic for man include *Leptospira* (leptospirosis), *Borrelia* (Lyme disease and relapsing fever), and *Treponema*. Four human diseases are caused by members of the genus *Treponema*: venereal syphilis (caused by *T. pallidum* subspecies *pallidum*), endemic syphilis (*T. pallidum* subspecies *endemicum*), yaws (*T. pallidum*, subspecies *pertenue*), and pinta (*T. carateum*) [6, 8]. The spirochete is a microaerophilic bacterium, with a flat-wave morphology, varying from 6 to 20 μm in length and a diameter of 0.10–0.18 μm [8]. This ultrastructural feature places the bacterium below the resolution of conventional light microscopy, thus requiring its visualization by dark-field or phase-contrast microscopy (Fig. 12.1c). The spirochete has a central protoplasmic cylinder bounded by a cytoplasmic membrane with an overlying thin layer of peptidoglycan and a very interesting outer membrane [9]. Unlike the outer membranes of typical gram-negative bacteria, that of *T. pallidum* lacks the potent proinflammatory glycolipid lipopolysaccharide (LPS) [10]. The outer membrane of *T. pallidum* contains an

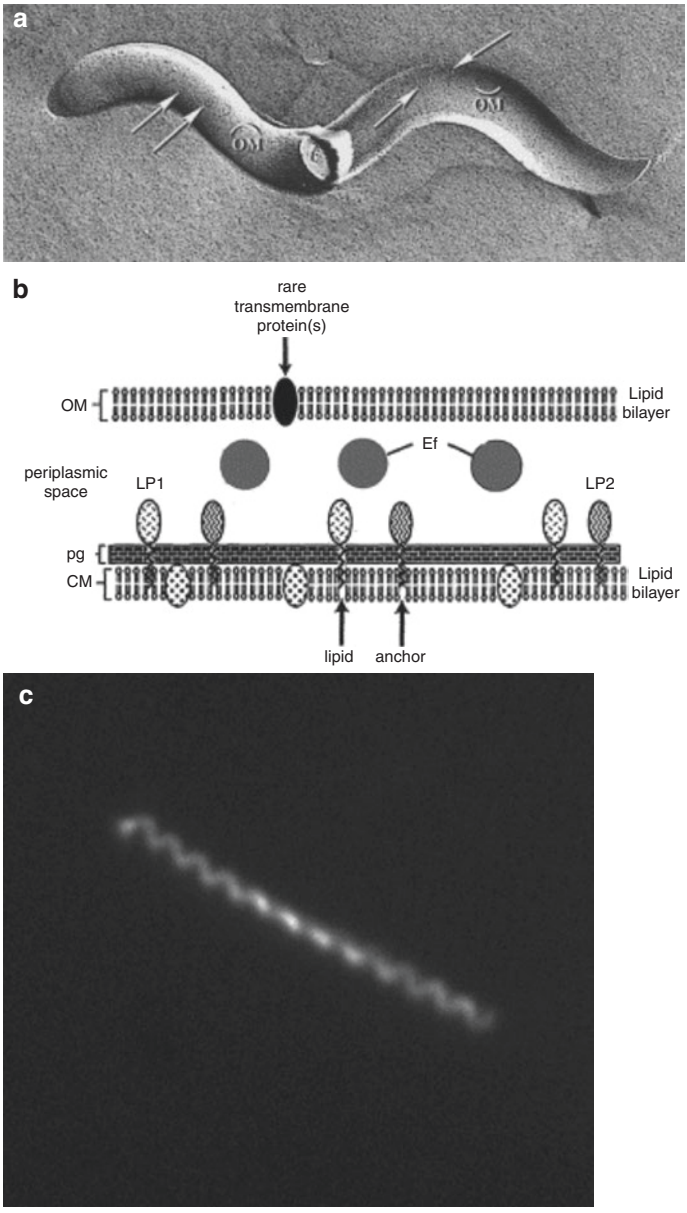

Fig. 12.1 (**a**–**c**) *T. pallidum* ultrastructure. (**a**) Membrane architecture of *T. pallidum* subspecies *pallidum*, as demonstrated by freeze-fracture electron microscopy. The figure shows the paucity of outer membrane (OM) transmembrane proteins. (**b**) Proposed molecular architecture of *T. pallidum*. The OM is depicted as having rare transmembrane proteins, while major immunogens are lipoproteins (LP1 and LP2) anchored to the periplasmic leaflet of the OM. The bacterium is also shown with periplasmic endoflagellum (*Ef*) and peptidoglycan (*pg*)-cytoplasmic membrane (*CM*) complex (Adapted with permission from Salazar et al. [2]). (**c**) Dark-field microscopy showing a single spirochete with its classic morphology (Courtesy of Carson Karanian in the Salazar laboratory)

extraordinarily low density of integral outer membrane proteins (OMPs) [11] (Fig. 12.1a, c), and the bacterium's abundant lipoproteins, a major pathogen-associated molecular pattern (PAMP), are located on the cytoplasmic membrane and not the OM [12–14]. The paucity of proteins and prototypical PAMPs on the spirochetal outer membrane is the basis for the bacterium's impressive capacity for immune evasion, thus its well-deserved designation by Radolf as a "stealth pathogen" [1, 2, 12, 13]. Two or three flagella, the organelles that allow the spirochete to move, originate at each end of the bacterium and twist around the body of the organism within a very thin periplasmic space. This configuration allows for the characteristic back-and-forth motility. *T. pallidum*'*s* genome is a circular chromosome of 1,138,006 base pairs and contains 1041 open reading frames (ORFs) [10]. The absence of plasmids, pathogenicity islands, transposable elements, and restriction–modification systems point out that the spirochete has little capacity for uptake of exogenous DNA, almost certainly explaining why the bacterium has not yet developed resistance to penicillin.

Epidemiology

According to the World Health Organization (WHO), in 2008, approximately 11 million people newly acquired syphilis, and 36 million were estimated to have active infection (new cases + existing untreated cases) [3]. Although venereal syphilis has reemerged in the United States and Europe since the 1980s [15–17], most individuals (>90%) who acquire syphilis reside in underdeveloped and poor regions of the world with poor access to health care [18]. The United States and Western Europe have seen a steady rise in primary and secondary syphilis from historically low rates since 2010. This rise is driven largely by increasing rates among men, particularly men who have sex with men (MSM). Information on neurosyphilis rates in the United States is limited, as this was removed as a reporting category in 2005 [19, 20]. In Eastern Europe and Russia, the social changes and disruption of medical services, which followed the breakup of the Soviet Union, led to marked increases in syphilis rates [21]. Prevention strategies subsequently led to a steady decrease in the overall disease burdens in this region of the world. By contrast, in China, a country where syphilis was virtually eradicated in the 1970s, there has been a dramatic resurgence of the disease in the last two decades [22]. The incidence of syphilis reported in China was 0.2/100,000 in 1993 [23], rising to an estimated 11.7/100,000 in 2009 [24]. This increase has been attributed to migration of large segments of the population from rural Chinese communities to large urban centers, limited syphilis screening practices, lack of adequate partner notification, and social barriers to accessing STD health-care services [25]. In China, as in other parts of the world, the incidence of neurosyphilis tracks the overall incidence of venereal syphilis in the general population, with a roughly 10–20-year delay in diagnosis.

The proliferation of antibiotics and their widespread use has changed the modified the neurologic clinical presentation of venereal syphilis, when compared to

historical controls. Symptomatic neurosyphilis, especially with detectable spirochetes in the CSF, is primarily seen during early syphilis. In addition, syndromes like syphilitic uveitis have become more common. On the other hand, late manifestations such as general paresis and tabes dorsalis are less common [26], and gummatous syphilis is now exceedingly rare [27].

It is important to highlight that the worldwide epidemiology of syphilis has also been greatly influenced by the HIV epidemic [28–30]. Early neurosyphilis is more common than late neurosyphilis and presents most frequently in patients with HIV. Although the association between syphilis and HIV infection does reflect similar behavioral risk factors for their acquisition and transmission, it is now known that complex biologic relationships between these two diseases contribute to high coinfection rates [31–33]. The presence of a syphilitic chancre can facilitate HIV transmission by increasing the host's susceptibility to infection with the virus and the HIV-infected host's infectiousness to discordant sexual partners. The former is associated with the disruption of the protective epithelial and mucosal barriers present in genital chancres and enrichment of the lesion with activated lymphocytes, macrophages, and dendritic cells, all of which are potential targets and donors for HIV [34–36] and which differentially increase expression of key HIV co-receptors (i.e., CCR5 and DC-SIGN) in untreated patients [36, 37]. With respect to increased infectiousness, *T. pallidum* is capable of inducing HIV expression of selective genes which can promote viral replication [38]. In untreated HIV–syphilis-coinfected patients, CD4 counts are measurably decreased and HIV viral load is increased [39]. There is a recently described increase in cases of syphilitic optic neuritis which raises the question of whether some syphilis isolates may have increasing tropism for this site [40].

Clinical Syndromes Associated with Neurosyphilis

CNS invasion by the syphilis spirochete can occur during any stage of the disease and can present with a variety of clinical syndromes (Fig. 12.2). Long-term follow-up studies conducted in the pre-antibiotic era provided evidence that up to 1/3 of all untreated syphilis patients developed neurosyphilis [5, 41]. In those individuals who developed neurosyphilis, 30% had asymptomatic meningitis [5, 41], 10% developed some form of meningovascular syphilis, 30% had tabes dorsalis, and 10% had paresis. The remaining patients had other forms of CNS disease, including optic nerve compromise and other cranial nerve neuropathies. The reality is that combinations of each of the clinical syndromes associated with neurosyphilis, including asymptomatic and symptomatic meningitis, meningovascular syphilis, and CNS parenchymatous compromise, occur very frequently [42]. In the modern era, asymptomatic and atypical presentations of neurosyphilis, so-called formes frustes, are increasing in relative frequency compared to the classic neurosyphilitic syndromes [26, 43]. The clinical spectrum of neurosyphilis presentations in adults will be described below.

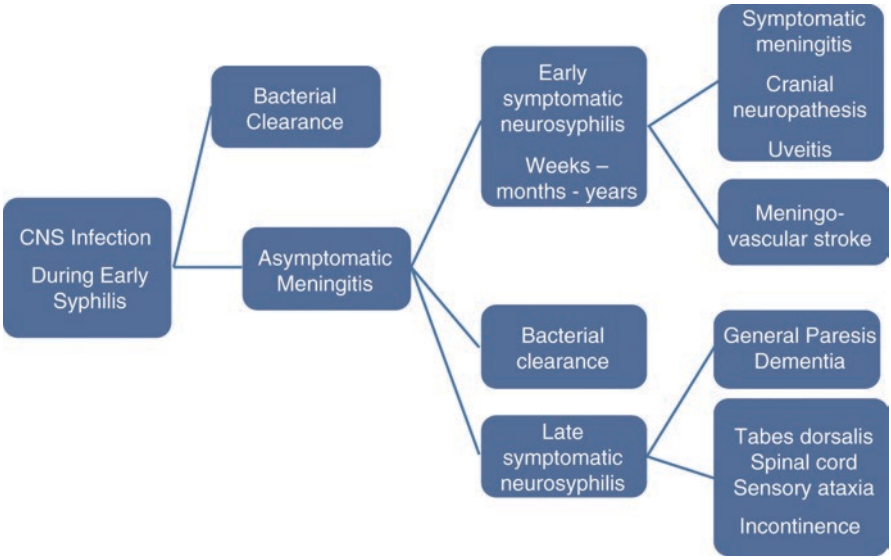

Fig. 12.2 Natural history and clinical syndromes associated with neurosyphilis

Asymptomatic Neurosyphilis

Asymptomatic neurosyphilis is classically defined and established by the presence of one or more abnormalities in the spinal fluid of a patient with confirmed venereal syphilis (generally primary or secondary syphilis) and with no clinical symptoms or signs of neurologic disease. CSF abnormalities include lymphocytic pleocytosis (typically < 100 cells/μL), elevated protein values (usually < 100 mg/dL), and/or a reactive CSF venereal disease research laboratory (VDRL) test. Rabbit infectivity (RIT) studies conducted in the 1920s and 1930s [5, 44–46], which were corroborated in the 1980s and 1990s [47, 48], established definitively that the CSF abnormalities seen in asymptomatic early syphilis patients are indeed associated with CNS invasion by *T. pallidum*. In the majority of patients with either early or late venereal syphilis, spinal fluid abnormalities resolve spontaneously; in the remainder, they either persist without development of overt neurologic symptoms or worsen with the eventual appearance of a neurosyphilitic syndrome. Natural history studies indicate that in the case of asymptomatic untreated neurosyphilis, most CSF alterations resolve without treatment [5]. To be sure, Merritt et al. [5] reported that in these patients the incidence of late asymptomatic neurosyphilis was no higher than 10%. These same natural history studies provided evidence that asymptomatic neurosyphilis was a predecessor of meningeal, meningovascular, and parenchymatous syphilitic neurologic syndromes and that asymptomatic neurosyphilis diagnosed during late syphilis carried a worse prognosis than asymptomatic neurosyphilis during early infection. Not surprisingly, progression from asymptomatic to

symptomatic neurosyphilis increases in rough proportion to the extent of CSF abnormalities in these same patients.

Although the clinical importance of diagnosing asymptomatic neurosyphilis was well appreciated in the pre-antibiotic era [49], there was diversity of opinion as to when lumbar puncture should be performed [50, 51]. Europeans argued for later spinal fluid examination to avoid over-treating persons whose CNS infections were going to resolve spontaneously, while the Americans advocated early examination of the spinal fluid to identify persons with severe CSF abnormalities who would benefit from more intensive arsenical therapy. Ironically, the same dilemma has resurfaced today as a result of numerous case reports suggesting that single-dose intramuscular penicillin could lead to CNS relapse in HIV-infected individuals with severe compromise of their immune system [52]. This idea is in accord with clinical studies suggesting a higher prevalence of asymptomatic neurosyphilis among early syphilis patients coinfected with HIV [53–55]. Regardless of HIV status, current CDC STD treatment guidelines do not recommend performing a spinal tap in individuals with either primary or secondary syphilis and without clinical signs and symptoms of neurologic disease at the time of diagnosis [56].

Symptomatic Syphilitic Meningitis

Syphilitic meningitis most often occurs within the first year after first acquiring the disease but can also present several years after the initial infection. Symptomatic syphilitic meningitis can occur as an early or late manifestation of venereal syphilis. Up to 10% of symptomatic meningitis cases occur in patients initially diagnosed with secondary syphilis and most cases occur during the first 2 years following the initial contact with the bacterium. Although headache and meningismus are not uncommon in early syphilis, particularly in patients with secondary syphilis, a full-blown meningeal syndrome (headache, confusion, nausea, vomiting, and a stiff neck) is seen in less than 10% of all cases of neurosyphilis diagnosed during this state of the disease [57]. In their classic series, Merritt and Moore [57] could find only 80 such cases over a 15-year period, and they estimated that symptomatic meningitis may complicate between 0.3 and 2% of early syphilis cases. These authors described three distinct clinical presentations: (1) acute hydrocephalus without focal signs unrelated to increased intracranial pressure; (2) meningitis of the vertex, presenting with seizures, focal neurologic deficits (e.g., hemiplegia, aphasia), and changes in sensorium; and (3) basilar meningitis with cranial nerve palsies, especially of nerves III, VI, VII, and VIII. Eighth cranial nerve involvement can be unilateral or bilateral and can affect either or both the acoustic and vestibular nerves. In these patients, CSF changes were more intense than those described for patients with asymptomatic meningitis, including more pronounced CSF lymphocytosis (generally between 200 and 400 cells/μL) and higher CSF protein levels (usually between 100 and 200 mg/dL). Neuroimaging studies may show enhancement of the meninges, cranial nerves, and/or spinal roots. The differential diagnosis for this condition is broad and includes viral meningitis, neuroborreliosis, tuberculous and

fungal meningitis, parameningeal processes (e.g., abscess), and noninfectious pathology such as sarcoidosis and carcinomatous meningitis. Reactive serological tests for syphilis in blood and CSF, along with the subacute onset of signs and symptoms typical of meningitis, help to distinguish meningeal syphilis from other conditions listed above in the differential diagnosis.

Meningovascular Syphilis

T. pallidum also induces an infectious arteritis which can affect any arterial vessel in the brain or spinal cord, resulting in thrombosis, ischemia, and infarction. Meningovascular syphilis represents an early to late syphilis overlap syndrome, although most patients are diagnosed in the late end of the syphilitic continuum. The spinal cord, brainstem, or cerebrum may be involved separately or together, although the majority of patients typically suffer middle cerebral artery infarctions [5]. Not surprisingly, the most common neurologic findings are contralateral hemiplegia/hemiparesis, homonymous hemianopsia, and aphasia. Death can result from involvement of the posterior cerebral circulation [58]. The relatively young age (30–50 years) of patients with meningovascular syphilis helps to distinguish this syndrome from other forms of vascular stroke (i.e., atherosclerotic). Onset may be sudden, although most patients have prodromal symptoms, such as headache, vertigo, insomnia, irritability, personality, and behavioral changes, which occur weeks to months before the thrombotic event. In the original neurosyphilis series by Merritt et al. [5], only a handful of patients had neurologic deficits suggesting involvement of more than one blood vessel in the brain. However, the use of MRI and magnetic resonance angiography imaging suggests that most patients have diffuse and often bilateral involvement of the brain [59], as would be expected with any systemic form of CNS vasculitis. Meningovascular syphilis can also involve vessels in the spinal cord, leading to infarction of the anterior or less commonly posterior spinal arteries. The spinal variant lacks prodromal symptoms and is usually sudden in onset. The differential diagnosis of meningovascular syphilis is broad and includes fungal and tuberculous meningitis and rheumatologic causes of cerebral vasculitis, including systemic lupus erythematosus, granulomatosis with polyangiitis, and polyarteritis nodosa.

The Parenchymatous Syndromes

The parenchymatous syndromes, general paresis and tabes dorsalis, are the last to occur in the neurosyphilis temporal sequence. These two syndromes are thus generally considered “tertiary forms” of neurosyphilis and account for more than 50% of all cases of neurosyphilis. Both syndromes are four- to sevenfold more common in men than women. According to Stokes [45], paresis accounted for 11% of neuropsychiatric admissions in the United States and around 7% of all cases of mental disease in the French, German, American, and Russian armies during the Second World War. The virtual disappearance of tabes dorsalis, out of proportion to the

decline in the incidence of paresis, is one of the most striking changes in the epidemiology of neurosyphilis in the modern age. Nevertheless, it is very important that clinicians remain aware for this rare dementing illness, in particular because a substantial degree of reversibility can be seen when paresis is promptly recognized and treated [60–63].

General paresis is a chronic spirochetal meningoencephalitis which severely disturbs the structure and function of the cerebral cortices, particularly the frontal and temporal lobes [5]. The typical clinical picture is a slow, often insidious, onset of neuropsychiatric disturbances coupled with progressive deterioration in cognitive function. The presentation, however, may be abrupt. In one case series, the duration of symptoms varied between 24 h and 5 years, and approximately 20% of patients had seizures [64]. As the disease worsens, patients experience loss of motor control to the point of paralysis along with worsening loss of bowel and bladder control. The constellation of signs and symptoms can be remembered with the mnemonic PARESIS: *p*ersonality (emotional lability, paranoia), *a*ffect (carelessness in appearance), *r*eflexes (hyperactive), *e*ye (Argyll Robertson pupils), *s*ensorium (illusions, delusions, especially megalomania, hallucinations), *i*ntellect (decreased recent memory, judgment, insight), and *s*peech (slurred). A retrospective analysis of a Chinese population found the most common clinical signs to be positive sucking reflex and hyperreflexia [65]. The dramatic postmortem pathologic findings described by Merritt et al. [5] have been visualized on a number of occasions in patients by MRI, now an essential tool for making the diagnosis [60, 61, 66]. The alterations in personality and behavior and the temporal lobe findings on MRI can lead to an incorrect diagnosis of herpetic encephalitis in some patients [67–70]. Some changes of general paresis may be irreversible, but in these cases treatment halts the progression of disease [71].

Originally described by Moritz Romberg, and later by Guillaume Duchenne as "locomotor ataxia" [72], tabes dorsalis is caused by a demyelinating process in the posterior spinal cords, which ultimately leads to the development of an ataxic, wide-based gait and foot slap (tabetic gait), paresthesias of the lower extremities, shooting or lightning pains (sudden onset, rapid radiation, and disappearance), bladder disturbances, fecal incontinence, impotence, loss of position and vibratory sense, absent ankle and knee jerk reflexes, and loss of deep pain and temperature sensation. Ataxia is widely regarded as one of the cardinal symptoms of tabes, and between 50 and 80% of patients exhibit a positive Romberg sign. The characteristic "lightning" or lancinating pains experienced by at least 75% of patients are usually present at the outset of the disease, typically affecting the lower extremities and occurring episodically. Ten to 20% of patients experience visceral crises including recurrent episodes of sudden, agonizing epigastric pain with nausea and vomiting which can last for days and mimic surgical emergencies. Intestinal, rectal, and laryngeal crises also can occur. Decrease or loss of tendon and patellar reflexes with preservation of muscle strength is a common, relatively early, neurologic finding. Formication, the sensation of insects crawling on the skin, can be seen as an uncommon paresthesia. Degenerative ocular changes also are common components of the tabetic syndrome. The Argyll Robertson pupil, though not limited to tabes or even

syphilis, is a characteristic late feature. Frequency of this finding has been decreasing, and in a retrospective study of 149 patients with neurosyphilis, only 5 demonstrated the Argyll Robertson pupil [26]. Primary optic atrophy occurs over a period of months to years, beginning peripherally and proceeding to the center of the nerve, producing progressive concentric constriction of the visual fields with retention of normal vision, referred to as "gun barrel" sight [73].

CNS Gumma

The CNS gumma, the rarest form of neurosyphilis, was uncommon even in the pre-antibiotic era [5]. Rare cases continue to appear in the modern literature [74–76]. Because of the likelihood that a CNS gumma will initially be mistaken for a tumor or other type of space occupying lesion (e.g., toxoplasmosis in an AIDS patient), this entity well exemplifies the reputation of syphilis as the great mimicker. The pathologic features of gumma within the CNS are no different than those occurring outside it. Merritt et al. [5] considered gumma of the CNS to be a chronic, localized form of syphilitic meningitis that extends from the pia mater into the adjacent brain or spinal cord. In a recent, comprehensive review of the literature, Fargen et al. [75] found two-thirds of the lesions occurred in the cerebral convexities of which the majority was located in the frontal lobes or frontoparietal region. The pituitary was the most common site outside the cerebral hemispheres.

Movement Disorders

Movement disorders are an increasingly recognized manifestation of neurosyphilis, and their presentation is characterized by a chronic course and frequent misdiagnosis [77]. Several orofacial dyskinesias have been described as manifestations of general paresis. The "candy sign" is characterized by repetitive rolling and sucking associated with jaw movements [78, 79]. A coarse rest and action tremor was described, in the setting of cognitive decline and generalized bradykinesia, which responded partially to penicillin therapy [80]. Cerebellar ataxia [81] and focal dystonias [82] have been described infrequently, attributed to meningovascular and gummatous syphilitic lesions. Parkinsonism was seen historically in association with neurosyphilis [83, 84], though this is a subject of debate and may have been a phenomenon as much of misdiagnosis and concomitant infection with syphilis in Parkinson's disease patients as it was to the generation of Parkinsonism by neurosyphilis [85].

Ocular Syphilis

Ocular complications may occur as part of a neurosyphilis syndrome or as an isolated manifestation [5, 86]. Anterior or posterior uveitis or panuveitis, the most common abnormalities, can occur during either early or late syphilis and presents

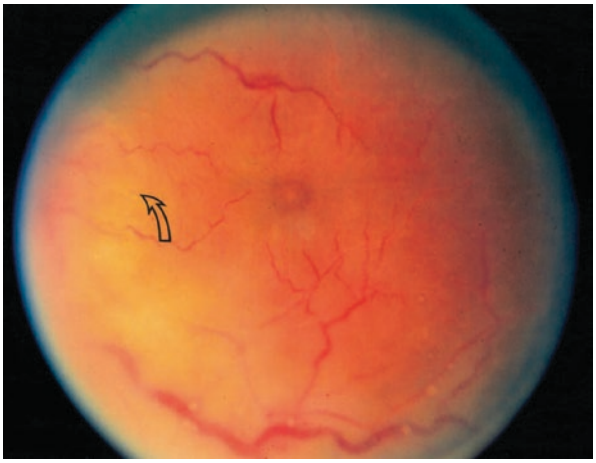

Fig. 12.3 Syphilitic neuroretinitis. Acute syphilitic neuroretinitis in the left eye, with markedly swollen optic nerve (*arrow*) and adjacent retinal edema including the fovea, occlusive retinal arteriolitis involving the inferior central vessels at the optic nerve head, vitreitis, and inferior serous retinal detachment (not shown). Patient was HIV positive with a CD4 cell count of 222 cells/μL (Adapted with permission from Ormerod et al. [87]. ©2001 Infectious Diseases Society of America)

with diminished visual acuity (Fig. 12.3). Other ocular syndromes include episcleritis, vitreitis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment. Primary optic atrophy is unique to late syphilis and is most associated with tabes dorsalis, which it closely resembles pathologically [5, 73]. The differential diagnosis includes tuberculosis, rheumatoid arthritis, sarcoidosis, toxoplasmosis, histoplasmosis, and rarely ocular *Toxocara canis* infections. The presence of pupillary abnormalities distinguishes syphilis from these other processes. Unless scarring has occurred, improvement with treatment can be dramatic.

Otosyphilis

Syphilis can cause hearing loss via two mechanisms during early or late infection. One is osteitis of the temporal bone with destructive changes in the membranous cochlea and labyrinth. The other, almost certainly more common, is inflammation and atrophy of cranial nerve VIII. Involvement of cranial nerve VIII typically begins with high-frequency hearing loss and progresses to a complete unilateral or bilateral loss of cochlear and vestibular function [88]. Syphilitic labyrinthitis has been known to mimic Ménière's disease. In the post-antibiotic era, otosyphilis has become liberally defined as an unexplained sensorineural hearing loss in the presence of a reactive treponemal serologic test [89, 90]. As noted by Pletcher [91], this definition lacks a clear causal relationship between syphilis and the clinical symptoms.

Nevertheless, in such cases, treatment is usually indicated since there are no diagnostic measures that can reliably eliminate the possibility of syphilis.

HIV and Neurosyphilis

Whether coinfection with HIV worsens the manifestations of syphilis and/or accelerates the course of the disease remains a point of contention among experts in the field and public health authorities. A number of case reports and small series have documented ophthalmologic and neurologic complications, as well as unusual or highly destructive non-neurologic syphilis syndromes in HIV-infected patients [52, 92, 93], leading many authorities to conclude that infection with HIV poses a higher risk of complications, particularly neurologic, during active early syphilis [31, 92]. Despite these findings, a multicenter prospective, randomized study sponsored by the CDC failed to demonstrate a benefit of enhanced therapy in patients either without or with HIV coinfection [56]. The differences in clinical presentation between HIV-coinfected and HIV-uninfected patients were in fact trivial. While HIV-infected patients with primary syphilis tended to present with more genital ulcers and genital ulcers were present more frequently in HIV-infected patients with secondary syphilis, manifestations of disseminated infection, including neurologic and ophthalmological complications, were not worsened by concomitant HIV infection. Thus, if atypical and aggressive presentations of syphilis do occur more frequently among HIV-infected patients, they likely represent a very small percentage of total cases, an assessment shared by several groups [93, 94]. Four separate studies have suggested that serum RPR titers $\geq$32 or CD4 counts below 350 in HIV-infected patients pose a greater risk of developing asymptomatic neurosyphilis [53, 95–97]. The long-term benefits of lumbar puncture and the value of more intensive therapy in this patient subset remain unproven [55, 98]. Based on available evidence, the CDC currently does not recommend routine lumbar puncture in patients with early syphilis, regardless of HIV status or CD4 count [99]. Of course, patients with reactive serologies and neurologic symptoms or clinical findings should always undergo lumbar puncture regardless of disease stage or immunologic status [99].

Pathologic Features

Perivascular infiltrates composed of lymphocytes, histiocytes, and plasma cells, accompanied by varying degrees of endothelial cell swelling and proliferation, are the histologic trademarks of syphilis regardless of anatomic site or stage of disease. Spirochetes are abundant in early syphilis lesions and often are observed in and around blood vessels, occasionally even protruding into the lumen in histologic specimens. By contrast, spirochetes are not easily demonstrable in tertiary syphilis lesions. Asymptomatic neurosyphilis and syphilitic meningitis are due to diffuse leptomeningitis [5]. The pathologic features of meningovascular syphilis explain the syndrome's variable mixture of focal neurologic signs with superimposed

encephalitis [5, 100]. In this syndrome, there is diffuse thickening and lymphocytic infiltration of the meninges with two kinds of arteritis: (1) *Heubner's* endarteritis, affecting large- and medium-sized arteries, characterized by crescentic collagenous thickening of the intima, thinning of the media, and dense, inflammatory changes (lymphocytes and plasma cells) within the adventitia and (2) *Nissl–Alzheimer* endarteritis of small vessels, characterized by the proliferation of endothelial and adventitial cells. *Paresis* and *tabes dorsalis* are considered a neurodegenerative processes of brain or spinal cord parenchyma, hence their designation as "parenchymatous." In paresis, diffuse meningovascular inflammatory changes are associated with striking and progressive loss of cerebral cortical neurons, resulting in gross cerebral atrophy (greatest in the frontal and temporal lobes), and proliferation of astrocytes and glial cells. Microglial cells are hypertrophied and elongated. Spirochetes are often readily detectable, usually in the gray matter, with little correlation between the clinical picture and the location and distribution of organisms. Tabes dorsalis is characterized by demyelination of dorsal root ganglia with secondary Wallerian degeneration of the posterior columns of the spinal cord. In early tabes, the leptomeninges and dorsal roots are heavily infiltrated with lymphocytes and plasma cells. These inflammatory changes diminish as the disease becomes chronic, eventually disappearing in so-called burnt-out cases.

A gumma is a circumscribed mass of granulation tissue, so named because of its rubbery or gummy gross consistency. The gumma of tertiary syphilis histologically is comprised of a dense infiltrate of lymphocytes, plasma cells, epithelioid cells, and multinucleated giant cells surrounding a caseous, necrotic core; proliferating fibroblasts and fibrosis also may be present [75]. Endarteritis and perivascular inflammation help to distinguish syphilitic gummas from those caused by tuberculosis. Obliterative endarteritis involving the *vasa vasorum*, the nutrient vessels of the aortic adventitia, is the key pathologic lesion in cardiovascular syphilis [101]. The ascending aorta and arch are most frequently affected because the *vasa vasorum* are most plentiful in these regions of the aorta. These changes eventually give rise to intimal thickening and wrinkling patchy medial necrosis and adventitial scarring with destruction of elastic fibers and weakening of the aortic wall.

Laboratory Diagnosis of Neurosyphilis

No laboratory gold standard exists for the diagnosis of neurosyphilis [102]. Diagnosis of neurosyphilis is thus stage dependent and requires a combination of clinical presentation and serologic and CSF laboratory studies. Because *T. pallidum* cannot be cultivated on artificial medium, laboratory diagnosis relies on direct detection of the pathogen in patient specimens and/or reactivity in serological tests. Confirmation would require inoculation of biologic samples into rabbit testicles, a procedure which is now only available in a research environment due to the time and resource intensive nature of the procedure. RIT was considered highly sensitive and was shown to detect even low numbers of treponemes in CSF samples. Interestingly, a reevaluation of the diagnostic yield of RIT showed few positive

results from CSF obtained from patients diagnosed with neurosyphilis, perhaps due to partial treatment from prior antibiotics exposure [103]. Below we will first describe available serologic assays for the diagnosis of venereal syphilis, followed by available CSF studies for the diagnosis of neurosyphilis.

Serological Tests for the Diagnosis of Venereal Syphilis

Venereal syphilis serodiagnosis depends upon the use of two distinctly different types of antibody reactivities, the so-called nontreponemal and treponemal tests [104]. The term "nontreponemal," derived from the long-held belief that the inciting antigens are lipids liberated from inflamed tissues, is probably a misnomer given that cardiolipin is a major phospholipid constituent in *T. pallidum* [105]. The standard nontreponemal test is the VDRL slide test in which heat-inactivated serum is tested for its ability to flocculate or agglutinate a standardized suspension of a cardiolipin–cholesterol–lecithin antigen [104]. Most diagnostic laboratories now use the RPR card test, which uses finely divided charcoal particles as a visualizing agent, for routine screening and following the response to therapy. As a general rule, RPR titers on the same serum specimens tend to be higher than VDRL titers. The TRUST is a macroflocculation assay in which the charcoal is replaced with toluidine red; its sensitivity is equivalent to that of the RPR, while its specificity is slightly higher. Nontreponemal tests are reported as the highest dilution giving a fully reactive result. A fourfold change in titer using the same nontreponemal test method is necessary to demonstrate a significant difference and should be performed in the same laboratory and, if possible, on the same day. Sera with extremely high nontreponemal titers may give weakly reactive, atypical, or even negative reaction at low dilutions because antibody excess prevents the agglutination reaction. Most laboratories circumvent this "prozone" phenomenon, which occurs in approximately 1% of reactive sera [106], by routinely diluting all samples at least 16-fold. While one-third of patients diagnosed with primary and tertiary syphilis have nonreactive nontreponemal tests [27, 107], the majority of secondary syphilis patients have a nontreponemal test titers of at least 1:8. A decline in nontreponemal test titers is the only means of monitoring therapeutic response. Treatment success is currently defined as a fourfold decrease in nontreponemal titer no later than 1 year following therapy for early syphilis and 2 years for late latent syphilis [99]. CSF examination to exclude neurosyphilis is indicated for all patients who do not achieve at least a fourfold decline during the appropriate interval following therapy [55]. The biologic significance of persistent nontreponemal test reactivity in "serofast" persons (i.e., individuals who show a 2 dilution or greater decrease in nontreponemal titer but do not serorevert) is unknown, and there is no evidence that such individuals benefit from lumbar puncture and/or additional therapy [55].

Treponemal tests should always be performed when primary syphilis is suspected because of their greater sensitivity than nontreponemal tests (86% vs. 70%) [107]. Treponemal tests also should be performed for suspected tertiary syphilis even when nontreponemal tests are nonreactive. It is important to remember that a

reactive treponemal test usually remains reactive for life. There are several specific anti-treponemal serologic assays available [108]. Until recently, the FTA-ABS test was the gold-standard confirmatory treponemal test. In this test, the patient's serum is used to immunolabel treponemes fixed to glass slides. Labeled organisms are visualized using a FITC-conjugated antihuman immunoglobulin antibody, and the sample is scored by the laboratory technician based upon the intensity of the fluorescence. Because of the subjectivity involved in the interpretation of this assay, it is no longer considered the gold-standard treponemal test [109]. The microhemagglutination assay for *Treponema pallidum* antibodies (MHA-TP) is a passive hemagglutination assay of formalinized, tanned erythrocytes sensitized with *T. pallidum* antigen that can be used to test preabsorbed patient sera. The MHA-TP has now been supplanted by the TP-PA test, a modification that uses gelatin particles sensitized with *T. pallidum* antigens to reduce the number of nonspecific interactions. All three tests measure both anti-treponemal IgG and IgM serum antibodies without distinguishing the immunoglobulin class which is responsible for reactivity. Numerous EIAs, which use recombinant *T. pallidum* antigens and detect IgM and IgG, have recently been developed for syphilis diagnosis.

There is now a well-established consensus that serologic tests for syphilis perform well in persons coinfected with HIV and with some cautions can be relied upon for accurate diagnosis in such individuals [99]. HIV-infected individuals may have a higher incidence of false-positive nontreponemal tests [110, 111]. In addition, nontreponemal test titers in HIV-infected individuals tend to be higher at presentation (including prozone phenomena) and can remain persistently elevated posttreatment [56, 112–114]. These serologic findings probably reflect the B-cell dysregulation associated with HIV infection. Lastly, there are well-documented, albeit extremely rare, cases of HIV-infected patients with secondary syphilis with nonreactive syphilis serologies in which a prozone was ruled out [115, 116]. Skin biopsy for histopathological examination as well as direct detection of *T. pallidum* should be performed if serologic test results are negative in an HIV-infected individual with a high suspicion of secondary syphilis.

Specific Tests Used in the Diagnostic Algorithm of Neurosyphilis (Table 12.1)

Table 12.1 summarizes specific clinical parameters and laboratory criteria for the diagnosis of neurosyphilis. While a reactive CSF VDRL constitutes definitive evidence for neurosyphilis, a presumptive diagnosis can be based solely on the presence of an elevated CSF protein and/or pleocytosis. Given the limited and conflicting data on performance [117, 118], the CSF RPR is currently not recommended in place of the CSF VDRL. The CSF FTA-ABS has high sensitivity but low specificity because reactivity may be due to the passive transfer of IgG anti-treponemal antibodies across the blood–brain barrier rather than intrathecal production of antibodies [119]. Because of the lack of specificity, the CDC does not recommend performing treponemal tests on CSF. Pleocytosis, long regarded as the hallmark of

Table 12.1 Diagnostic criteria for neurosyphilis

Confirmed (requires 1, 2, *and* either 3, 4, or 5)
1. Clinical signs consistent with neurosyphilis
2. A reactive serum treponemal test
3. A reactive VDRL in CSF
4. Detection of *T. pallidum* DNA in CSF by PCR
5. Identification of treponemes in nervous tissue by silver stain, immunofluorescence (DFA-TP), or immunohistochemical staining
Probable (requires 1, 2, *and* 3)
1. Clinical signs consistent with neurosyphilis
2. A reactive serum treponemal test
3. Elevated CSF protein or leukocyte count in the absence of other known causes

Adapted from the 2010 Sexually Transmitted Diseases Surveillance Case Definitions for Nationally Notifiable Diseases

an active inflammatory process [5, 49], should resolve within weeks to months following appropriate therapy (see below). When positive, the CSF VDRL should be monitored quantitatively but may not normalize. An elevated protein may, likewise, persist indefinitely. Current CDC and IDSA recommendations do, however, call for lumbar puncture in patients who have non-neurologic forms of tertiary syphilis given that an abnormal CSF would result in a change in treatment regimen (see below).

Treatment Recommendations for Neurosyphilis (Table 12.2)

Patients allergic to penicillin requiring treatment for neurosyphilis should be desensitized.

Parentally administered aqueous penicillin G is the preferred therapy for all forms and stages of syphilis. Table 12.2 presents current CDC guidelines for the treatment of neurosyphilis [99]. Aqueous penicillin G administered as three to four million units IV every 4 h or continuous infusion for 10–14 days is the currently recommended regimen; failures with this regimen are virtually nonexistent. If compliance can be assured, procaine penicillin 2.4 MU IM daily with probenecid 500 mg four times a day for 10–14 days can be considered as an alternative. Though not mandatory, CDC guidelines allow for follow-up of intravenous therapy with three divided doses of IM benzathine penicillin G (BPG) to ensure prolonged penicillinemia comparable to that during treatment of non-neurologic tertiary syphilis. Syphilitic otitis and ocular syphilis, both frequently associated with neurosyphilis, should be treated as neurosyphilis regardless of the results of lumbar puncture. Penicillin-allergic patients whose compliance with therapy or follow-up is questionable should be desensitized and treated with BPG. Doxycycline and tetracycline have long established track records as alternatives to penicillin with a reasonable amount of published data, some recent and including HIV-infected persons and indicating efficacy comparable to that of BPG [120–125]. Doxycycline is preferred

Table 12.2 Treatment recommendations for neurosyphilis

Drugs of choice
1. Penicillin G three to four million units intravenously every 4 h or 24 million units as a continuous intravenous infusion for 10–14 days OR
2. Penicillin G procaine 2.4 million units IM daily plus probenecid 500 mg four times daily oral, both for 10–14 days
Alternatives
1. Ceftriaxone 2 g IV once daily for 10–14 days
2. For patients with serious penicillin allergies who refuse desensitization or those who cannot be treated with penicillin and ceftriaxone, an alternative is oral doxycycline (200 mg twice daily) for 21–28 days

both because of its twice daily dosing, ensuring better compliance, and its lipophilicity, enabling it to cross the blood–brain barrier. Pharmacokinetics data and limited clinic studies suggest that ceftriaxone is effective for treating both early and late syphilis, including neurosyphilis [124, 126–128], although the optimal dose and duration of therapy for either have not been determined.

Unfortunately, there is no microbiological test of cure for neurosyphilis. Thus, to establish success of treatment for this disease, the clinician must use a variety of surrogate markers, most importantly resolution or stabilization of clinical abnormalities and by normalization of CSF findings. Both a clinical examination and a lumbar puncture should be performed 3–6 months after the initial treatment and every 6 months thereafter until the CSF VDRL is nonreactive. In general, it is expected that all CSF abnormalities will resolve by 2 years following treatment. Retreatment will be necessary if any follow-up studies show increasing pleocytosis or if there is a fourfold increase in CSF VDRL titer.

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Drug-Induced Aseptic Meningitis and Other Mimics

13

Germán Morís and Juan Carlos García-Moncó

Abstract

Meningitis refers to inflammation of the cerebrospinal fluid (CSF) and the meninges that surround the brain and spinal cord. Aseptic meningitis or viral meningitis has a benign, self-limited course. Aseptic meningitis can result from noninfectious causes such as medications or systemic conditions. Drugs that have been implicated as possible causes of aseptic meningitis (drug-induced meningitis or DIAM) include nonsteroidal anti-inflammatory drugs, antibiotics, immunosuppressants, and antiepileptic drugs, although monoclonal antibodies have emerged as culprit of DIAM. Systemic lupus erythematosus (SLE) stands as the single most frequent underlying condition associated with DIAM. The pathogenic mechanisms of DIAM are not fully understood, but there is evidence to suggest that they may be diverse, perhaps different for the various types of drugs. Most of the authors invoke a hypersensitivity mechanism (especially type 1 and 3). Medication-induced aseptic meningitis must remain a diagnosis of exclusion after other more common infectious causes have been effectively excluded. Thus, a thorough history on prior drug intake is key to avoid expensive diagnostic procedures or lengthy and unnecessary treatments. In cases where bacterial meningitis is a possibility, we suggest to treat the patient with a third-generation cephalosporin, only rarely linked to DIAM and active against the most likely organisms of community-acquired meningitis. Aside from DIAM, several systemic and neurological disorders, including SLE, sarcoidosis, Behçet disease, Sjögren's syndrome, and primary angiitis of the central nervous system,

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may also mimic infectious meningitis; therefore, differentiating from infectious meningitis is difficult, particularly considering the similar CSF profile and clinical presentation making the etiological diagnosis and management of these patients challenging.

Keywords
Meningitis • Drugs • Nonsteroidal anti-inflammatory drugs • Antibiotics Monoclonal antibodies • Immune globulins • Systemic lupus erythematosus

Introduction

Aseptic meningitis is a clinical syndrome that encompasses leptomeningeal inflammation of the brain and is characterized by fever, headache, vomiting, and meningeal symptoms with lymphocytic cerebrospinal fluid (CSF) pleocytosis, normal glucose level, and sterile cultures.

Aseptic meningitis is more commonly caused by viral organisms but can also be due to noninfectious etiologies including several systemic diseases, mainly autoimmune conditions due to the presence of meningeal immune reaction. In addition, drugs may induce aseptic meningitis by direct meningeal irritation when the drug is given intrathecally, but in the last years, an increasing list of drugs has been recognized as potential agents to produce meningitis when administered in oral or intravenous preparations. Therefore, the condition of aseptic meningitis is no longer tantamount to viral meningitis, even though the two terms often are used interchangeably.

Drug-Induced Meningitis (DIAM)

Several drugs can induce meningitis, which constitutes a diagnostic and therapeutic challenge. The situation becomes more complex if the offending drug is an antibiotic, where the decision of withdrawing the drug needs to be weighed against the risk of missing the treatment of an underlying infectious disorder. The incidence of DIAM is unknown because cases are underreported, and perhaps because many DIAMs are included in reports of viral meningitis. Recent series and case reports have increased the number of drugs capable of inducing a meningeal inflammation. Aside from the classical nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, immunosuppressive–immunomodulatory drugs (IS–IM), and antiepileptic drugs, mainly lamotrigine, a number of monoclonal antibodies stand out as new offending drugs (Table 13.1). The clinical profiles do not allow for a distinction between drugs, and the CSF profile, often with neutrophilic pleocytosis, may cause confusion with infectious meningitis. Moreover, DIAM patients may have an underlying disorder, particularly lupus erythematosus or HIV infection, which may also cause meningitis.

Table 13.1 Drugs involved in DIAM

Drug group	No. of reported cases	Drugs involved (no. of cases)	Sex	Age range (mean ± SD)	Range of latency (median)	Prior exposure to drug (%)
NSAIDs	77	Ibuprofen (48)	61% female	21–73 (39 ± 85)	30 min–4 months (8 h)	34
		Sulindac (7)				
		Naproxen (7)				
		Tolmetin (1)				
		Diclofenac sodium (3)				
		Ketoprofen (1)				
		Celecoxib (1)				
		Dexibuprofen (1)				
		Piroxicam (1)				
		Ketorolaco (1)				
		Rofecoxib (6)				
Antibiotics	74	Sulfamethizole (1)	60% female	1–90 (46 ± 23)	10 min–3 months (6 h)	31
		TMP–SMX (34)				
		TMP (12)				
		Isoniazid (1)				
		Ciprofloxacin (2)				
		Penicillin (1)				
		Metronidazole (3)				
		Cephalosporin (2)				
		Pyrazinamide (1)				
		Sulfisoxazole (1)				
		Amoxicillin (9)[a]				
		Fumagillin (1) Moxifloxacin (1)				
		Minocycline (1)				
		Ornidazole (1)				
		Rifampicin (1)				
		Valacyclovir (2)				
Immunosuppressive or immunomodulatory agents	23	Adalimumab (1)	53% female	31–78 (51 ± 11)	3 h–5 months (48 h)	26
		Cetuximab (8)				
		Efalizumab (2)				
		Infliximab (5) Etanercept (1)				
		Leflunomide (1)				
		Methotrexate (1)				
		Salazopyrin (2)				
		Sulfasalazine (2)				

(continued)

Table 13.1 (continued)

Drug group	No. of reported cases	Drugs involved (no. of cases)	Sex	Age range (mean ± SD)	Range of latency (median)	Prior exposure to drug (%)
SLE group	28	Ibuprofen (17)	89% female	21–73 (38 ± 14)	20 min–2 weeks (3.5 h)	32
		Tolmetin (1)				
		Sulindac (1)				
		Naproxen (1)				
		Diclofenac (1)				
		TMP–SMX (3)				
		TMP (1)				
		Sulfisoxazole (1)				
		Dexibuprofen (1)				
		Rifampicin (1)				

The SLE group comprises all the patients with systemic lupus irrespective of the offending drug (see text)
One patient can develop various DIAM episodes in relation with more than one drug
TMP–SMX trimethoprim–sulfamethoxazole, *IS–IM* immunosuppressive or immunomodulatory agents, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SLE* systemic lupus erythematosus
[a]Six patients were on amoxicillin plus clavulanic acid

A thorough history on drug intake must be performed in patients with meningitis to avoid expensive diagnostic procedures and lengthy, unnecessary prolonged antibiotic therapy or high dose of immunosuppressants. Until proper microbiological studies rule out an infectious etiology, the use of a third-generation cephalosporin is advised given their low frequency of association with DIAM.

When a patient develops meningitis in possible relation with any drug, the clinical syndrome should meet the criteria of DIAM:

(a) Temporal relationship with the drug intake (including a positive reintroduction test when it is possible)
(b) CSF pleocytosis
(c) Negative testing for microorganisms
(d) Absence of other explanation and complete resolution following discontinuation of the drug [1]

Clinical Characteristics and CSF Profiles of Patients of DIAM

The majority of patients with DIAM presented headache, fever, vomiting, meningismus, and changes in the mental status (Table 13.2). Less frequent are arthralgias, rash, myalgias, facial edema, lymph nodes, and liver tests abnormalities, which also occur in infectious meningitis with a variable frequency. Nausea and vomiting were more frequent in patients with NSAID-induced meningitis, while

Table 13.2 Clinical signs and symptoms (%) of drug-induced aseptic meningitis

	Total
Fever	89
Headache	83
Meningeal signs	72
Nausea–vomiting	49
Abnormal consciousness[a]	45
Rash	12
Abdominal pain	5
Arthromyalgias	16
Hypotension	9
Facial edema	13
Focal neurologic deficit	6
Seizures	5
Papilledema	4
Lymphadenopathies	4
Abnormal liver function	10
Photophobia	27
Phonophobia	3

[a]Includes somnolence–coma and confusional states

seizures were more common in antibiotic-induced meningitis. The latter is not surprising, since some antibiotics, particularly beta-lactams, may induce seizures. It should be kept in mind that seizures are present in up to 20% of patients with bacterial meningitis as confusing factor [2]. Therefore, clinical presentation does not help in differentiating drug-induced from infectious meningitis, either viral or bacterial organisms.

There are minimal differences in the presentation of the meningitides induced by the different drugs that would suggest a specific underlying drug. Seizures are recorded in patients with antibiotic-induced meningitis but can, in turn, be provoked also by antibiotics (particularly beta-lactams at high doses in a setting of renal failure). Thus, it seems more likely that seizures in DIAM are related to the meningitis and not to the offending drug [3]. NSAID-induced meningitis is more common in women (61% of the patients, Table 13.1) with an autoimmune disorder and previous exposure to the drug. The preponderance of ibuprofen in this group may reflect the popularity of nonprescription ibuprofen products, but drug-specific factors may also be at play. Finally, COX-2 inhibitors may also be implicated.

Antibiotic-related DIAM is also slightly more common in women (60%), and 40% of the patients have an underlying disorder. Antibiotic most frequently associated with aseptic meningitis is trimethoprim (TMP) with or without sulfamethoxazole (SMX), followed by amoxicillin. There are only two reports in the literature of cephalosporin-induced DIAM including cephalexin, cefazolin, ceftazidime, cefotaxime, and ceftriaxone [4, 5]. Thus, third-generation cephalosporins are first-line therapy in suspected DIAM until an infectious etiology could be ruled out. Two cases of DIAM have been associated with the use of metronidazole [6, 7]. DIAM

has also been associated with rifampin and two antiprotozoal agents, fumagillin and ornidazole [8–10]. Interestingly, a case of DIAM secondary to moxifloxacin has been described [11]; however, DIAM has been also attributed to ciprofloxacin therapy suggesting a putative drug class effect [12].

Regarding antiviral agents, two cases of valaciclovir-associated DIAM have been reported, although the possibility of VZV-associated aseptic meningitis cannot be completely excluded [13, 14]. Interestingly, acyclovir has not been related to aseptic meningitis despite its frequent use in herpetic meningitis.

Forty-one percent of antibiotic-related DIAM patients harbored an underlying disorder (Table 13.3). Intriguingly, TMP–SMX-associated meningitis is frequent in HIV-infected patients, in part due to the widespread prophylactic use of this drug in this population, but may also reflect the fact that chronic HIV patients are prone to sulfonamide-induced hypersensitivity reactions.

Clinical presentation of the IS–IM group did not differ from the rest and did not show gender predilection. After DIAM induced by OKT3 was recognized in 1–5% of renal transplant patients [15], monoclonal antibodies and intravenous immunoglobulins (IVIG) have become the leading agents of this group. Monoclonal antibodies represent a new group in relation to DIAM, mainly tumor necrosis factor (TNF) inhibitors such as infliximab, adalimumab, and etanercept [16–25]. Three cases of DIAM have been associated with the use of efalizumab, a humanized monoclonal antibody binding to the CD11 molecule on the T-cell surface [26–28]. Two patients experienced drug-induced aseptic meningitis in a clinical study of an anti-CD44 humanized antibody in patients with acute myeloid leukemia [29]. Cetuximab, a chimeric monoclonal antibody against epidermal growth factor receptor used for cancer treatment, has also been associated with a few cases of DIAM. In case a first episode of cetuximab-induced aseptic meningitis appears, cetuximab may be reintroduced successfully with appropriate premedication 1 h prior to administration of cetuximab, such as antihistamine and a corticosteroid and a slower infusion rate [30–36].

IVIG administration is frequently accompanied by headache (5–80% of patients); although real incidence of aseptic meningitis is not clear, a recent study over a 6-year period identified an incidence and risk of 0.60% for all patients and 0.067% for all infusions [37]. The true incidence of DIAM might be higher, since many patients experiencing headaches do not undergo lumbar puncture. DIAM secondary to IVIG affects females four times more than males. It is observed in patients receiving high- and low-dose IVIG regimens, but IVIG with high dimer values is associated more frequently with DIAM [38]. Fast infusion rates, poor hydration, and a history of migraine may predispose to the development of IVIG-induced aseptic meningitis. Some measures may be beneficial in preventing or reducing the incidence of aseptic meningitis. It is recommended to start the initial infusion at a slow rate, particularly for those who are at risk. Prehydration and good fluid intake throughout treatment are also recommended. In patients who experienced aseptic meningitis during prior infusions, acetaminophen and antihistamines can be given as a premedication therapy although steroids have not been proved useful. If all preventive measures fail to control the aseptic meningitis with IVIG, switching to

Table 13.3 Underlying disorder (%) in patients with drug-induced aseptic meningitis

	Underlying	Condition
Drug group	Common (>10%)	Uncommon (<10%)
NSAID (*n* = 38) 49%	Systemic lupus erythematosus (*n* = 22) 58%	Undifferentiated connective tissue disease (*n* = 1) 3%
N total = 77	Mixed connective tissue disease (*n* = 7) 18%	Isolated rheumatoid factor and antibodies to the SS-A antigen positivity of uncertain origin (*n* = 1) 3%
		Isolated positive antinuclear antibodies of uncertain origin (*n* = 1) 3%
		Ankylosing spondylitis (*n* = 1) 3%
		Rheumatoid arthritis (*n* = 2) 5%
		Sjögren's syndrome (*n* = 1) 3%[a]
		Dermatomyositis (*n* = 1) 3%[a]
		Seronegative acute oligoarthritis (*n* = 1) 3%
		Autoimmune thyroiditis (*n* = 1) 3%
Antibiotics (*n* = 30) 41%	HIV infection (*n* = 9) 30%	Sjögren's syndrome (*n* = 2) 7%
N total = 74	Systemic lupus erythematosus (*n* = 6) 20%	Crohn's disease (*n* = 1) 3%
		Rheumatoid arthritis (*n* = 1) 3%
		Interstitial cystitis (*n* = 1) 3%
		Type 1 diabetes mellitus (*n* = 1) 3%
		Type 2 diabetes mellitus (*n* = 1) 3%
		Autoimmune hypothyroidism (*n* = 1) 3%
		Rhizomelic pseudopolyarthritis (*n* = 1) 3%
		Temporal arteritis (*n* = 1) 3%
		G6PD deficiency (*n* = 1) 3%[b]
		Acute nonlymphoblastic leukemia (*n* = 1) 3%
		Bladder cancer and chronic renal insufficiency (*n* = 1) 3%
		Trisomy 21 (*n* = 1) 3%
		Kidney transplantation (*n* = 1) 3%
Immunomodulators/ immunosuppressors (*n* = 23)	Rheumatoid arthritis (*n* = 6) 26%[b]	Non-small cell lung cancer (*n* = 2) 9%
N total = 23	Squamous cell carcinoma (*n* = 6) 26% [c]	Psoriasis (*n* = 2) 9%[d]
	Crohn's disease (*n* = 3) 13%	Unclassified oligoarthritis (*n* = 1) 6%
		Undifferentiated spondyloarthritis (*n* = 1) 6% Ankylosing spondylarthritis (*n* = 1) 6%
		Ulcerative colitis (*n* = 1) 6%

The different underlying conditions were arbitrarily split into common (>10% of cases) and uncommon (<10%)

G6PD deficiency: glucose-6-phosphate dehydrogenase deficiency

[a]The patient suffered from dermatomyositis and Sjögren's syndrome

[b]One patient suffered from rheumatoid arthritis and mixed type III cryoglobulinemia. Another patient suffered from rheumatoid arthritis and epilepsy

[c]One patient suffered from squamous cell carcinoma and HIV infection

[d]One patient suffered from psoriasis and Graves' disease

subcutaneous immunoglobulin (SCIG) could be considered, given the very rare occurrence of aseptic meningitis with SCIG [39]. The meningeal reactions are usually self-limited, as symptoms self-resolved within 5–7 days.

DIAM has also been described with several drugs prescribed in diverse autoimmune disorders, including leflunomide, methotrexate, salazopyrine, and sulfasalazine [40–46]. The latter cross-reacts with sulfamethoxazole, and both likely share a common pathogenic mechanism. Polymorphic N-acetyltransferase 2 (NAT2) is involved in the metabolism of several compounds such as sulfapyridine, the active metabolite of sulfasalazine; thus, NAT2 phenotype may be a risk factor of adverse drug reactions in patients treated with sulfonamides, and slow acetylator could be associated with DIAM in relation to sulfasalazine [46].

Lamotrigine is the main antiepileptic agent associated with DIAM. Forty cases of suspected lamotrigine-associated aseptic meningitis have been reported to the Food and Drug Administration, although only 25 patients had a CSF profile consistent with meningitis [47]. Outside the USA, five additional cases of CSF pleocytosis after lamotrigine intake have been published [48–52]. The clinical picture is similar to other drug groups, and symptoms appeared from hours to more than 1 month after the initial dose, which varied from 12.5 to 150 mg. As with other DIAMs, the CSF profile showed pleocytosis of around 100 cells/mm^3 (neutrophilic predominance in two-thirds of the cases). Complete recovery in several days after discontinuation of the drug is the rule. One patient died, but death was not attributable to lamotrigine [47], and another patient developed an abducens palsy [52]. Since 2012, no additional cases of lamotrigine-induced meningitis have been reported.

Four patients have been reported who developed meningitis after carbamazepine therapy, one of them with Sjögren's syndrome (SS) and trigeminal neuralgia, two with manic-depressive syndrome, and another with isolated trigeminal neuralgia. The clinical picture was indistinguishable from other DIAM. One patient had myoclonus with normal carbamazepine levels. There was peripheral eosinophilia (30% of total WBC count) in two of them and 2% eosinophils in the CSF in one patient [53–57].

The interval between drug intake and the development of meningitis varies between minutes and 4 months for all the drug groups, and prior exposure to the drug is present in 30% of patients irrespective of the group (Table 13.1). This low rate is striking, considering the high prescription rate of NSAIDs and antibiotics and the fact that IS–IM drugs are employed periodically to treat autoimmune disorders or neoplasms. There is no relation between DIAM development and the dose of the drug employed, usually within the therapeutic range.

The CSF of DIAM patients shows pleocytosis of several hundred to several thousand cells per mm^3, normal-to-low glucose values, and increased proteins (Table 13.4). The number of cells was higher in the NSADs group than in the other two groups, as were the protein values. Neutrophils predominated, with an average over total cell count of 69% in NSAIDs cases, of 58% in antiepileptic drugs, of 63% in IS–IM, and 51% in antibiotics.

Table 13.4 CSF characteristics of patients with drug-induced aseptic meningitis

Drug group	Cells/mm^3 median (range)	Predominant cells (% of patient)	Median glucose value (range), mmol/L	Median protein value (range), g/L
NSAID	235 (8–5000)	Lymphocytes (26%)	3.44 (1.5–6.0)	1.2 (0.49–8.57)
		Neutrophils (69%)		
		Eosinophils (2%)[a]		
Antibiotics	125 (5–19,000)	Lymphocytes (41%)	3.32 (2–8.65)	1.07 (0.27–3.90)
		Neutrophils (58%)[b]		
Immunomodulators/ immunosuppressants	160 (18–2300)	Lymphocytes (29%)	2.94 (1.4–3.4)	0.91 (2.12–0.44)
		Neutrophils (63%)[c]		
Lupus	282 (8–5000)	Lymphocytes(23%)	3.1 (1.5–6)	1.25 (0.5–8.57)
		Neutrophils (77%)		

[a]In two cases, there were macrophages and histiocytes in CSF smear
[b]There were two cases with monocytes representing 95 and 24% of the total cell count and two cases with plasma cells and eosinophils representing 57 and 14% of the total cell count
[c]There was one case with monocytes representing 39% of the total cell count

Eosinophils were noted in patients from the NSAIDs group (ranging between 13 and 60% of the total cell count) [58, 59], from the antibiotic group (range, 2–24%) [12, 60, 61], and in patients receiving IVIG (less than 5%) [62]. The presence of eosinophils in the CSF is likely underreported, since counting these fragile cells is difficult and requires experience [58]. The presence of eosinophils in the CSF is more common in DIAM than in infectious meningitis, except for those of parasitic origin, and their presence reinforces the allergic condition of DIAM. Minor differences in the CSF profiles among drugs from the same group were likely due to the different timing of the lumbar punctures and to different stages of the disease.

Polymorphonuclear leukocytes are the first cells recruited in inflammatory processes, including the acute phase of meningitis, which may justify the neutrophilic pleocytosis present in these patients. The presence of increased levels of interleukin-8, granulocyte colony-stimulating factor, and macrophage inflammatory protein 1-alpha in the subarachnoid space contributes to their accumulation in the CSF. Differences in the CSF profile of DIAM induced by different drugs or even among patients who took the same drug could be partly justified by the different timing at which spinal tap was performed. Only in few cases, there was intracranial hypertension, but in the majority of the reports, the opening CSF pressure was not measured [63, 64].

When performed, neuroimaging was normal in all patients except for a few cases. In two patients with NSAID-induced DIAM, a diffuse hemispheric enhancement was evident (by MRI in one case and by CT scan in the other), reflecting a blood–brain barrier breakdown [65, 66]. Brain MRI in another patient with NSAID (dexibuprofen)-induced meningitis showed several small, non-enhancing reversible hyperintense lesions within the supratentorial gray matter, the basal ganglia, and the cerebellar hemispheres [67].

Underlying Conditions in Patients with DIAM

Systemic lupus erythematosus (SLE) stands as the single most frequent underlying condition associated with DIAM (Table 13.3). The analysis of the clinical and CSF profiles of this group of patients not shared any special or typical characteristic. The predominance in females is marked (90%) as expected for lupus, but there are no other obvious differences from the rest of parameters (Tables 13.1, 13.2, and 13.4).

Migraine has been suggested as a predisposing condition to DIAM [62, 68–71], but the retrospective analysis of these heterogeneous case reports does not allow for the determination of the exact prevalence of predisposing conditions such as migraine. To further complicate matters, the high prevalence of migraine in the normal population (6–12%) [72] and its even higher prevalence in populations also prone to DIAM such as SLE patients should be considered [73]. Finally, in two latter studies of DIAM, a relationship between a previous migraine and the developing of DIAM in relation with IVIs has not been found [37, 38].

Recurrent DIAM

There are 49 patients with recurrent DIAM, totaling 117 episodes, with a mean age of 47 (SD 21) (range, 2–87) and female predominance (71%) (Table 13.5). In 16 patients, meningitis was associated with NSAIDs (18 episodes), in 24 patients, with antibiotics (45 episodes), and in only a few cases, with IS–IM and antiepileptic drugs. The highest number of episodes reported in a single patient was five [74, 75].

An underlying disorder was present in 30 (63%) patients, with SLE being the most frequent (10 patients), followed by Sjögren's syndrome (3 patients), autoimmune subclinical hypothyroidism (3 patients), rheumatoid arthritis (3 patients), human immunodeficiency virus infection (2 patients), idiopathic thrombocytopenic purpura (2 patients), Crohn's disease (1 patient), undifferentiated connective tissue

Table 13.5 CSF characteristics in recurrent episodes of DIAM

	Latency range (median)	Cells/mm^3 median (range)	Predominant cells (%)	Glucose mg/dL median (range)	Protein mg/dL median (range)	Time to recovery median (range)
1st episode (n = 49)	15 min–4 months (24 h)	155 (8–3600)	Lymphocytes (28%) Neutrophils (72%)	3.16 (1.5–5.5)	1.17 (0.32–7.6)	48 h (24–336 h)
2nd episode (n = 49)	15 min–14 days (4 h)	209 (9–5440)	Lymphocytes (27%) Neutrophils (71%)[a]	3.16 (3.1–6.2)	1.18 (0.21–5.9)	48 h (12–384 h)
3rd episode (n = 15)	30 min–14 days (5 h)	200 (20–2050)	Lymphocytes (36%) Neutrophils (64%)	3.33 (1.6–11.9)	1.22 (0.86–4.67)	48 h (24–336 h)

[a]There was one case with 99 monocytes representing 99% of the total cell count

disease (1 patient), seronegative acute oligoarthritis (1 patient), atopic grass pollen-induced rhinitis (1 patient), and one patient with positive rheumatoid factor and SS-A antigen. Cancer treatment was the offending drug in a patient with Sjögren's syndrome and another with dermatomyositis. CSF analysis of these episodes revealed a polynuclear pleocytosis that was not more pronounced with subsequent episodes. There was no change in the differential cell count, protein content, or glucose contents. The latency from exposure to the drug and the recovery rate was also similar between the different episodes.

Differential Diagnosis

One of the most important problems in DIAM is assessing the causal relationship between drug intake and meningitis development, a probability that is based on clinical judgment, although there are scales to establish the causality of an adverse event and drug exposure, the most popular being the Naranjo adverse drug reaction probability scale. This scale is composed by ten items and provides a probability category of definite, probable, possible, or doubtful [76]. The only confirmatory test of DIAM, however, would be drug rechallenge, occasionally reported in the literature in inadvertent cases but ethically unjustified.

The differential diagnosis of DIAM is broad and includes infectious etiologies. A meningeal syndrome accompanied by CSF neutrophilic pleocytosis suggests acute bacterial meningitis, which needs to be ruled out by CSF culture. Over 85% patients with bacterial meningitis present with fever, headache, meningismus, and signs of cerebral dysfunction (i.e., confusion, delirium, or a declining level of consciousness ranging from lethargy to coma) [2]. Therefore, distinction on clinical grounds alone is not possible. As mentioned, in cases where bacterial meningitis is a possibility, we suggest to treat the patient with third-generation cephalosporins, which are known to cause only two cases of DIAM and would be active against the most frequent organisms in a healthy individual, until the appropriate CSF studies are available. The neutrophilic pleocytosis in DIAM is intriguing and could be facilitated by the presence of increased levels of interleukin-8, granulocyte colony-stimulating factor, and macrophage inflammatory protein 1-alpha in the subarachnoid space [77].

Antibiotics are probably underrecognized as etiologic agents of recurrent meningitis and must be considered also in their differential diagnosis together with anatomical skull defects, parameningeal infectious foci, immunodeficiencies, and Mollaret's disease [50].

Since recovery upon drug discontinuation is the rule, chronic infectious meningitis (tuberculous, fungal, etc.) would only rarely pose a diagnostic problem. Meningitis due to parasites may need to be ruled out in those cases with CSF eosinophilia that occur in the appropriate epidemiological context.

Viral aseptic meningitis is another important consideration in terms of frequency, although less critical in terms of prognosis and management including meningitis due to VIH infection. Clinically, it is marked by fever (76–100%),

nuchal rigidity, and headache that may be accompanied by vomiting, rash, diarrhea, pharyngitis, arthralgias, and myalgias. Neutrophils may occasionally dominate the CSF profile early in the infection, although there is usually a shift to lymphocytic predominance over the first 48 h. It could be argued whether certain cases of DIAM would in fact correspond to viral meningitis considering the difficulty of making a definitive diagnosis in viral infections. The time to recovery after drug withdrawal may be of help, since it is rapid in DIAM (1–5 days) but usually takes 10–14 days in viral meningitis [78].

Among the noninfectious etiologies of meningitis, SLE is an important consideration, and DIAM needs to be specifically distinguished from lupus aseptic meningitis. About 1% of lupus patients develop lymphocytic meningitis (less than 50 cells/mm^3), usually transient and early in the course of SLE, at times during a flare-up. The rapid onset and resolution of the signs and symptoms as well as the lack of data of SLE activity, especially a fall in serum complement levels, argue against an exacerbation of SLE [79–82]. Some authors have emphasized the risk–benefit ratio of NSAIDs prescription in LES patients [83].

Sjögren's syndrome is occasionally accompanied by meningitis, which appears in up to 20% of patients with neurological involvement [84, 85]. Other disorders that need to be considered when DIAM is suspected include sarcoidosis, Behçet disease, primary angiitis of the central nervous system, Vogt–Koyanagi–Harada syndrome, and carcinomatous meningitis.

CSF pleocytosis occasionally accompanies migraine, but the cell count is almost always lymphocytic and rarely exceeds 100 cells per mm^3. Since NSAIDs are commonly used to treat migraines and they can lead to DIAM, these drugs could play a role in producing pleocytosis, but this aspect has never been assessed systematically. The syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaDNL) is characterized by variable neurological deficits, headache, fever, and lymphocytic pleocytosis. The predominance of lymphocytes and the concomitant focal neurologic deficit helps to differentiate this entity from DIAM. As for migraine, the hypothetical role of drugs, such as NSAIDs, should be assessed in this disorder [86].

The abrupt onset in some patients with DIAM may suggest an intracranial vascular event, especially in patients with predisposing disease such as idiopathic thrombocytopenic purpura. Neuroimaging helps rule out a vascular lesion [51, 52].

A new group of offending drugs has emerged, including monoclonal antibodies, particularly the TNF inhibitors. Anti-TNF therapy predisposes patients to infections, including infectious meningitis, making an even more challenging situation. Aseptic meningitis should be recognized by physicians caring for patients receiving these drugs, because their use is on the rise. Monoclonal antibodies-induced meningitis probably is underrecognized, with milder cases not being further investigated. Headache is a common reaction to monoclonal antibody therapy and may be part of a clinical spectrum that includes serum sickness and meningitis. Effective measures can be taken to minimize the incidence of monoclonal antibodies-induced meningitis specifically and include the use of maintenance regimens rather than episodic

treatments, avoidance of prolonged drug holidays, and avoidance of monotherapy [18]. Finally, pretreatment with intravenous hydrocortisone may be helpful in those patients with prior DIAM episodes.

Pathogenesis

The pathogenic mechanisms of DIAM are not fully understood, but there is evidence to suggest that they may be diverse, perhaps different for the various types of drugs. Most of the authors invoke a hypersensitivity mechanism (especially type I and III) for NSAID-, IS–IM-, and antibiotic-related cases.

Some patients have eosinophilia, urticaria, pruritus, or bronchospasm, which would be consistent with a hypersensitivity reaction. However, it is striking that such reactions are mainly or exclusively confined to the CSF compartment in some patients.

NSAID-Induced Meningitis

NSAIDs are among the most commonly used agents in clinical practice. They are employed as anti-inflammatory, analgesic, and antipyretic agents for a wide spectrum of clinical conditions. Their anti-inflammatory properties are primarily due to inhibition of prostaglandin synthesis ought to its action as cyclooxygenase inhibitors. Nevertheless, cyclooxygenase inhibition, responsible for other CNS side effects of NSAIDS, is not likely involved in DIAM for several reasons. First, patients can tolerate other NSAIDs both before and after the meningitis episode, and not all drugs in this group lead to meningitis [58, 66, 87–90]. Second, CSF penetration is similar for all the NSAIDs [91]. Lastly, selective cyclooxigenase-2 (COX-2) inhibitors have been also associated with cases of aseptic meningitis [92].

Individual predisposition is suggested by the fact that some patients have developed meningitis after the intake of different unrelated NSAIDs [74, 93, 94]. One patient experienced aseptic meningitis induced by three different NSAIDs including a COX-2 inhibitor (naproxen, ibuprofen, and rofecoxib) [95]. The short latency period after rechallenge argues against accumulation of NSAIDs or their metabolites within the CNS. In addition, studies in SLE susceptible mice suggested that only certain drugs lead to meningitis [96]. Furthermore, a specific cell-mediated immunity to ibuprofen has been described in SLE patients who had not been previously exposed to this drug, perhaps due to cross-reactivity with some natural constituents to which the autoimmune reaction is directed and could be facilitated by a lack of suppressor cells [97].

The temporal relationship between drug intake and meningitis, the presence of prior exposure to the drug and disappearance of symptoms after discontinuation, and the more severe symptoms upon drug reexposure as well as accompanying signs such as facial edema, conjunctivitis, and rash suggest a hypersensitivity

reaction. However, skin prick and intradermal skin tests in a patient with recurrent ibuprofen-induced meningitis were negative [98]. In contrast, serum Ig E was increased in a patient with recurrent DIAM due to NSAIDs and returned to normal upon resolution, thus supporting a type I hypersensitivity reaction [99].

Type III and IV hypersensitivity reaction may also be implicated, although the role of immune complexes is controversial. Immune complex levels in the CSF have been found to range from normal and to increase in NSAIDs meningitis [79, 88, 100, 101]. The possibility that ibuprofen would potentiate the activity of a preexisting autoantibody, resulting in complement fixation and development of an acute meningitis as part of an immune process confined to the CNS, has been proposed [100] as well as the direct activation of innate immunity such as ligation of toll-like recognition receptor [102]. The possibility that the drug in combination with a CSF protein would act as a hapten seems unlikely, since NSAIDs do not reach high concentrations in the CSF [88].

Taken together, the available data suggest that NSAID-related meningitis develops in individuals rendered susceptible by an underlying autoimmune disorder who were previously sensitized or had a natural immunity to the drug. Thus, idiosyncratic reactions to NSAIDs are the likely causes. Why that reaction is confined to the meninges is obscure but might involve cross-reactive mechanisms with antigenic determinants of the CNS.

Antibiotic-Induced Meningitis

As for NSAIDs, prior exposure, greater severity on reexposure, and resolution following drug discontinuation are suggestive of hypersensitivity, but data are contradictory. Evidence for a type I hypersensitivity reaction in one case of amoxicillin-induced DIAM was not supported by normal values of specific IgE in serum and CSF. However, a report of a CSF plasma cell population appearing during an amoxicillin-related DIAM and disappearing with drug withdrawal suggests type III hypersensitivity involvement [103]. Immune complexes have been detected in the serum of three patients with TMP–SMX-induced meningitis, although they were absent in the CSF [75, 104]. Immune complexes were found in serum and CSF of a patient with cephalosporin-related DIAM [4]. The deposition of immune complexes in the choroid plexus would contribute to meningitis development [75].

The infratherapeutic levels of TMP–SMX in a patient rechallenged with this drug argue against a direct toxic effect [71]. The increased risk of TMP–SMX-associated meningitis in HIV-infected patients could be associated with the widespread prophylactic use of this drug in addition to the susceptibility of these patients to develop sulfonamide-induced hypersensitivity reactions. In one case of cephalosporin-related DIAM [4], immune complexes were present both in serum and CSF, and there was an increased IgG value in the CSF. Other mechanisms potentially involved include interleukin-6 production and upregulation of vascular cell adhesion molecule-1 expression [6, 7].

Immunosuppressive or Immunomodulatory (IS–IM) Agents

The operating mechanisms for the side effects of monoclonal antibodies are unclear and may involve cytokine release and enhanced contribution of brain TNF-alpha in cases on TNF inhibitor therapy [16–23]. A serum sickness-like reaction has been postulated, but in cases of infliximab-induced meningitis, antibody titers to infliximab (which are associated serum sickness-like disease) were not obtained [18, 22, 23]. Moreover, the development of meningeal inflammation may be influenced by the transport of serum monoclonal antibody across the blood–brain barrier to bind to a cross-reacting neural antigen [105]. Aseptic meningitis could be also a consequence of the blocking of the specific reaction of the monoclonal antibody, for example, interfering the adherence of the T lymphocytes to neurons produced by efalizumab [26]. Finally, toll-like receptors (TLRs) are critical triggers of the immune response during meningitis, and the signaling induced by TLRs is a key pathway for cytokines production [106], and the relationship between TLRs and TNF has been demonstrated [107].

The possibility that IVIG-induced DIAM is caused by sensitivity to the stabilizing agents of the commercial preparations such as polyethylene glycol, maltose, sucrose, or glycine seems unlikely since this syndrome has developed in the same patients who received other prior immunoglobulin preparations and there are several different commercial products that induced aseptic meningitis. The presence of eosinophils in the CSF of some patients has led to suggest hypersensitivity reaction caused by the direct entry of the immunoglobulins into the cerebrospinal compartment [62]. A cytokine-mediated inflammatory reaction is induced by the interaction of the infused IgG, derived from an allogenic pool of over 500 donors, with antigenic determinants on the endothelial cells of the meningeal vasculature. Activation of the complement system triggered by immunoglobulin macroaggregates could also play a role [108], as could the activation of TNF-alpha-primed neutrophils by atypical antineutrophil cytoplasmic antibodies present in IVIGs [109, 110]. Intriguingly, aseptic meningitis did not occur in patients receiving a standard replacement dose of IVIGs for a congenital immunodeficiency.

Lamotrigine

Lamotrigine is a phenyltriazine derivative with anticonvulsant and mood-stabilizing properties. The mechanism of lamotrigine-induced meningitis is unclear and may differ from the other drugs. The clinical picture resembles an acute hypersensitivity reaction based on the greater severity of symptoms upon subsequent exposure.

Other Agents Associated with DIAM

Aseptic meningitis is a complication of chemotherapy, including pemetrexed [111] and cytarabine [112, 113]; the latter may also associate cerebellar dysfunction [114].

DIAM has also been reported with salicylate overdose [115], hepatitis B vaccination [116], phenazopyridine [117], dexchlorpheniramine [118], pentoxifylline [119], vitamin B complex [120], ranitidine [121, 122], and allopurinol [123, 124].

Intrathecal Agents

Bacterial or fungal meningitis has been occasionally developed in patients receiving intrathecal agents used for diagnostic or therapeutic reasons [125]. More frequent, however, is the development of aseptic meningitis. The group of offending drugs is large and heterogeneous and includes radiological contrasts, steroids, anesthetics, chemotherapeutic agents, aminoglycosides, opioids, and baclofen [126–129]. A direct chemical irritation of the meninges is the most plausible mechanism. Most patients recover fully in days without sequelae.

Vaccines

One of the major concerns in any large-scale vaccination program is the appearance of aseptic meningitis, particularly with measles–mumps–rubella vaccine. All commercially available mumps vaccines contain live attenuated virus. The incidence of mumps vaccine-associated meningitis may be 1 case in 1000 vaccine recipients. The syndrome is usually observed within the third week after immunization [130].

Other Mimics Associated with Aseptic Meningitis

Aside from drug-induced cases, aseptic meningitis may appear as part of the spectrum of diverse noninfectious conditions (Table 13.6).

Table 13.6 Leading noninfectious cause of aseptic meningitis

Drug-induced aseptic meningitis
Neoplastic meningitis
Primary angiitis central nervous system meningitis
Vogt–Koyanagi–Harada syndrome
Headache associated with neurologic deficits and CSF lymphocytosis syndrome Spontaneous intracranial hypotension
Systemic conditions:
(a) Systemic lupus erythematosus
(b) Sarcoidosis
(c) Systemic lupus erythematosus
(d) Sjögren's syndrome
(e) Sarcoidosis
(f) Behçet disease
(g) Wegener's granulomatosis

Systemic Lupus Erythematosus

SLE is a complex autoimmune disease that involves multisystem. Neuropsychiatric involvement in SLE is broad and is present in 14–75% of patients. Meningitis is a rare manifestation of neuropsychiatric SLE and is observed in 1% of patients with SLE. Aseptic meningitis in SLE patients is usually transient and often occurs often during flare-ups [80, 131]. In a study of a LES population, 1.63% of the patients developed meningitis, and in 40% of the episodes, no microorganisms were identified. None of the patients was taking any of the drugs related to DIAM, and most of them had a high SLE activity index. The median CSF cell count was 142 per mm^3 (range, 20–1440), with a mean CSF/plasma glucose ratio of 0.33 [81]. SLE-induced aseptic meningitis may also be associated with myelopathy or brain vasculitis [132] or showed leptomeningeal abnormalities on brain MRI [133]. The pathogenesis of aseptic meningitis in patients with SLE is unclear and could be due to meningeal irritation secondary to SLE activity or to inflammation of brain small vessels. Due to the coexistent SLE activity, steroids might speed patients' recovery.

Spontaneous Intracranial Hypotension

Spontaneous intracranial hypotension (SIH) is characterized by low CSF pressure secondary to spontaneous CSF leak. SIH typical manifestations are quite similar to aseptic meningitis [134] with headaches (orthostatic headache type) accompanied by other symptoms, such as stiffness of the neck, nausea, vomiting, and photophobia. CSF examination may show normal or high protein concentration up to values of 100 mg/dL. Leukocyte count may be normal, but a lymphocytic pleocytosis of up to 200 cells/mm^3 has been reported. When conservative management fails, epidural blood patch is the treatment of choice [135].

Sjögren's Syndrome

SS is a systemic autoimmune disorder characterized by chronic inflammation of exocrine glands such as the lachrymal and salivary glands, leading to xerophthalmia and xerostomia. Extraglandular manifestations of the disease occur in one-third of the patients, including a relatively common peripheral neurological involvement, although central neurological disorders have been also associated with SS. Aseptic meningitis has been described in around 20% of the patients with CNS involvement [136] and was recurrent in a few cases [137]. CSF analysis shows a moderate lymphocytic pleocytosis, increased proteins, normal glucose, and oligoclonal bands. Steroid therapy usually leads to disappearance of the symptoms [84, 85].

Sarcoidosis

Sarcoidosis is a systemic granulomatous disorder of unknown etiology diagnosed on the basis of clinical and histologic evidence. Neurologic manifestations occur in

more than 5% of sarcoidosis patients and may be the presenting feature in one-half of individuals with neurosarcoidosis. Aseptic meningitis is characterized by headache, meningismus, and a sterile CSF with a predominantly lymphocytic pleocytosis, increased proteins, and low glucose in 20% of patients, and oligoclonal bands typically appear. Recurrent aseptic meningitis could be the only manifestation of sarcoidosis. Corticosteroid therapy is the core therapy [138, 139].

Behçet Disease

Behçet disease is an inflammatory condition with characteristic recurrent oral ulcers, genital ulcers, eye involvement-type uveitis or retinal vasculitis, skin lesions, and a wide variety of systemic manifestations, including central nervous system involvement. Neurologic involvement ranges from 5 to 50% of the patients. Cerebral venous sinus thrombosis may occur, as well as posterior fossa parenchymal lesions. An isolated aseptic meningitis without parenchymal lesions is also described, varying in frequency among populations studied from <1% of cases to 16% [140, 141]. CSF analysis shows a neutrophilic pleocytosis which may later transition to a lymphocytic predominance up to 400 cells per mm^3, increased proteins, and normal glucose. Oligoclonal bands are found in only a minority of patients. Aseptic meningitis as the sole manifestation of Behçet disease has been reported. Steroids are used to treat exacerbations [142, 143].

Primary Angiitis Central Nervous System Meningitis

Primary angiitis of the central nervous system is an idiopathic vasculitis confined to the CNS. The typical clinical scenario is unexplained neurological deficit associated with abnormal CSF analysis findings, which consisted in moderate lymphocytic pleocytosis (<250 cells per mm^3) and protein increase and normal glucose. CNS biopsy is the gold standard diagnostic test, and immunosuppressive therapy is the mainstay of treatment [144, 145].

Neoplastic Meningitis

Neoplasia must be considered as an outcome for patient with aseptic meningitis. Neoplastic meningitis can be seen in up to 5% of patients with solid tumors, such as lung cancer, breast cancer, and melanoma, with an even higher incidence in cases of hematologic malignancy, such as acute lymphoblastic leukemia and non-Hodgkin lymphoma. Neoplastic meningitis could account for mononuclear pleocytosis, increased CSF proteins, and low glucose. Leptomeningeal enhancement on MRI is usually suggestive of neoplasia as the cause of the aseptic meningitis. Atypical cells should be seen in CSF, so that large amounts of CSF samples (>10 mL) are needed to achieve the definite diagnosis. When the suspicion is a hematologic neoplasia,

flow cytometry analysis is the diagnostic technic of choice. Radiation therapy, systemic chemotherapy, and intrathecal treatment must be considered, but neoplastic meningitis is associated with a poor prognosis [146, 147].

Vogt–Koyanagi–Harada Syndrome

Vogt–Koyanagi–Harada (VKH) syndrome is a rarely seen multisystemic, autoimmune, and inflammatory disease. It is observed frequently with neurologic, auditory, and skin manifestations. The primary pathogenesis is T-cell-mediated autoimmune response directed toward melanocyte or melanocyte-associated antigens. CSF lymphocytic pleocytosis was found in more than 80% of VKH patients. The most effective therapy includes prompt initiation of high-dose systemic corticosteroids followed by early administration of nonsteroidal immunosuppressant [148, 149].

HaDNL Syndrome

HaDNL syndrome is a rare, self-limited, benign disorder characterized by multiple episodes of sudden onset of headache with temporary neurologic deficit and CSF lymphocytosis. HaNDL is most often seen during the third and fourth decades of life. Most patients have nonspecific infectious symptoms several weeks prior to presentation (cough, rhinitis, diarrhea, and malaise). Neurologic deficits last between 5 min and 1 week and include sensory symptoms, language disorders, and hemiparesis. Meningeal signs are not found [150]. HaDNL can present as sudden onset of focal neurological deficits which are clinically and radiologically indistinguishable from an ischemic stroke and treated with intravenous thrombolytic therapy [151].

When the CSF is studied, CSF opening pressure is elevated in more than 50% of cases, even leading to impending cerebral herniation [152], glucose is normal, and there is a lymphocytic pleocytosis (around 200 cells/mm^3) with increased proteins. There is no IgG synthesis and oligoclonal bands are absent. Complete recovery is the rule and no specific treatment is needed [153, 154]. The etiopathogenesis of HaNDL remains obscure, but a post-infectious or inflammatory mechanism in which autoantibodies are directed against neuronal or vascular antigens leading an aseptic leptomeningeal vasculitis has been proposed; the presence of antibodies directed against the CACNA1H subunit of the T-type voltage-gated calcium channel in one study supported this inflammatory or autoimmune hypothesis [155].

Other Mimics

Anecdotal causes of aseptic meningitis of noninfectious etiology include rupture of dermoid, epidermoid, or neuroepithelial cysts intracranial vascular malformations;

colloid cysts: hypertrophic pachymeningitis; endocarditis; relapsing polychondritis; Fabry disease; subarachnoid hemorrhage; and parameningeal infections [156–162].

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Central Nervous System Infections in Patients Immunocompromised by Antineoplastic and Other Immune-Modulating Therapies

14

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Abstract

Central nervous system (CNS) infections in patients receiving immunosuppressive therapy for cancer or other systemic conditions often present complex diagnostic challenges as signs of infection may be absent or atypical. This chapter outlines a systematic clinical approach based on the etiology of immunosuppression, general examination, and presence of concurrent systemic infections. Patients with impaired barrier function, neutropenia, B cell depletion, and T cell abnormalities are included. The laboratory and imaging diagnosis, management, and prognosis of infections such as PML, VZV, human herpesvirus 6, and fungal infections likely to be seen by practicing neurologists are discussed and contrasted with conditions that mimic infection. Infections associated with mycophenolate, cyclosporine, tacrolimus, rituximab, brentuximab, and alemtuzumab are described. Human immunodeficiency virus-associated infections are covered in Chap. 15.

Keywords

Aspergillus • Corticosteroids • Limbic encephalitis • *Listeria* • Natalizumab Progressive multifocal leukoencephalopathy • Rituximab • Tacrolimus • Tumor necrosis • Alpha inhibitors • Varicella-zoster virus

Introduction

Despite improved infection prophylaxis and antimicrobial regimens, CNS infections remain significant sources of morbidity and mortality among both cancer patients and a growing, diverse population of patients receiving immune-modulating

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therapy for nonneoplastic conditions. Major at-risk cancer patient groups include recipients of hematopoietic cell transplants (HCT) or solid organ transplants (SOT), patients with primary and metastatic brain and spinal tumors, and intensively treated patients with leukemia, lymphoma, and other hematologic malignancies. Nonneoplastic conditions whose therapies involve chronic immune modification include both primary neurological diseases and systemic conditions such as rheumatoid arthritis, inflammatory bowel disease, lupus, sarcoidosis, psoriasis, myasthenia gravis, multiple sclerosis, and neuromyelitis optica. Whereas other chapters in this volume are organized by pathogen, this section groups patients by their clinical diagnosis and its degree of disease and drug-associated immunosuppression. Table 14.1 summarizes the patient groups emphasized in this chapter. While some

Table 14.1 Immunocompromised patients: infectious risk factors and syndromes

Patient risk group: type of deficit	Infectious risks	Relevant drugs or other therapies	Special features/ syndromes
Barrier disruption Neurosurgery +/− Shunts Ventricular drains Radiation therapy	Bacteria: skin-derived organisms *S. aureus* *S. epidermidis* *Propionibacterium* *Enterobacteriaceae* *S. bovis* Viruses: HSV CMV VZV Fungi: *Aspergillus* *Candida*	Corticosteroids VEGF inhibitors Radiation therapy	Meningitis lacks classic signs DRESS (increased risk for HSV)
Neutropenia HCT, SOT Intensive chemotherapy without transplant	Bacteria: *S. pneumoniae* GNR Fungi: *Aspergillus* *Mucor* *Candida* Viruses: CMV HSV Adenovirus	Indwelling catheters Chemotherapy	PALE
B-lymphocyte/ immunoglobulin deficits CLL, multiple myeloma splenectomy	Bacteria: *S. pneumoniae* *H. influenzae* *Klebsiella* Viruses: Measles WNV Enteroviruses	Rituximab Brentuximab Mycophenolate	PML versus IRIS

Table 14.1 (continued)

Patient risk group: type of deficit	Infectious risks	Relevant drugs or other therapies	Special features/ syndromes
T-lymphocyte/ macrophage dysfunction: HCT HIV	Viruses: HHV6 HHV7 VZV CMV EBVPTLD JCV(PML) Fungi: *Cryptococcus* Parasites: *Toxoplasma gondii*: *Strongyloides* Bacteria: *Listeria* *Nocardia* *M. tuberculosis*, *Treponema pallidum* Histoplasmosis Blastomycosis	Donor-derived organisms Corticosteroids Bortezomib Cyclosporine Tacrolimus Alemtuzumab Mycophenolate	PRES Wernicke's encephalopathy
T-lymphocyte/ macrophage dysfunction: SOT	Donor acquired: Rabies, Arenavirus, LCMV WNV, PLUS: organisms listed under HCT	ATG Azathioprine	PTLD, PCNL
Drug- and neurological dysfunction-related deficits: Multiple sclerosis	Bacteria: UTI-related sepsis/ meningitis Viruses: VZV PML WNV	Neurogenic bladder Corticosteroids Natalizumab Rituximab Fingolimod Dimethyl fumarate	IRIS LTEM: NMO, WNV
Drug-related immune deficits: Rheumatoid arthritis SLE Sarcoidosis Psoriasis Myasthenia gravis Uveitis Polymyositis	Viruses: VZV PML	Corticosteroids Rituximab Etanercept Mycophenolate Methotrexate Infliximab Adalimumab Alemtuzumab Anakinra	De novo demyelination TNF-alpha Inhibitors VZV EBV JCV (PML)

ATG anti-thymocyte globulin, *CMV* cytomegalovirus, *DRESS* drug rash eosinophilia systemic signs, *EBV* Epstein-Barr virus, *GNR* gram-negative rods, *HCT/SOT* hematopoietic cell transplantation/solid organ transplantation, *HSV* herpes simplex virus, *IRIS* immune reconstitution inflammatory syndrome, *JCV/PML* John Cunningham virus/progressive multifocal leukoencephalopathy, *PCNSL* primary central nervous system lymphoma, *LCMV* lymphocytic choriomeningitis virus, *LTEM* longitudinally extensive transverse myelitis, *NMO* neuromyelitis optica, *PALE* posttransplant acute limbic encephalitis, *PTLD* posttransplantation lymphoproliferative disorder, *SLE* systemic lupus erythematosus, *TNF* tissue necrosis factor, *UTI* urinary tract infection, *VEGF* vascular endothelial growth factor, *VZV* varicella-zoster virus, *WNV* West Nile virus

guidelines are offered for antibiotic choice in selected infections, clinicians are encouraged to consult with their own institutional infectious disease departments to assure appropriate coverage based on institutional antibiotic resistance and nosocomial trends.

Clinical Approach to Potential CNS Infection: Diagnostic Guidelines

1. The *net state of immunosuppression* is a useful construct to remind the consultant to consider all components of infectious risk. These include patient disease and duration, treatment regimen and timing, prophylactic and vaccination exposures, transfusions, community and nosocomial epidemiologic trends, and travel and zoonotic exposures.

   The mnemonic **P-N-E-U-M-O** may help clinicians remember diagnostic pitfalls:

P: Presentation and course of CNS infections in the types of patients considered in this chapter may differ from those without immunosuppressive therapies [1].

N: Noninfectious conditions may mimic CNS infection. Examples of such processes include immune reconstitution inflammatory syndrome (IRIS), posterior reversible encephalopathy syndrome (PRES), paraneoplastic processes, and radiation and chemotherapy complications and toxicities, such as demyelination caused by some drugs.

E: Emerging, **U**nique pathogens and novel syndromes related both to malignancies and to their treatment challenge clinicians' diagnostic acumen.

M: Multiple infectious pathogens may coexist with or without noninfectious processes.

O: Ongoing risk of infection extends both before and long past the active cancer or immunomodulating treatment period. A patient's immune system may be impaired at one point in the course of the illness but dysfunctional during vigorous reconstitution at another point in the disease.

2. *Epidemiology*: A few cancer patient groups account for the majority of CNS infections. Patients with leukemia or lymphoma represent more than a quarter of all cancer patients with any type of CNS infection, and 16% of patients with CNS infections in series from large cancer centers and tertiary care hospital have primary brain tumors. Three quarters of bacterial or fungal meningitis cases occur in recent neurosurgical patients [2]. Certain drugs, such as natalizumab and alemtuzumab, confer increased risk for specific infections. Table 14.1 correlates both types of immune deficit and notable drug therapy associations with specific infectious pathogens.

3. *Clinical Syndrome*: Physical examination distinguishes two general syndromes that may be of diagnostic value:

(a) Diffuse meningoencephalitis/encephalitis presentations with headache and altered sensorium are more common with bacterial or viral infections or fungi such as *Candida* or *Cryptococcus*.
(b) Focal signs and symptoms reflect localized parenchymal process due to such entities as *Toxoplasma gondii*, *Aspergillus* species, or *Nocardia*. Focal cerebral infarction raises suspicion of bacterial or fungal infective endocarditis, varicella-zoster virus (VZV), *Aspergillus*, or *Zygomycetes*. Brainstem syndromes may suggest *Listeria*, WNV, or noninfectious entities such as Wernicke's or osmotic demyelination [3].

Ocular pathology occurs with several viruses including cytomegalovirus (CMV), VZV, and Epstein-Barr virus (EBV). Table 14.2 reviews differential diagnostic considerations both infectious and noninfectious based on characteristic focal signs and symptoms. The clinician should be aware that these are not invariable findings and that many atypical combinations of signs and symptoms can occur.

Special Neurodiagnostic Laboratory Considerations

Interpretation of cerebrospinal fluid (CSF) data in immunocompromised hosts can be misleading. Patients who are profoundly pancytopenic may have no pleocytosis even in the presence of bacterial or fungal infection, as may those whose T cell function fails to evoke an inflammatory response to viral pathogens such as varicella-zoster virus (VZV). (See discussion by Aksamit in Chap. 1.)

Computed tomography (CT) and magnetic resonance imaging (MRI) in immunocompromised patients also pose several potentially confusing issues:

1. The use of corticosteroids reduces contrast enhancement on both CT and MRI.
2. Diffuse meningeal or dural enhancement can be demonstrated after repetitive seizures, lumbar puncture reaction to calvarial metastases, or neoplastic or chemical meningitis.
3. Increased FLAIR in the subarachnoid space can indicate infection and hemorrhage or can be seen in patients ventilated with high partial pressures of oxygen.
4. Ring-enhancing lesions have an extensive differential diagnosis including metastases, abscesses, primary glial tumors, infarction, contusion, radiation necrosis, demyelination, and sarcoidosis. The use of diffusion-weighted imaging to improve distinction between infections and other processes is discussed in Chap. 2.

Table 14.2 Physical examination: potential localizing clues to underlying pathogen

Mass	Sinusitis	Leukoencephalopathy	Stroke	Limbic	Basal ganglia	Brainstem	Spinal cord
Bacterial abscess	Mucoraceae	PML	VZV	HHV6	WNV	Listeria	VZV
EBV/PCNSL	*Aspergillus*	PRES	IE	HSV1/2	E/WEE	VZV	HSV2
Cysticercosis	*Pseudomonas*	IRIS	Mucor		EBV	WNV	WNV
Mycobacterium tuberculosis		ADEM	*Aspergillus*		Toxo		EBV
ADEM		Drug	Chagas	VGKCC		PRES	=
IRIS		CAA	Vasculitis	Seizures		Wernicke's	RT
RT		Radiation injury	Tumor			Osmotic demyelination	
Tumor		GVHD	Coagulopathy			Whipple's	
			Radiation injury			Anti-Hu	

Blue infectious causes; *Red* noninfectious causes that can mimic infections; *ADEM* acute disseminated encephalomyelitis, *CAA* cerebral amyloid angiopathy, *E/WEE* eastern/western equine encephalitis, *GVHD* graft versus host disease HHV6 human herpesvirus 6, *HSV* herpes simples virus, *IE* infective endocarditis, *IRIS* immune reconstitution inflammatory syndrome, *PML* progressive multifocal leukoencephalopathy, *PRES* posterior reversible encephalopathy syndrome, *RT* radiation therapy, *VGKC* voltage gated potassium channel antibodies, *VZV* varicella-zoster virus, *WNV* West Nile virus

At-Risk Patient Populations

Neurosurgical Patients

Patients with primary and secondary brain tumors represent 25% of CNS infection in patients with cancer. Bacterial meningitis is the most serious infection occurring because of multiple risk factors including barrier disruption, deficits in T cell immunity with prolonged corticosteroids and poor wound healing after steroids, radiation therapy, and repeat craniotomies. Abscesses can occur more than several years after treatment [4]. *Staphylococcus aureus* is the most common pathogen after craniotomy, and *Listeria monocytogenes* incidence has declined in a recent Memorial Sloan Kettering Cancer Center series.

Three infectious syndromes occur exclusively among patients treated with surgery and radiation for brain tumors:

1. Carmustine-containing wafers (Gliadel®) are approved for treatment of high-grade astrocytic tumors both at initial diagnosis and at the time of recurrence. They induce a vigorous cerebritis with vasogenic edema. Two radiographic patterns have been described: a ring-enhancing abscess and a "Swiss cheese-like appearance" [5]. External ventricular drains and repetitively accessed Ommaya reservoirs also are associated with meningeal infection.
2. Radiation therapy can complicate wound healing as can bevacizumab and other vascular endothelial growth factor (VEGF) inhibitors, particularly when given within 1 month of surgery, may further raise the risk of wound infection [6].
3. Radiation therapy alone and chemoradiation with temozolomide may predispose patients to herpes simplex virus (HSV) or CMV encephalitis. HSV infection also has been observed during phenytoin- or carbamazepine-initiated hypersensitivity reactions [7, 8] (Fig. 14.1).

Hematopoietic Cell Transplantation and Solid Organ Transplantation (HCT, SOT)

The neurological complications of HCT and OCT have been reviewed recently in detail [9]. Below are highlighted six infectious conditions of clinical importance in the transplant population. Each is discussed in individual chapters in this volume, but the clinical context for transplantation patients is emphasized here. Most clinically significant neurological complications occur within the first 100 days after HCT, but it should be remembered that neurological infectious problems can surface even many years later [10].

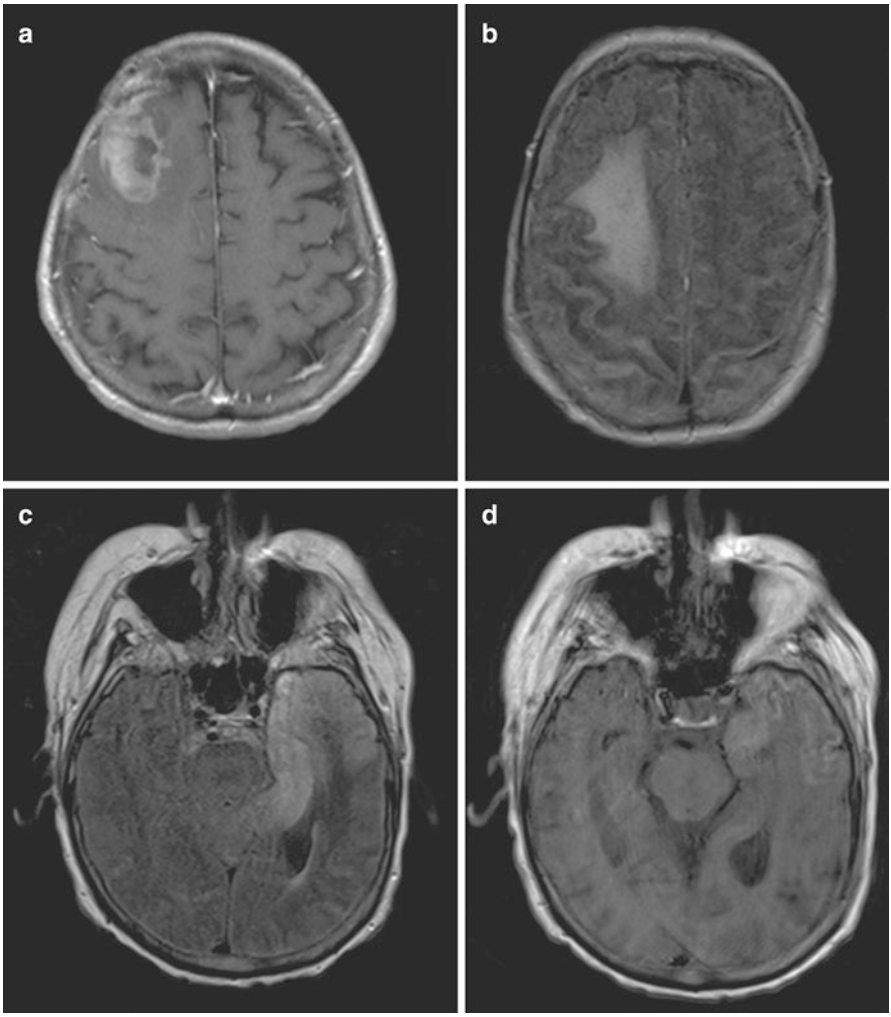

Fig. 14.1 Herpes simplex encephalitis concurrent with DRESS. A 57-year-old woman presented with seizures and was found to have a right frontal mass that proved to be a primary CNS lymphoma on biopsy of the gadolinium-enhancing area. (**a**) She was given phenytoin for seizures. During chemotherapy with methotrexate, temozolomide, and rituximab, her FLAIR signal remained about the same, (**b**) but clinically she deteriorated, developing short-term memory problems and a diffuse maculopapular rash along with transaminase elevations. Scans showed expansion of the left temporal cortex (contralateral to the tumor) (**c**) with bright signal in the left temporal cortex on unenhanced T1 images consistent with cortical necrosis. (**d**) CSF had 56 WBC, and PCR was positive for HSV. This case illustrates HSV infection concurrent with the DRESS syndrome (drug rash, eosinophilia, and systemic symptoms) due to antiepileptic drug hypersensitivity reaction. Radiation therapy also has been reported to provoke HSV or CMV encephalitis

Early Posttransplant Period (<30 Days)

HHV6

During the period of neutropenia following HCT, bacterial, viral, fungal, nosocomially acquired, and donor-derived infections are important sources of morbidity as is reactivation of infections such as neurocysticercosis and toxoplasmosis. A syndrome specific to the time of hematopoietic cell engraftment is characterized by rash, fever, and headache about 2–5 weeks posttransplant. This must be differentiated from posttransplant acute limbic encephalitis (PALE) due to HHV6 and characterized by amnesia, hyponatremia, CSF pleocytosis, seizures, and bihippocampal FLAIR abnormality that may be difficult to recognize as it can be quite minimal or appear after a several-day delay [11]. HHV6 (as well as cytomegalovirus (CMV)) lack thymidine kinase and are not sensitive to acyclovir, so ganciclovir, cidofovir, and foscarnet have been used individually or in combination, though there is no FDA-approved antiviral drug for this infection [12].

Middle Period (1–6 Months)

Varicella-Zoster Virus (VZV)

In the immunocompromised population, risk of VZV begins right after the procedure and extends for years. The most common syndromes are dermatomal VZV with a high risk of postherpetic neuralgia in patients with cancer and disseminated VZV [13]. Major complications of VZV include infratentorial and supratentorial stroke, retinal necrosis, pontine myelitis, cerebellar ataxia, cranial and spinal neuropathies, and spinal cord infarction. Multifocal VZV vasculopathy with temporal artery infection mimicking giant cell arteritis has been described recently [14, 15]. More than 35% of patients have no rash, and many have no pleocytosis. Any cancer patient with multifocal vasculopathy or unexplained radiculopathy should have CSF VZV PCR, which, however, may be positive in only slightly more than half of patients [16]. Diagnosis is more accurately confirmed by measuring anti-VZV IgG antibody in the CSF and documenting a reduced serum to CSF ratio.

Immunocompromised patients may not receive live attenuated VZV vaccine, and HCT recipients should receive prolonged valacyclovir prophylaxis. Active VZV infection is treated with IV acyclovir with addition of ganciclovir or foscarnet for treatment resistance and for retinal involvement [17].

Invasive Fungal Infections: *Candida* and *Cryptococcus* are likely to produce nonfocal meningeal syndromes, whereas *Aspergillus* and Mucoraceae invade sinuses and blood vessels producing cranial nerve palsies and stroke.

Cryptococcus neoformans

Cryptococcus neoformans is the most frequent cause of lymphocyte-predominant meningitis in patients with HIV. Other patients with T-lymphocyte defects, including all transplant recipients, are at risk for this fungus. The lungs are the most common extra-CNS site. Meningitis onset may be surprisingly indolent in patients who

do not mount an effective inflammatory response. Markedly elevated intracranial pressure is frequent, and cell counts may be misleading in pancytopenic patients. Cryptococcal antigen in the CSF is a sensitive and specific diagnostic tool. A recent clinical trial demonstrated superiority of combined therapy with 5-flucytosine and amphotericin B over either drug alone [18]. IRIS has been observed with successful cryptococcal treatment in the non-HIV population.

Aspergillus

Patients at risk for *Aspergillus* infections often have AML or myelodysplastic syndromes. HCT recipients with active GVHD are also at risk as are those with long-term indwelling IV lines and long-term steroid use and use of fludarabine and alemtuzumab [19]. The disease has a high propensity to form aneurysms in vessels of the CNS, with a posterior fossa predilection, and may present with devastating intracerebral hemorrhage. Clues to this fungus' often-difficult presentation are sinusitis and headache, persistent fever with negative cultures, and persistent neutrophilic meningitis. Galactomannan detection in the CSF and sinus biopsy are two early diagnostically helpful tools. A similar clinical presentation can be seen with mucormycosis, a fungus that also can spread from the sinuses to the frontal lobes with frontal infarction.

Late Complications (>6 Months)

Posttransplantation Lymphoproliferative Disorders (PTLDs)

PTLDs are a diverse group of lymphoid proliferations occurring after HCT or SOT. They range from hyperplasia to aggressive, usually B cell lymphomas with CNS involvement in 10–15%. Up to 70% are Epstein-Barr virus (EBV) positive. EBV-negative PTLDs occur later after organ transplant. The pathogenesis involves defective T cell regulation of EBV-specific B cell proliferation. Median time from organ transplant to PTLDs is about 6 months but can occur many years later [20]. Multiple ring-enhancing lesions are often seen, but there is a wide spectrum of potential MRI characteristics.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by lytic infection of oligodendrocytes by a ubiquitous polyomavirus, the JC virus (John Cunningham virus). Primary infection, present in more than 50% of the adult population, is asymptomatic, and the virus remains latent in the lymph nodes, bone marrow, kidney, and other host cells. Latency may also occur in the CNS, although this is less well established [21]. PML was originally recognized in 1958 as a rare condition in patients with hematologic malignancies. However, in the last three decades, there has been a 50-fold increase in PML incidence with the advent first of AIDS and then of intensive immunosuppressive regimens for organ transplantation and for a range of connective tissue and autoimmune conditions [22]. Table 14.3 summarizes the drugs that have been associated with increased risk of

Table 14.3 Drug-related risk of progressive multifocal leukoencephalopathy

Generic drug	Molecular target	Neurological	Non-neurological	References
Natalizumab	A4 integrin CD49d	MS	Crohn's disease	NMSS [89]
Rituximab	CD20	MS, NMO, MMN, myasthenia gravis, inflammatory myositis	Lymphoma, autoimmune diseases (LE)	Clifford et al. [37, 72] Carson et al. [62] Tuccori et al. [68]
Alemtuzumab	CD52	MS	Hematologic malignancies	Piccinni et al. [60]
Efalizumab[a]	CD11a	None	Psoriasis	Tyler [70] Korman et al. [71]
Brentuximab	CD30	None	T cell lymphoma	Von Geldern et al. [75] Jalan et al. [76]
Ibritumomab	CD20	None	B cell NHL	Keene et al. [59]
Mycophenolate	Inhibitor inosine-5′-monophosphate dehydrogenase	Myasthenia gravis SLE Autoimmune glomerular disease	HCT and SOT NMO	Neff et al. [79] Mateen et al. [31] Berger [78]
Infliximab	Anti-TNF-α	Neurosarcoidosis	Sarcoidosis, RA	Keene et al. [59]
Adalimumab	Anti-TNF-α	None	RA	Keene et al. [59]
Fludarabine	Antimetabolite purine analogue	None	CLL HSCT	D'Souza et al. [69]
Azathioprine	Antimetabolite purine analogue	Myasthenia gravis NMO	SLE Sjogren's, vasculitis	Mateen et al. [31]
Tacrolimus, cyclosporine	Calcineurin inhibitors		HCT, SOT	Mateen et al. [31]

Data from Bosch et al. [24], Schmedt et al. [23], Berger [78], and other references noted in table
CLL, chronic lymphocytic leukemia; *HCT*, hematopoietic cell transplantation; *NMSS*, National Multiple Sclerosis Society; *NMO*, neuromyelitis optica; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SOT*, solid organ transplantation
[a]Withdrawn from market

PML. In many instances, it is difficult to ascertain the relative risks posed by the underlying condition and by concurrently administered medicines. Table 14.3 derives from case reports, small series, and data from a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System [23]. Additional drugs were culled from the review by Bosch et al. using the BIOGEAS (Biological Agents in Autoimmune Diseases) registry [24]. The condition rarely has been described in patients with no prior known immunodeficiency state or with isolated CD8+ T-lymphocyte deficiency [25, 26].

While oligodendrocytes are the primary target of PML infection, other infected cells include granule cells leading to a pure cerebellar syndrome and fulminant JC virus encephalopathy of cortical pyramidal neurons [27, 28]. Definitive diagnosis requires the demonstration of enlarged oligodendroglial nuclei, bizarre astrocytes, and demyelination along with techniques confirming the presence of JCV. JCV by

PCR in the CSF in the absence of a better explanation for patient's symptoms is also used as a criterion [29]. Regardless of underlying immune deficiency, radiographic abnormality is usually an enlarging supratentorial white matter lesion or lesions with mass effect. Variable contrast enhancement can be seen with immune reconstitution. The posterior fossa is a favored site, but an increasingly broad spectrum of imaging features is recognized (Fig. 14.2) [30]. As illustrated by the examples in the figure, the differential diagnosis of PML varies with the underlying reason for immune compromise. For example, in a transplant recipient, PRES, EBV-associated PTLD, and de novo demyelinating disease are concerns. With rituximab, ADEM, PRES, mycobacterial disease, enteroviral meningitis, CMV, and WNV all could cause diagnostic confusion with PML. With TNF-alpha inhibitors, unmasking of demyelination may resemble PML as discussed later in this chapter. In the MS population on natalizumab, the disease may be difficult to sort out from MS exacerbation. Further, after withdrawal of the drug, IRIS may develop, or IRIS and PML may coexist (Fig. 14.3 and discussion below).

PML in the transplant population occurs at a median time of 27 months in solid organ recipients versus 11 months among HCT recipients. Case fatality rate was 84% in a recent series, a rate considerably higher than that of HIV patients on HAART or multiple sclerosis patients treated with natalizumab (see below) [31]. There is no effective therapy save for reduction in immunosuppression, if possible. A study of mefloquine in a group of largely HIV-positive patients showed no benefit [32].

PML provides an appropriate transition to consideration of the next section covering growing populations of at-risk patients immunocompromised not by cancer but by immunosuppressive therapies that alter B and T cell function. When PML is suspected, immunosuppressant or immunodulatory therapy should be suspended. If PML is associated with a therapy that has a long half-life, the use of plasma exchange (PLEX) is recommended. Immune restoration may lead to transient worsening of the disease [33] (Fig. 14.4).

Nonneoplastic Conditions

Multiple Sclerosis

Increasingly, patients with multiple sclerosis are treated with intensive immunosuppressive regimens that alter both B and T cell functions. Not surprisingly, some of these regimens have led to infectious complications not previously seen in this population group. The infection that has occasioned the greatest concern is PML in patients on natalizumab (Tysabri®), a humanized monoclonal antibody against the very late activating antigen-4 that prevents lymphocyte trafficking into the CSF. Three initial reports of PML led to the discontinuation of FDA's 2004 approval by early 2005 [34, 35]. One of the original three cases of PML associated with natalizumab received this drug for Crohn's disease [36]. As the risk of PML is related to duration of immunosuppression, cases have continued to be reported. An

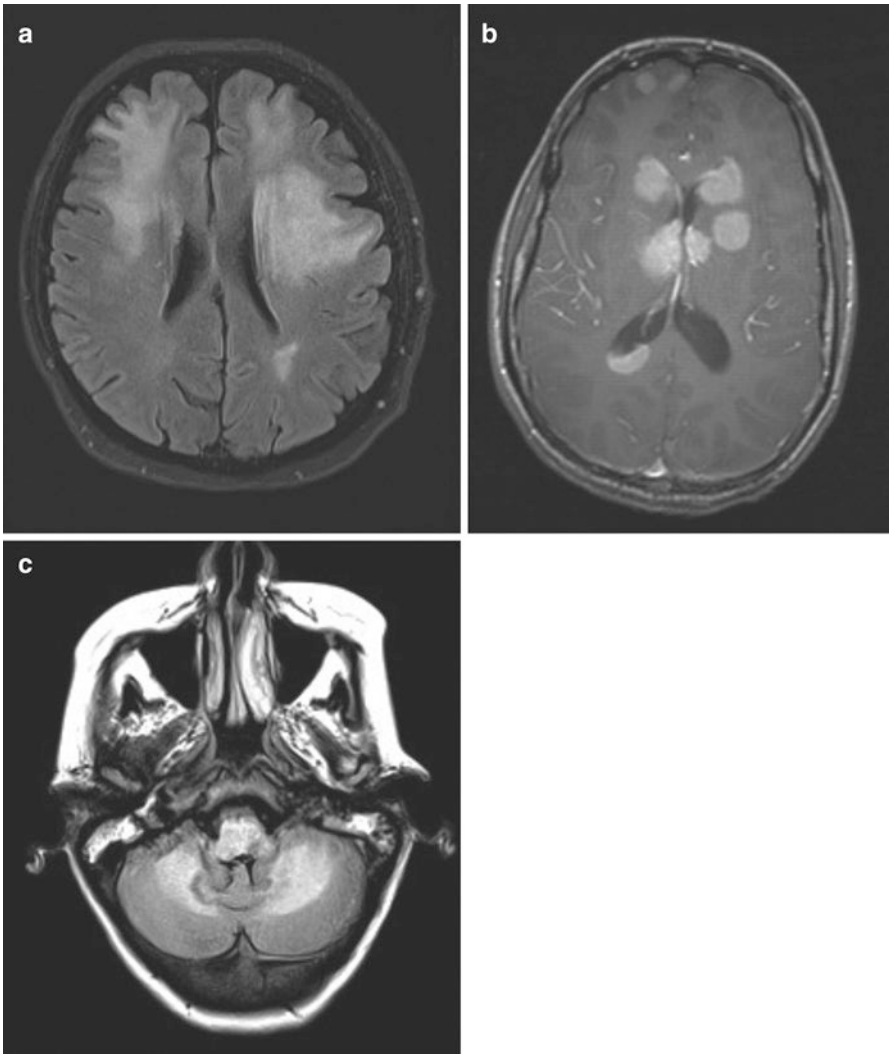

Fig. 14.2 Varied presentations of progressive multifocal leukoencephalopathy. (**a**) A patient with multiple myeloma received multiple chemotherapy regimens over a 2-year period and was on prednisone for much of this time as well as tacrolimus after an HST transplant. He presented with altered personality, abulia, and a nonenhancing multicentric process in the white matter shown on axial FLAIR images (**a**). The differential diagnosis included PRES, PML, or drug toxicity. JC virus was found in the CSF. (**b**) Hematopoietic cell transplant recipient presented 6 months after transplant with rapid onset of confusion and obtundation. Multifocal white matter lesions were found on FLAIR images (not shown), which enhanced vividly after gadolinium. EBV was found in the CSF. T1-weighted gadolinium-enhanced scan shows EBV-associated lymphoma. (**c**) Patient with untreated CLL developed facial numbness followed over 6 weeks by progressive ataxia and somnolence. JC virus was found in her acellular CSF. As she was untreated, the risk factor for opportunistic infection in this case appeared to be the hematologic malignancy itself rather than immunosuppressive therapy

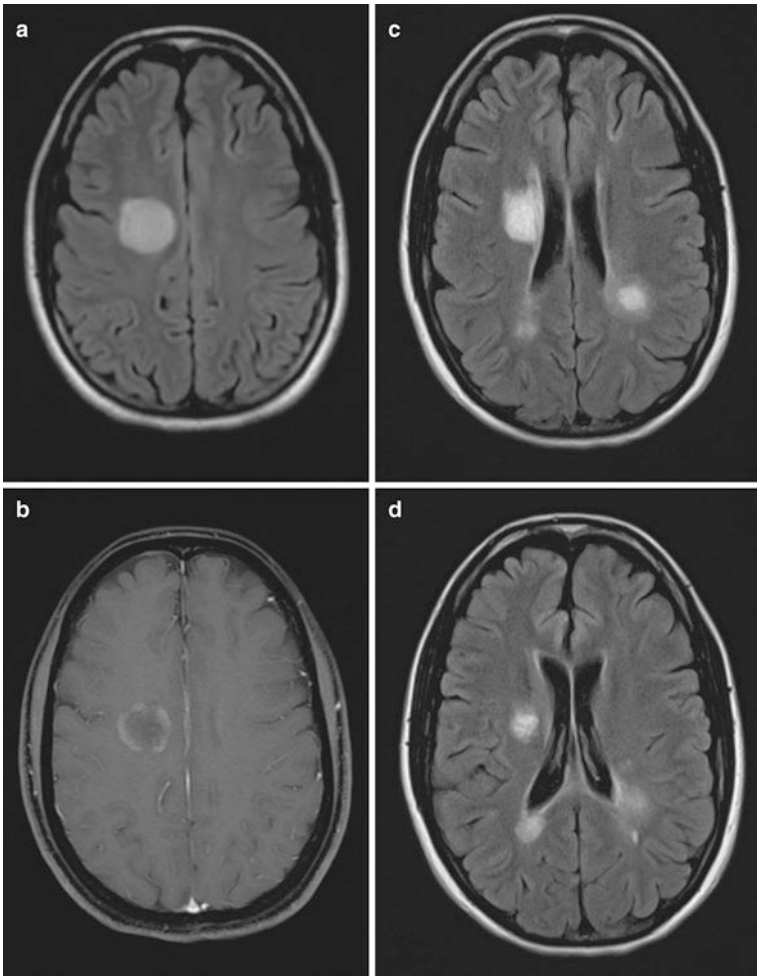

Fig. 14.3 Natalizumab-associated IRIS versus PML. A 28-year-old with multiple sclerosis had been on natalizumab for 2 years. Drug was discontinued in anticipation of conception, but after 4 months without established pregnancy, a follow-up scan at a time when the patient was asymptomatic showed a large FLAIR abnormality with partial ring enhancement (**a**, **b**). Seventeen days later the patient developed Gerstmann syndrome. The right hemisphere lesion no longer enhanced, but new lesions had developed in the left hemisphere and corpus callosum (**c**, **d**). In panel (**c**), the left hemisphere lesion shows concentric circles of hyperintensity consistent with demyelination. The differential diagnosis was PML versus natalizumab withdrawal-associated IRIS. JCV was negative in the CSF, and patient recovered completely after high-dose corticosteroid treatment. Natalizumab treatment has been resumed for more than 1 year without complication usually hypointense on T1 and hyperintense on T2-weighted imaging compared to the normal white matter. Signal intensity and CT attenuation changes are subject to temporal changes. The subcortical arcuate (U) fibers are typically involved at first, creating sharp, scalloped margins (Fig. 14.1b, c). Rarely, faint marginal contrast enhancement may be encountered, particularly in the acute phase of demyelination. In HIV patients receiving antiretroviral therapy (HAART), marked enhancement can be observed, particularly during the immune reconstitution syndrome [8]

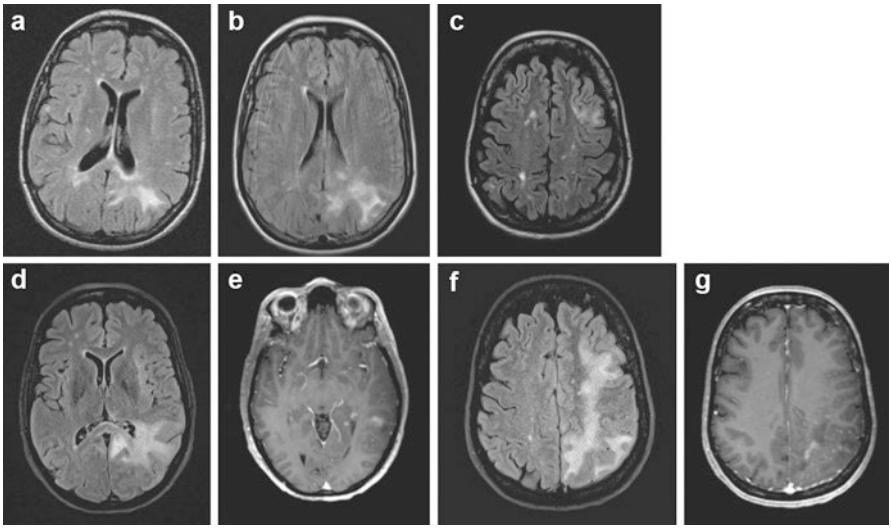

Fig. 14.4 Natalizumab-associated PML. After 25 courses of natalizumab, a 57-year-old patient complained of memory problems. New white matter lesion without enhancement was identified in the left parietal region (**a**). Lumbar puncture revealed JC virus, and natalizumab was withdrawn. Seventeen days after the first scan, there is progression of the original area and new nonenhancing signal abnormality in the left frontal white matter (**b**, **c**). Eighteen days later, after seven courses of plasmapheresis to remove natalizumab, clinical condition was worse with more extensive FLAIR abnormality in the original area (**d**) that now exhibits gadolinium contrast enhancement (**e**) as do parts of the now very extensive confluent left hemisphere affected areas (**f**, **g**) consistent with immune reconstitution (IRIS)

early series comes from Clifford and colleagues who described 28 cases of natalizumab-associated PML. Eight of these were fatal. Median treatment duration prior to onset of symptoms was 25 months with impaired cognitive and motor performance being the major issues. Several patients had seizures. In all but one case, JCV was detected in the CSF. Plasma exchange (PLEX) led to exacerbation of symptoms and enlargement of MRI lesions within a few days to weeks after PLEX, indicating immune reconstitution inflammatory syndrome (IRIS), a phenomenon defined as worsening of symptoms during immune system recovery and not explained by recurrent infection or other process. IRIS appears to be more severe and frequent in these patients than in HIV patients [37]. In a subsequent series encompassing MedWatch reports from Biogen Idec, 42 cases of natalizumab-related PML were described. All except two were managed by PLEX and discontinuation of natalizumab. Twenty-three patients developed contrast enhancement after removal of natalizumab, while 17 had contrast enhancement on MRI before drug withdrawal. IRIS occurred in all patients. Early PML/IRIS was associated with worse survival and neurological outcome [38].

As of May 2013, 347 cases of PML had been reported to the FDA and the European Medicines Agency (EMA) teams (Biogen Idec, 2013). Data are available

to physicians online to assist with explanation of risk to patients (medinfo.biogenidec.com/medinfo). Twenty percent of these PML-infected MS patients have died, and the survivors have varying degrees of disability. The lowest number of months on therapy before PML developed is 12. There are approximately 90,000 patients worldwide on the drug of which over 40,000 are in the USA. Prior immunosuppressive use (azathioprine, mycophenolate, mitoxantrone, methotrexate, or cyclophosphamide) raises risk of PML by fourfold [39]. Since 2011, a JCV serologic test (JCV Stratify) has been available. Gorelik and colleagues detected JCV seropositive in 54% of MS patients [40]. In the non-MS population seropositivity increases steadily in each decade from 50% at age 20–29 to 68% in those 50–59 years old. Seropositivity for JC virus in the blood increases the incidence of natalizumab-associated PML to as much as 1 per 100 patients after 2 years of treatment [41]. However, seronegativity does not completely eliminate the possibility of PML. Recently patients receiving natalizumab for more than 2 years were analyzed for viremia. Viremia occurred in 35% of 49 patients. Four of these were seronegative for JCV antibody. In some of these seronegative patients, the blood showed T cell responses to JC virus proteins. Chen showed that subclinical JCV reactivation is common in patients with MS on natalizumab and is related to transient reduction in the JCV-specific cellular immune response [42]. Stem cells and pre-B cells may migrate from the bone marrow as MS patients on natalizumab have increased circulating CD34+ cells. PML risk stratification algorithms therefore remain imperfect, and a single measurement of JC virus antibody is insufficient as a complete risk mitigation strategy [43]. Clinical vigilance and critical review of serial MRI scans remain essential.

Natalizumab appears rather specifically to increase risk for PML as other opportunistic infections are less common. A fatal case of HSV encephalitis has been reported, and numerous cases of dermatomal VZV reactivation are recorded. PML risk may be related to the sustained reduction in lymphocyte counts in the CSF more than 6 months after cessation of therapy. With the latest figures, the PML risk can be quoted to patients as 1/100,000 in the first year, 127/100,000 in the second year, and 171/100,000 in the third year with an average risk of 1/1000 in exposed individuals [44]. Because of the PML risk, natalizumab is available only through a restricted distribution program called the TOUCH® Prescribing Program.

A study looking at discontinuation of the drug for a holiday described relapse in 28% with median time to relapse of 3 months. About a third of these were particularly severe relapses reminiscent of an IRIS phenomenon [45]. Very similar figures in a smaller number of patients are reported from the Netherlands [46]. Up to 40% of patients in other series, again at median interval of 3 months from the end of therapy, experience significant relapses [47]. These observations have led to concern about discontinuation of therapy. In one recent series, 38% of patients experienced unusually widespread inflammatory activity on MRI exceeding that of their pre-natalizumab therapy, and CSF findings were suggestive of IRIS [48]. Other infections may occur with possibly increased frequency in natalizumab-treated patients including herpes infections, *Pneumocystis jiroveci*, and *Mycobacterium avium intracellulare*.

For the clinician wary of MS relapse but concerned about opportunistic infection, the question becomes one of how to predict who is at risk. Clinically the differential diagnosis is difficult: symptoms and radiographic findings may be hard to sort out from new MS lesions except for a predominance of neurobehavioral, motor, language, and visual symptoms with PML. Unlike MS-related relapsing lesions, optic nerve and spinal cord lesions are not present. Blood testing for JCV has been of some value. Rudick and colleagues analyzed almost 13,000 blood and urine samples from almost 1400 patients. JCV was found in plasma in four patients using a commercial test and two more using an ultrasensitive assay (detecting 10 copies per mL compared to 50 copies per mL). Thus, about 0.5% of the entire study group was JCV positive. None of the patients went on to develop PML, and none of the five patients in the studies who developed PML had detectable virus in the blood before developing disease [44]. Urine alone also is unhelpful, but a newer ELISA antibody test may be helpful [40]. These investigators used urine antibody test as a screen and then tested blood. Of these patients, 53.6% were serum antibody positive, and many urine-negative patients had positive serum antibody tests. One hundred percent (17/17) of the patients who went on to develop PML tested positive 16–180 months before symptoms. Thus, patients without detectable levels of anti-JCV antibodies are at low risk, but more patients are needed to confirm these findings. A particular note of caution is necessary here since after discontinuation of the drug, virus may persist [49]. In this study 11 of 13 MS patients had plasma exchange to remove natalizumab. Even though all 13 developed IRIS, 7 of the patients had persistent JC virus DNA in the CSF.

There are no known interventions that can adequately treat PML. Three to five sessions of plasma exchange (PLEX) over 5–12 days accelerate natalizumab clearance and are favored by many specialists. Steroids can help suppress the inflammation of IRIS. However, corticosteroids also have significant impact on the virus-specific T cell response to JCV, and a recent study suggests that methylprednisolone treatment decreased JCV-specific CD8+ T cells impairing control of JCV [50]. Thus, steroids likely should be used to treat but not to prevent PML-IRIS. Neurologists need to follow patients longitudinally because some of ongoing deficits after PML may be due to smoldering PML and not to MS.

Fingolimod

FDA approval of the first oral disease-modifying drug for multiple sclerosis fingolimod (Gilenya®) occurred in September 2010. Fingolimod is a sphingosine 1-phosphate receptor modulator. It inhibits egress of naïve and central memory lymphocytes from lymph nodes but does not impede effector memory T cells. Numbers of lymphocytes in peripheral blood are reduced to approximately 30% of baseline values. In the premarketing studies, an increased risk of dermatomal VZV was noted [51]. Serum VZV titers are obtained prior to the first drug dose, and antibody-negative patients are vaccinated before fingolimod treatment as recommended by the manufacturer Novartis' advisory, 2013. Following vaccination, fingolimod treatment should be postponed for 1 month. The use of live attenuated vaccines should be avoided during and for 2 months following treatment with fingolimod.

While the manufacturer's guidelines emphasize cardiac precautions, there are no specific guidelines for dose reduction or discontinuation in patients with markedly lowered lymphocyte counts. Post-marketing experience includes case reports of VZV and multiple cranial neuropathies as well as VZV encephalitis and vasculopathy [52, 53]. In the past 3 years, IRIS after withdrawal of fingolimod has been reported as well.

Dimethyl Fumarate

Approved in April 2013 is dimethyl fumarate (Tecfidera®), a drug that has been available in Europe for the treatment of psoriasis for several years. PML has been described in four patients, two of whom had psoriasis and were on the drug for at least 3 years [54, 55]. Other immunosuppressives had been used in some of the patients as well. IRIS developed in at least one of these patients. Unlike other immune-based therapies associated with PML, this is not a monoclonal antibody, and prior exposure in other patients to treatment for sarcoidosis and cancer as well as efalizumab use, all known risk factors for PML, confounds interpretation. In total, there have been four reports of PML in patients treated with fumarates [56]. An immune deficiency panel with T-lymphocyte subsets is suggested before institution of therapy, and at the author's institution, we also ascertain JCV status before using the drug.

Infections in Patients with Rheumatologic/Autoimmune Disorders

The diseases grouped here include rheumatologic conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) and immune thrombocytopenia as well as diseases of immediate relevance to neurologists including myasthenia gravis and neurosarcoidosis. They share immunosuppressive and biological therapies that produce predictable risks for specific infections as well as a wide array of autoimmune diseases induced by the drugs themselves. More than 1500 cases of nearly 50 different systemic autoimmune disease have been reported though one European registry of patients treated with biological therapies [57]. The long-term uses of corticosteroids and the more recent introduction of rituximab account for much of this risk. Two recent studies analyzed cases of PML with the FDA Adverse Event Reporting System in the setting of rheumatic diseases, mostly SLE and RA. The most frequently used drug was rituximab, and, while the authors acknowledge limitations that preclude definite causality, a specific signal is emerging with regard to rituximab and PML [58]. Similar data came from an analysis of Health Canada Drug Product Database [59]. As more oral agents are approved, clinicians will need to be alert to similar infectious risks that perhaps may be specific to the individual agents. For example, alemtuzumab appears to be a potent immune modulator in multiple sclerosis patients and already has been reported to be associated with PML when given for hematologic malignancies [60].

In 2009, of a national estimate of hospitalized patients with PML, 82% were HIV associated, 8.4% had hematologic cancers and solid cancers (2.8%), and rheumatic diseases including SLE, RA, and other connective tissue diseases accounted for fewer than 1% [61]. Carson and colleagues reported 57 cases of PML occurring after rituximab use for rheumatologic disorders and noted that these cases, gleaned from a number of cancer and academic centers, from the manufacturer and from FDA reports probably represent an underestimate. Ninety percent of the cases were fatal [62]. The major clinically relevant demographic point is that the populations at risk are expanding [63].

Rituximab

After 13 years of clinical use, rituximab has found indications in various neoplastic and autoimmune disorders such as lupus, rheumatoid arthritis, non-Hodgkin lymphoma, and multiple sclerosis. It was approved by the US Food and Drug Administration in 1997 and by the European Medicines Agency in 1998. Directed against CD20, it has been associated with prolonged B cell depletion for many months though immunoglobulin levels are largely unchanged. Infectious complications with CNS implications either through direct involvement of the CNS or through organ dysfunction-related encephalopathy include reactivation of hepatitis B, PML, CMV, and enteroviral meningoencephalitis and increased severity of WNV, babesiosis, and *Pneumocystis jiroveci* [64–67]. Case series of PML in patients receiving rituximab in polychemotherapy regimens led to the black box warning. Retrospective study suggested that the inclusion of rituximab into standard chemotherapy for NHL cause was associated with a higher incidence of PML [68]. Another study of chronic lymphocytic leukemia associated PML with both fludarabine and rituximab at some point during their course [69].

The FDA, European Medicines Agency, and WHO have all issued warnings of PML following rituximab administration. Informed decision making and patient's informed consent for these therapies, ways to detect virus, and attempts to minimize immunosuppression must be investigated and emphasized in physician education [70]. Analyzing the role of specific drug toxicity is difficult in diseases that themselves produce some immunosuppression and that are often treated with multiple types of immune-altering drugs. For example, PML has been observed in RA and SLE without rituximab and in psoriasis patients treated with efalizumab alone or in combination with other immune suppressive regimens [71]. Sarcoidosis presenting as PML has been reported, and the authors note that it may be responsive to cidofovir, a drug that has not proved helpful in the AIDS population raising the question of whether less heavily immunosuppressed patients may respond to therapies ineffective in AIDS patients [62]. Consistent subsequent series suggest an increased PML risk on the order of about 1 case per 25,000 RA patients. In these patients, inflammatory PML may occur even with low CD20 counts [72].

Other monoclonal antibodies such as adalimumab also have been associated with PML and other viral infections. Similarly, the fusion protein efalizumab as well as

abatacept and anakinra confers increased PML risk when used for RA [22, 73, 74]. Brentuximab, an antibody-drug conjugate linking the antimicrotubule agent monomethyl auristatin E to a CD30 monoclonal antibody, has also been reported to produce PML with PML-IRIS in several patients [75, 76].

Mycophenolate mofetil (MMF) also has been associated with diffuse large B cell EBV-associated lymphoma in a patient with SLE [77, 78]. Increased risk in renal transplant recipients seems to occur with incorporation of MMF in the antirejection regimen [79]. PML can occur in patients with minimal immunosuppression, and the MRI appearance may differ considerably when host response produces an exuberant inflammatory response [25, 26].

Tumor Necrosis Factor Inhibitors

Inhibition of tumor necrosis factor (TNF-α) is an effective rheumatoid arthritis treatment for patients resistant to conventional diseases-modifying drugs, and this class of drugs is used also for ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease, and uveitis and as an alternative in steroid-refractory neurosarcoidosis. Strangfeld and colleagues explored associations between anti-TNF-α therapy and viral disease from the German biologics registry. One-half of the cases of VZV they found were linked with adalimumab or infliximab, and another 15% had had etanercept. The VZV rate in this study was 11.1 per 1000, a risk comparable to patients over age 80. The risk increased when patients were switched to adalimumab or infliximab but not to etanercept. One-fifth of the infections were severe enough to require hospitalization. The increased risk for this population therefore was considerably less than that of the transplant patients [80, 81]. However, the differential diagnosis may be complicated by concurrent infectious processes; for example, during *Listeria* sepsis while receiving infliximab, a patient also developed lesions that could be drug-related demyelination, and the future use of TNF-α inhibitors depends on the interpretation of this neurological complication (Fig. 14.5). Other drugs associated with an increased incidence of VZV when used in the RA population include cyclophosphamide, azathioprine, and prednisone but not, at least in one survey, methotrexate [82]. Live virus VZV is contraindicated in patients receiving TNF-α inhibitor drugs. Therefore, administration of the vaccine before anti-TNF-α therapy appears reasonable [83].

As potent immunomodulators, TNF-α inhibitors and other biological therapies have been reported to cause the appearance of systemic autoimmune diseases (SLE, vasculitis, sarcoidosis) and organ-specific illnesses such as optic neuritis, multiple sclerosis, and forms of peripheral demyelinating neuropathy (CIDP, multifocal motor neuropathy with conduction block, and Lewis–Sumner syndrome) [24]. In anti-TNF-α-associated neurological syndromes, discontinuation of treatment does not always resolve the disorder, and long-term immunotherapy may be required to control the condition.

The unmasking of clinically latent MS by this class of drugs is complicated by an often ambiguous MRI appearance that generates a complicated differential

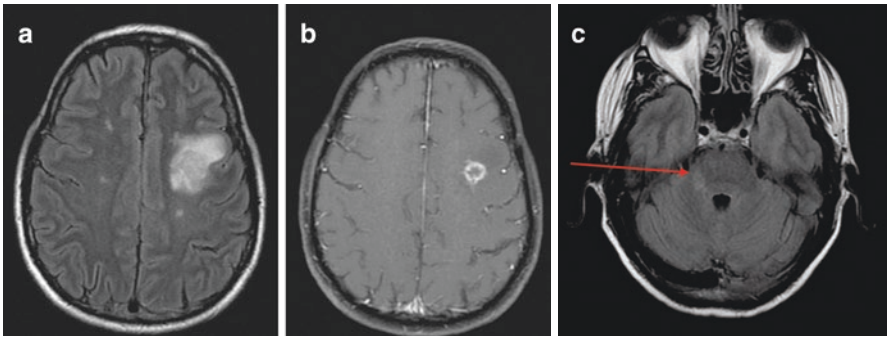

Fig. 14.5 Simultaneous drug toxicity and infection? A 58-year-old patient with steroid-refractory ulcerative colitis was started on infliximab therapy. After two courses of infliximab, abdominal pain, fever, and confusion led to diagnosis of *Listeria* bacteremia. CSF culture was negative and there was no pleocytosis. Seen on FLAIR and T1 gadolinium-enhanced scans is a ring-enhancing lesion that was assumed to be *Listeria* abscess (**a**, **b**). However, simultaneously multiple new areas of nonenhancing white matter abnormalities developed supratentorially and infratentorially (*arrow*) consistent with demyelination evoked by his recent TNF-α therapy (**a**, **c**). CSF was negative for both *Listeria* and oligoclonal bands, and follow-up MRI showed resolution of all areas

diagnostic list of rapidly evolving sometimes enhancing multifocal lesions raising concern about PML, PTLD, and other infections. De novo appearance of demyelinating disease and both remission and exacerbation of preexisting MS have been reported in patients receiving this class of drugs. Etanercept is the most frequently implicated medicine [84]. Diagnosis can be difficult as is evident in the 21 reported cases of optic neuritis associated with TNF-α inhibition with adalimumab many of whom were receiving the drug for uveitis, iridocyclitis, and other primarily ocular conditions [85]. In this group of rheumatologic diseases, MS emerging in the context of immune dysregulation is reminiscent of cases described during immune reconstitution following HCT [86]. The MRI differential diagnosis is further complicated by the substantial proportion of patients with PRES who have underlying autoimmune conditions and whose multifocal abnormalities on MRI may cause diagnostic confusion [87]. While clinical evidence concerning the management of CNS or PNS neurological events arising while patients are receiving TNF-α antagonists remains inconclusive, this class of drugs should be avoided in patients with MS or other CNS demyelinating diseases [88].

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The Neurological Spectrum of HIV Infection

15

Iñigo Corral and Carmen Quereda

Abstract

Neurological manifestations are frequent in human immunodeficiency virus (HIV)-infected patients and represent a great diagnostic and therapeutic challenge. They may be caused by many different mechanisms: the HIV, opportunistic infections or tumors, autoimmunity, and complications of systemic diseases or drugs, including the antiretrovirals. Patients may suffer several simultaneous neurological diseases, and the HIV and some opportunistic infections may affect simultaneously various levels in the nervous system. Highly active antiretroviral therapy (HAART) has produced a decline in opportunistic diseases and neurological disorders associated with severe immune depression. However, the prolonged survival of patients has increased morbidity due to chronic disorders, such as cerebrovascular disease and HIV-associated neurocognitive disorders. The central nervous system constitutes a reservoir for HIV replication in patients with controlled systemic disease. HAART itself is related to new emerging neurological problems: the specific neurotoxicity of the drugs and the appearance of neurological immune reconstitution inflammatory syndromes.

Keywords

Human immunodeficiency virus • HIV-associated dementia • HIV-associated neurocognitive disorders • Immune reconstitution inflammatory syndromes Toxoplasma encephalitis • Primary central nervous system lymphoma Progressive multifocal leukoencephalopathy • Antiretroviral therapy *Cryptococcus*

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Introduction

The human immunodeficiency virus (HIV) infects both macrophages and CD4+ lymphocytes. Infected macrophages and lymphocytes invade the central nervous system (CNS), where the HIV may cause direct or indirect damage. CD4 lymphocyte depletion causes cellular immune depression, which may condition CNS opportunistic infections. In consequence, neurological manifestations are frequent in HIV-infected patients and tend to occur in advanced stages of HIV infection. Approximately 50% of untreated acquired immune deficiency syndrome (AIDS) patients will suffer neurological manifestations along the course of the disease [1] even a higher frequency of HIV-associated disorders (more than 75% of cases) demonstrated in neuropathology studies [2].

This dramatic clinical scenario began to change after the introduction of highly active antiretroviral therapy (HAART) in 1996, when a drastic decline in the incidence of opportunistic diseases and neurological disorders associated with severe immune depression was noted in developed countries [3, 4]. The prognosis and survival of patients with HIV infection substantially improved and continue improving in recent years, with the use of new antiretroviral drugs, more potent and less susceptible to resistances (i.e., integrase inhibitors) [5]. Other concerns, however, emerged in the care of HIV-infected patients in the HAART era. The prolonged patient survival results in an increased morbidity due to chronic disorders, with particular relevance for those involving the CNS, including cerebrovascular disease and HIV-associated neurocognitive disorders (HAND). HAART itself is related to new emerging neurological problems that result from the specific neurotoxicity of these drugs and the appearance of neurological immune reconstitution inflammatory syndrome (IRIS). In the clinical practice in developed countries nowadays, the most common causes of neurological consultation among HIV-infected patients are similar to those of the general population. Opportunistic CNS lesions present only as the first manifestation of disease, or in patients who do not adhere to treatment or with treatment failure due to drug resistance, or as IRIS.

Classification and Approach to the Patient

The approach to the patient with suspected neurological complications of HIV should consider three different yet complementary ways of classifying these disorders: (a) a pathogenic and etiological classification; (b) a chronologic classification, attending to the different stages of HIV infection regarding immune depression and antiretroviral treatment received; and (c) a neuroanatomical classification of the lesion. From a pathogenic point of view, the neurological disorders presenting in HIV-infected patients may be associated with (1) the infection of the nervous system by the HIV; (2) the disorder of cellular immunity, which facilitates opportunistic infections or tumors and may occasionally favor autoimmune neurological disorders; (3) the immune restoration induced by HAART; and (4) the neurological complications of other systemic diseases associated with the HIV and of the

different drugs used in these patients, including the antiretrovirals. The wide spectrum of opportunistic CNS infections reported in AIDS patients may be classified according to the causing microorganism in bacterial (conventional bacteria, mycobacteria, nocardia), fungal, viral, and parasitic infections.

As the specific neurological disorders depend on the immunological status of the patient, they correlate with the stage of systemic HIV infection (Table 15.1). In primary HIV infection, neurological disease may be similar to that of other acute viral infections, presenting as acute encephalitis, aseptic meningitis, or transverse myelitis. In the early stages of HIV infection, including primary infection, autoimmune neurological disorders may occasionally occur. Cases of Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, acute disseminated encephalomyelitis, and multiple sclerosis-like disease have been

Table 15.1 Pathogenic and chronologic classification of neurological complications of HIV infection

	Primary infection	Early stages (A, CD4 > 200/mm^3)	Late stages (B, C, CD4 < 200/mm^3)
HIV-associated	Acute encephalitis Aseptic meningitis Transverse myelitis	Mononeuritis multiplex HIV-associated myopathy	HIV-associated dementia Vacuolar myelopathy Distal symmetric polyneuropathy HIV-associated myopathy
Autoimmune	Guillain–Barré syndrome Acute disseminated encephalomyelitis Multiple sclerosis-like disease	Guillain–Barré syndrome Acute disseminated encephalomyelitis Multiple sclerosis-like disease Chronic inflammatory demyelinating polyneuropathy	–
Immune depression	–	Tuberculosis	Toxoplasma encephalitis Primary central nervous system lymphoma Progressive multifocal leukoencephalopathy Cryptococcal meningitis Tuberculosis Herpesvirus diseases Other opportunistic infections
Antiretroviral treatment	–	–	Zidovudine myopathy Antiretroviral neuropathy Immune reconstitution inflammatory syndrome Syndrome of neuromuscular weakness
Secondary disorders	–	–	Toxic–metabolic disorders

reported. Opportunistic infections and HIV-associated disorders present almost exclusively in advanced stages of the disease, usually with a CD4+ lymphocyte count under 200/mm^3. *Mycobacterium tuberculosis* infection is an important exception to this rule, because it can occur in patients without significant immunodepression [3]. In advanced stages, metabolic and toxic disorders are also common because of the frequency of systemic disease and the complexity of treatments received. Patients under HAART may suffer neurological IRIS in addition to the toxic effects of the drugs.

The neuroanatomical localization of the neurological syndrome presented by the patient will limit the differential diagnosis to the possible etiologies of the syndrome. A further limitation would be facilitated taking into account the stage of HIV infection, other clinical data, and the results of specific complementary studies (Table 15.2). However, the neurological diagnosis in patients with HIV infection is hampered by a number of difficulties. A major problem is that these patients may suffer several simultaneous neurological diseases. Autopsy studies frequently demonstrate more than one concomitant opportunistic disease, together with HIV-associated diseases [2]. In addition, the HIV and some opportunistic infections, such as *Cytomegalovirus* (CMV) or *Varicella-zoster virus* (VZV), may affect simultaneously various levels in the nervous system. Drug toxicity or withdrawal may complicate the picture in patients with illicit drug or alcohol abuse.

Encephalic Complications

The encephalic complications of HIV infection may be classified into focal lesions and diffuse encephalopathies (Table 15.2). Among the latter, a key point is whether the patient presents with attention deficit or alteration of the level of consciousness, in which case the patient probably suffers from diffuse infections or toxic–metabolic disorders. Attention and consciousness are preserved in HIV-associated neurocognitive disorders.

Focal lesions include opportunistic infections, primary or metastatic neoplasm, demyelinating lesions, and cerebrovascular diseases. The frequency of opportunistic infections of the CNS and PCNSL has dramatically decreased since the introduction of HAART, and CMV encephalitis is now rarely diagnosed [3, 4, 6].

HIV-Associated Dementia

The HIV invades the SNC soon after primary infection, and inflammatory markers and evidence of neural damage are found in early HIV infection [7, 8]. Approximately 25% of patients with acute HIV infection have impaired neuropsychological performance, which correlates with higher cerebrospinal fluid (CSF) HIV RNA [9]. Most patients, however, remain asymptomatic until advanced stages of disease because a significant HIV infection of the CNS occurs only in the setting of severe immune depression [10], and thus the frequency of HIV-associated dementia (HAD)

Table 15.2 Neuroanatomical and etiological classification of neurological complications of HIV infection

	Diffuse encephalopathies	Focal brain lesions	Myelopathies	Meningitis	Neuropathies
HIV	HIV-associated dementia Acute HIV encephalitis	–	Vacuolar myelopathy Transverse myelitis	Aseptic meningitis	Distal symmetric polyneuropathy Mononeuritis multiplex
Viral	CMV encephalitis	PML CMV encephalitis VZV encephalitis HSV encephalitis	Spastic tropical paraparesis CMV VZV HSV 1 and 2	VZV HSV 1 and 2 CMV	CMV polyradiculitis CMV neuropathy VZV polyradiculitis HSV 1 and 2 polyradiculitis
Bacterial	–	M. tuberculosis abscess or granuloma Bacterial abscess Nocardia abscess Syphilitic gumma	Epidural abscess Tuberculous granuloma Syphilis	*M. tuberculosis* *S. pneumoniae* *Listeria monocytogenes* *S. aureus* Syphilis	*M. tuberculosis* polyradiculitis Syphilis polyradiculitis
Fungal	–	Cryptococcal granuloma *Aspergillus* *Mucor* *Candida*	–	*Cryptococcus* *Candida sp.*	*Cryptococcus*
Parasitary	–	Toxoplasma encephalitis Cysticercosis	Toxoplasma	–	–

(continued)

Table 15.2 (continued)

	Diffuse encephalopathies	Focal brain lesions	Myelopathies	Meningitis	Neuropathies
Tumor	–	Primary CNS lymphoma Gliomas Other primary neoplasms Metastatic neoplasms	Epidural metastasis Epidural lymphoma	Lymphomatous meningitis Meningeal carcinomatosis	Lymphomatous polyradiculopathy
Autoimmune	–	ADEM Multiple sclerosis-like disease	–	–	Guillain–Barré syndrome CIDP
Other causes	Toxic–metabolic encephalopathy	Ischemic or hemorrhagic stroke	Vasculitis Disseminated intravascular coagulation		Antiretroviral neuropathy Other toxic neuropathies Cryoglobulinemia Diffuse infiltrative lymphocytosis syndrome Nutritional neuropathy Diabetic neuropathy Alcoholic neuropathy Uremic neuropathy

increases with the advance of systemic disease. In antiretroviral naïve patients, neurocognitive impairment is associated with AIDS events and a HIV RNA CSF/plasma ratio of at least one, suggesting a role for active CNS viral replication in its pathogenesis [11]. The mean CD4-cell count in patients with HAD is approximately 100/mm^3. In untreated patients with AIDS, the prevalence of dementia is close to 50% [12], but the characteristic pathological features have been found even more frequently in autopsy cases [2].

HAD can compromise cognitive, motor, and behavioral disorders. Any of these disorders may be the presenting symptom, and a psychiatric presentation with depression, acute psychosis, or mania is not uncommon. HAD usually begins insidiously, with difficulties in concentration, memory deficits, and psychomotor slowing progressing along weeks or months. The patient shows lack of motivation, apathy, irritability, emotional liability, and abnormal social behavior. These symptoms are frequently attributed to depression. Motor disorders include bradykinesia, incoordination, hypertonia, pyramidalism, and frontal regression signs. HAD has been considered classically as a subcortical dementia. Cortical deficits, such as aphasia, apraxia, and agnosia, are rare, but a frontal syndrome is common.

The diagnosis of HAD is clinical. Neuroimaging and CSF studies may support the diagnosis but are oriented to exclude other neurological disorders. Information from the family or friends of the patient is essential to confirm cognitive or behavioral symptoms. A diagnosis of HAD should be postponed in the case of existing confounding factors, as active drug or alcohol abuse and systemic or neurological opportunistic diseases. Neuropsychological deficits must be confirmed with appropriate tests. To detect minor deficits, tests should explore memory, executive function, and complex attention [13]. The best screening tests are those exploring psychomotor speed (i.e., trail making test). The International HIV Dementia Scale is a rapid test useful for screening and follow-up [14].

Cranial tomography (CT) and magnetic resonance imaging (MRI) may show cerebral atrophy and leukoencephalopathy, which consists in symmetric and confluent areas of hyperintensity in T2 and fluid-attenuated inversion recovery (FLAIR)-weighted MRI sequences (Fig. 15.1). MRI spectroscopy may detect an early reduction in N-acetyl aspartate due to neuronal loss, as well as an increase in myoinositol, a marker of gliosis, and choline, which reflects membrane remodeling after injury [15]. CSF may show normal findings or nonspecific mild increase in protein concentration or lymphocytes. The presence of markers of immune activation in CSF (increased β_2-microglobulin or neopterin) supports the diagnosis. High levels of HIV RNA in CSF correlate with the presence of HIV encephalitis at autopsy [16], but there have been contradictory results regarding its value as a diagnostic test for dementia, especially in patients under HAART. The presence of HIV DNA in monocytes correlates with cognitive impairment, both before and after HAART, and increased levels differentiate patients with and without dementia [17].

The HIV-associated neurocognitive disorders (HAND) are now classified into three categories: (1) HAD; (2) mild neurocognitive impairment (MNI), when cognitive deficits produce mild disability without dementia; and (3) asymptomatic

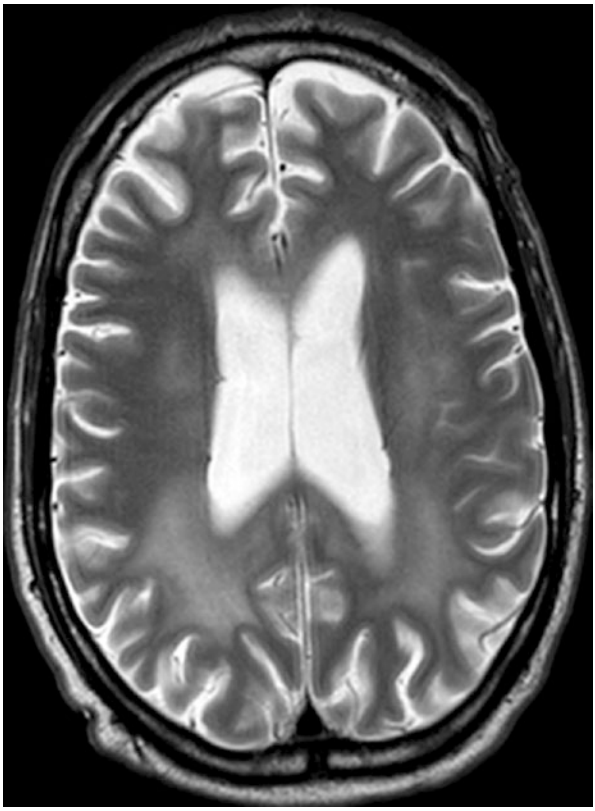


Fig. 15.1 Leukoencephalopathy of HIV-associated dementia. T2-weighted magnetic resonance imaging

neurocognitive impairment (ANI), when performance in neuropsychological test falls below that of controls, but there are no symptoms or functional impairment noted by the patient or informers [18]. The inclusion of ANI might overestimate the prevalence of HAND [19] but may be clinically relevant because it increases the risk for the more severe forms of HAND [20, 21].

Survival of HAD patients without treatment is less than 1 year. HAART is the standard therapy for HAD. The neuropsychological performance of HAD patients improves after months under HAART. Maximal improvement occurs between weeks 24 and 36 of therapy but may continue for more than 1 year [22]. In correlation with clinical improvement, HAART reduces CSF glutamate and other metabolites concentration, which are increased in HAD, lowers CSF HIV viral load, improves leukoencephalopathy in MRI, and reduces metabolic abnormalities of MR spectroscopy. However, many HAD patients improve incompletely or do not improve at all. Controlled trials of coadjutant treatment options for HAD have been disappointing [23].

HIV-Associated Neurocognitive Disorders in the HAART Era

In recent cohorts of patients receiving HAART, HAND was diagnosed in more than 50% of patients, although fortunately many of them remained asymptomatic [24–28]. Many factors may condition this high prevalence. On the one hand, the irreversible CNS damage caused by the HIV before treatment initiation or before HIV replication is controlled determines the persistence of cognitive deficits. Brain specimens from a cohort in the HAART era demonstrate that, among patients with HAND, the largest group represents patients without evidence of encephalitis in whom there is no correlation between brain HIV RNA and DNA and neuropsychological impairment [29]. This explains the association of HAND with a lower pretreatment performance [24], a lower CD4 nadir [25, 28, 30], a more advanced CDC stage, and a lower duration of controlled HIV replication [26]. Cerebral atrophy in MRI also correlates with data of previous HIV infection, as are nadir CD4 count and duration of the infection [31]. These results highlight the need for early antiviral treatment to prevent HAND, before irreversible neuronal damage is established, as virally suppressive antiretroviral treatment protects against cortical neurodegeneration [32].

On the other hand, comorbidities may influence the diagnosis of HAND [25]. Cognitive performance can be influenced by the presence of vascular risk factors (hypertension, dyslipidemia, diabetes, obesity), drug abuse, or patient's age and educational level [24, 27, 33]. Hepatitis C virus (HCV) coinfection may also impair cognitive function [28, 34], possibly through liver fibrosis and minimal hepatic encephalopathy, as no influence on cognition of HCV coinfection per se has been noted among patients without significant hepathopathy [35]. Specific treatment for HCV improves cognitive function in these patients [34].

Persistent systemic HIV replication associates with higher frequency of HAND [25, 30], but HAND prevalence is high even in patients with a successful control of HIV replication for years [26]. In one study, cognitive impairment and MRI spectroscopy alterations worsened over time despite adequate systemic HIV control [36]. The mechanisms underlying cognitive impairment and maintenance of neural injury in this circumstance are poorly understood, but recent evidence suggests a role of continuous immune activation within the CNS through infected monocytes. Markers of inflammation and monocyte activation in CSF persist despite a controlled systemic replication [23] and correlate with cerebral injury in MRI spectroscopy [15]. Even the only presence of latent infection in peripheral blood monocytes or in CNS microglia or astrocytes is associated with cognitive impairment [37, 38]. Latent infection within the CNS produces dysregulation of pro-inflammatory genes and neuronal degeneration [38].

The possibility of escape replication of HIV within de CNS in patients with controlled systemic replication may contribute to the high prevalence of HAND. Recent findings from several clinical studies have demonstrated that despite stable and successful control of HIV-1 in the periphery, 0.7–27% of individuals with HIV (depending on definition criteria used) still have detectable virus in the CSF [39]. In some patients CSF viral escape is persistent, which is

associated with higher levels of inflammatory cytokines in CSF. Neurocognitive dysfunction may be present in nearly 50% of cases of escape. Milder forms of viral escape may occur: one study detected low-level HIV RNA in CSF in 42% of patients during suppressive HAART, with worse neurocognitive performance associated with discordance in HIV RNA detection between plasma and CSF (12.7% of patients) [40].

A potential source of escape of HIV in CSF may be compartmentalized HIV replication within macrophage lineage cells, which may persist after treatment. In some patients with HAND, a compartmentalization of HIV in the CNS has been demonstrated by genetic differences between plasmatic and CSF viruses, especially in cases with controlled systemic replication and with drugs with low CNS penetration [41], which might favor persistent CNS replication and HAND [42]. The HIV viruses in CSF escape have enhanced tropism for macrophages, suggesting a low-level viral replication in macrophages or microglia [43]. Compartmentalization may condition less effect of antiretroviral treatment due to increased resistance in CSF than in plasma [44] or may cause more severe inflammatory responses in SNC with more irreversible damage. Compartmentalization may also occur early in HIV infection and can be present before antiretroviral therapy [43]. A low nadir CD4 count might favor migration of infected monocytes and lymphocytes to the CNS and compartmentalization.

HAART regimes with a higher penetration index give a better control of CNS replication [40], but contradictory results have been found regarding their effect on neuropsychological performance [22, 25, 28, 45–50]. Adding an integrase inhibitor and CCR5 antagonist to an standard HAART in patients with acute HIV infection did not show improved neuropsychological testing in a randomized study [51]. On the contrary, antiretrovirals with high CNS penetration might have a negative effect on neuropsychological performance [45] and may increase the risk of HIV dementia [52].

The pattern of cognitive impairment and cerebral atrophy in patients with HIV infection seems to have changed with HAART. In the pre-HAART era, there was a predominant involvement of motor skills, psychomotor speed, and verbal fluency, while in the HAART era, a greater impairment of memory and executive functions have been found [20], which correlates with greater temporal and frontal atrophy and less involvement of basal ganglia in MRI and pathological studies [25, 31]. Individuals with age over 50 have a higher proportion of amnestic cognitive impairment [20].

Persistent inflammation associated with HIV infection might facilitate neurodegenerative disorders in patients with an increasing age [23]. There are some parallels between HAND and Alzheimer disease. In patients with HIV infection, an abnormal metabolism of β-amyloid protein is suggested [53], and APOE e4 allele and older age are associated with the presence of amyloid plaques in the brain of HIV-infected patients and the probability of developing HAND [54]. Antiretroviral treatment with protease inhibitors may cause neurodegeneration altering amyloid precursor protein processing [55]. The present criteria for the diagnosis of HAND are not specific for the neural damage caused by the HIV and might not differentiate HAND from other neurodegenerative disorders. CSF analysis can help in the differential diagnosis between HAND and mild Alzheimer disease, because, while both show a decrease in β-amyloid 1–42, tau and phosphorylated tau levels are decreased in the later [53].

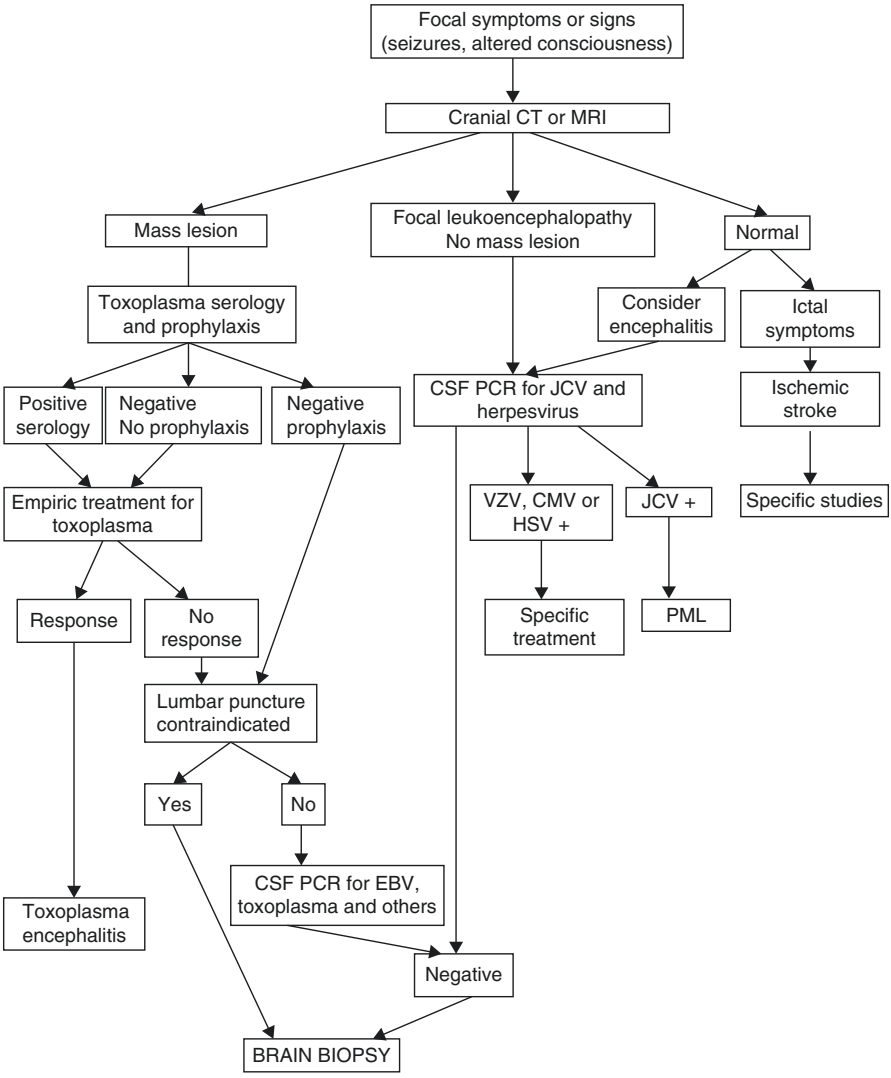
Focal Brain Lesions

For the evaluation of focal brain lesions, clinical presentation, temporal evolution, and CSF and radiographic features should be considered. Opportunistic infections and tumors are usually present at advanced stages of disease (CD4 under 200/mm^3) [3]. Although the spectrum of diseases that may cause focal lesions is wide, three diseases constitute the great majority of focal lesions: toxoplasma encephalitis (TE), PCNLS, and PML. In patients under HAART, PML seems the most frequent cause. The evolution of the diseases is typically in hours or days in TE, days or weeks in PCNSL, and weeks or months in PML. A diagnostic algorithm is proposed in Fig. 15.2. In some patients, the presence of systemic infection might suggest the possible etiology. Ring-enhancing lesions on CT or MRI are identical in abscesses caused by different microorganisms and may be difficult to distinguish from tumors. Single-photon emission computed tomography with thallium-201 and positron emission tomography with fluorodeoxyglucose are useful for the differentiation between neoplastic and infectious lesions. A definite diagnosis will frequently be established only by biopsy. If lumbar puncture is not contraindicated because of mass effect, it is helpful to perform specific CSF studies, such as cultures; polymerase chain reaction (PCR) for toxoplasma, mycobacteria, bacteria, JC virus (JCV), and herpesviruses; cytology; or immunophenotyping.

TE is the most frequent cause of focal brain lesions in AIDS. It usually results in reactivation of latent infection, and, therefore, IgG antibodies against toxoplasma are detected in more than 90% of cases. Clinical presentation consists in focal neurological deficits or seizures. Lesions most frequently locate at the cortico-subcortical union but may affect the basal ganglia and, rarely, the brainstem or cerebellum. Multiple lesions are found in more than 50% of patients. The characteristic lesions on CT are hypodense with perilesional edema and mass effect, with ring or nodular contrast enhancement. A target sign highly suggests TE. A rare diffuse form of TE has been reported in AIDS. The high frequency of TE justifies empiric treatment when it is suspected by radiology, even if serology is negative, which allows an *ex juvantibus* diagnosis. In a patient with negative serology under prophylaxis with co-trimoxazole, the probability of TE is very low, and empiric treatment is not indicated: a prompt brain biopsy should be scheduled. CSF PCR for toxoplasma has high specificity, but there are false negative results despite improved sensitivity with novel targets [3]. Treatment consists in an induction phase with two drugs (pyrimethamine and sulfadiazine, or clindamycin, with folinic acid) for at least 6 weeks. Steroids may be added in the presence of significant mass effect. An indefinite maintenance therapy should be given to avoid relapses. In fact, relapses may occur in 20% of cases and are related with inadequate maintenance therapy. In patients under HAART with more than 200 CD4/mm^3, maintenance therapy can be confidently suspended because the risk of relapse is very low in this setting.

PCNSL are diffuse B-cell or immunoblastic lymphomas, associated with the *Epstein–Barr virus* (EBV) [56]. PCNSL is multicentric in 40% of patients (up to 72% in autopsy series). They are most commonly supratentorial and frequently periventricular, and only 10% locate infratentorial. Spinal and meningeal forms are

rare. Most patients present focal neurological deficits. Intracranial hypertension, changes in mental status, and, occasionally, seizures may also occur. CT shows a hypodense, or sometimes hyperdense, lesion, with perilesional edema and mass effect, with ring enhancement after contrast. Dissemination through the ependymary surface is a very characteristic radiological sign of PCNSL. Detection of EBV in CSF by PCR has also shown a high diagnostic value for PCNSL. Prognosis is fatal in patients without antiretroviral therapy, with a mean survival of 1 month, which can be prolonged to 3 months with radiotherapy or steroids. In patients receiving HAART, survival is significantly prolonged, for years, and some achieve complete remissions [57]. Chemotherapy with high-dose methotrexate combined



with HAART may be effective without attenuating CD4-cell recovery and may be considered the first-line intervention [57].

PML is a CNS demyelinating disease caused by oligodendrocyte infection by the JCV, a DNA virus of the *Polyomavirus* family. It affects 4% of AIDS patients. JCV infection is practically universal in adults, and nonpathogenic strains may remain latent in the kidney and other organs [58]. Immune depression may favor replication of pathogenic strains (with rearrangements in the regulatory region of DNA), their hematogenous spread, and CNS infection. Alternatively, brain JCV latent infection may reactivate when immune surveillance fails. JCV binds serotoninergic 5-HT_{2A} and sialic acid receptors for integration in infected cells. Productive infection of neurons by a variant JCV has recently been demonstrated: infection of the granular cells of the cerebellum causes cerebellar syndrome without demyelination, and infection of pyramidal cells causes an acute encephalopathy [59].

PML manifests clinically as a slowly progressive focal deficit along weeks or months. It is often the first manifestation of AIDS. The most frequent initial symptoms are limb paresis, cognitive impairment, or visual symptoms. Seizures occur in 18% of patients, are associated with juxtacortical lesions, and have a good response to antiepileptic drugs [60]. Neuroimaging studies are, in the clinical context, the main clue to suspect the diagnosis [61]. CT shows characteristic hypodense lesions, without mass effect or contrast enhancement, in the periventricular or subcortical white matter. Subcortical lesions display a geographic pattern as a consequence of U fibers involvement. MRI is more sensitive than CT for PML lesions. Lesions are hyperintense in T2- and FLAIR-weighted sequences and hypointense in T1-weighted images (Fig. 15.3). Gadolinium enhancement is exceptional (5–10% of cases) and, when present, it is usually mild and peripheral. However, atypical nodular-enhancing lesions may occur in patients with high CD4 count [62]. In diffusion sequences, there is restriction in the active borders of the lesions.

Fig. 15.2 Algorithm for the management of HIV-infected patients with focal brain lesions. Cranial tomography (CT) or magnetic resonance imaging (MRI) should be performed in every HIV-infected patient presenting with focal symptoms or signs, seizures, or altered state of consciousness. MRI is more sensitive to detect leukoencephalopathies, encephalitis, or posterior fossa lesions. If CT is normal and symptoms had ictal presentation, an ischemic stroke should be considered, and the possible cause specifically investigated. In the presence of a mass lesion, empiric antitoxoplasma therapy is indicated in the case of a positive serology, but also if serology is negative, when the patient has not received prophylaxis with co-trimoxazole. Biopsy is indicated if no clinical or radiological improvement is noted after 2 weeks of treatment or the patient has negative serology and received prophylaxis, because in this case the probability of toxoplasma encephalitis is negligible. Before brain biopsy, if there is no contraindication for lumbar puncture because of the mass effect, an attempt for specific diagnosis by means of polymerase chain reaction (*PCR*) and other studies in cerebrospinal fluid (*CSF*) should be considered. If neuroimaging studies are normal, viral encephalitis must be considered, and CSF PCR for *Cytomegalovirus* (*CMV*), herpes simplex virus (*HSV*), and *Varicella-zoster virus* (*VZV*) should be performed. In the case of focal lesions suggesting focal leukoencephalopathy, CSF PCR for VZV or JC virus (*JCV*) may aid the diagnosis of VZV leukoencephalitis or progressive multifocal leukoencephalopathy (*PML*). If both are negative, brain biopsy is necessary

A characteristic pattern in MRI spectroscopy may help in the diagnosis of PML: there is reduction of N-acetyl-aspartate and increase in choline, lipids, and myoinositol. CSF is normal or can show mild protein elevation.

A definite diagnosis of PML can be made on the basis of imaging and clinical characteristics combined with PCR detection of JCV DNA in the CSF [63] given its high predictive values [64], avoiding the need for brain biopsy. Sensitivity, however, is always below 75%, and a negative result does not exclude the diagnosis. Sensitivity can be increased with repeated CSF studies. The confirmation of LMP diagnosis requires demonstration of the characteristic pathological changes and of JCV in biopsy specimens or autopsy. The differential diagnosis of PML includes other possible causes of leukoencephalopathy in patients with HIV infection. The leukoencephalopathy present in HAD may be confounded with PML. Aside from the clinical differences, the former is isodense in T1-weighted sequences, does not reach juxtacortical regions, and does not involve posterior fossa. Other diagnoses to consider are VVZ vasculopathy, multiple sclerosis-like disease, CMV encephalitis, posterior reversible leukoencephalopathy, leukoencephalopathy caused by heroin inhalation, ischemic stroke, and low-grade astrocytomas.

The natural course of PML is fatal within a mean of 4 months. Factors associated with shorter survival are lower CD4 count, brainstem or cerebellar involvement, and high JCV viral load in CSF in quantitative PCR [65]. A short percentage of patients

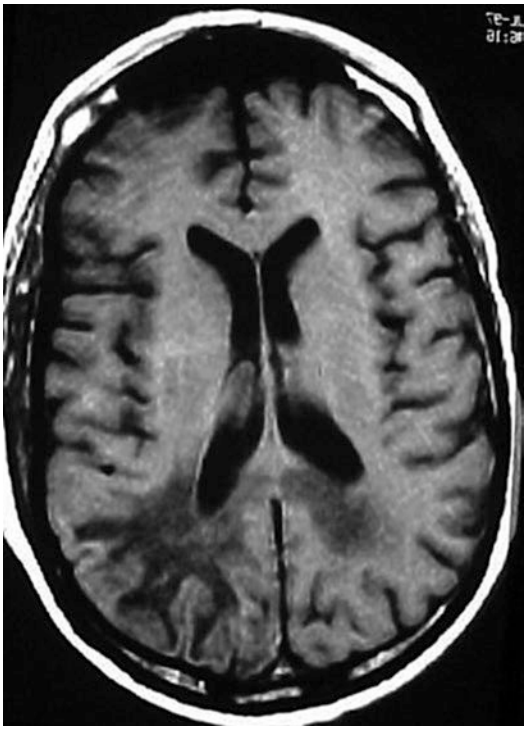


Fig. 15.3 Progressive multifocal leukoencephalopathy. T1-weighted magnetic resonance imaging

may stabilize or improve spontaneously, with survival for more than 30 months or even complete remission. They have a higher CD4 count, some of them over 300/mm^3, and show frequently contrast enhancement due to inflammatory infiltrates [66].

Since the introduction of HAART, the prognosis of PML has improved drastically. More than 50% improve or stabilize clinically, and the disease remains inactive after 1-year follow-up. MRI lesions also improve or stabilize in the majority of patients. Prolonged survival associates with restoration of the specific T-cell response against JCV [67] and reduction or negativization of JCV load [68]. However, efficacy of HAART is limited, since one-third of treated patients die due to progression of the lesions and half of survivors do not show significant neurological improvement [68]. A 3-year survival of only 27–50% has been reported despite HAART [5, 69]. PML is the AIDS-defining disease with higher mortality in the HAART era, after non-Hodgkin lymphoma. No specific treatment for PML has demonstrated efficacy, including cidofovir and mefloquine, which were reported beneficial in some cases [70]. Mirtazapine, a 5-HT_{2A} antagonist, has also been reported to improve LMP in some patients.

Multiple infections can cause brain abscess in AIDS patients. Tuberculous granuloma or abscess and nocardia abscess should be considered (Fig. 15.4). Fungal

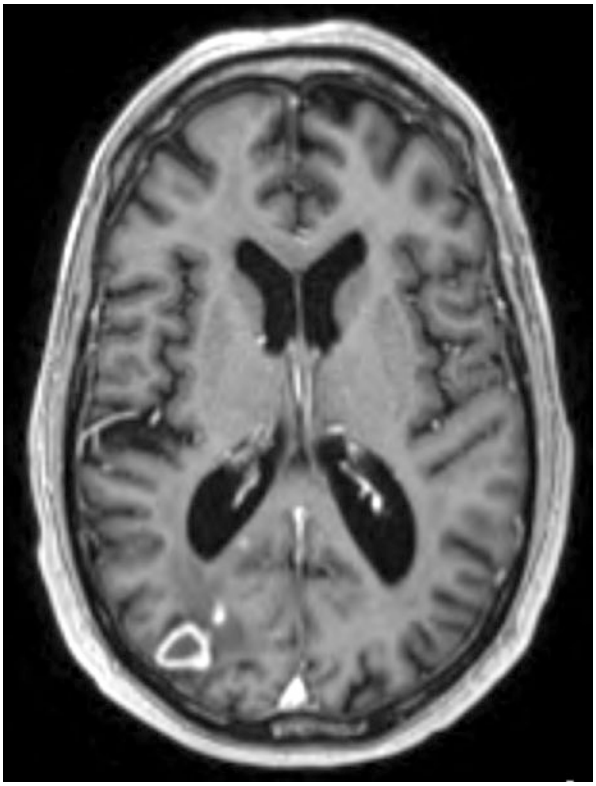


Fig. 15.4 Tuberculous granuloma. T1-weighted MRI, after intravenous gadolinium. Ring-enhancing lesion with perilesional edema and a small satellite nodular-enhancing lesion

granulomas or abscesses are uncommon and include those caused by *Aspergillus*, *Mucor*, *Histoplasma*, *Cryptococcus*, and *Candida*. Cases of syphilitic gumma and cysticercosis have been reported in patients with HIV infection. Brain tumors may be secondary to Kaposi's sarcoma, systemic lymphoma, or other solid tumors, whose incidence are increased in HIV infection. Primary brain tumors, such as gliomas, seem also increased in these patients. Demyelinating diseases, either a multiple sclerosis-like disease or acute disseminated encephalomyelitis, have been reported in primary infection and early stages of HIV infection but may occur also in advanced stages.

Encephalitis Caused by Herpesviruses

CMV is the most common herpesvirus causing neurological disease in AIDS patients. Risk for CMV diseases parallels the immune suppression and is maximal with CD4 counts below 50/mm^3 [3]. Median CD4 count in patients with CMV encephalitis is 20/mm^3 (range 2–94) [71]. CNS involvement by CMV usually takes place in the context of systemic CMV infection, particularly retinitis, and encephalitis frequently develops despite maintenance therapy against CMV. An impressive reduction in the frequency of CMV disease, including CNS disease, followed the introduction of HAART, and, nowadays, it has practically disappeared in developed countries.

Two clinicopathologic forms of CMV encephalitis can be distinguished, as extremes of a spectrum where mixed forms are common: ventriculoencephalitis and diffuse micronodular encephalitis [71, 72]. In ventriculoencephalitis, there is destruction of the ependymal layer and necrosis of periventricular parenchyma. Diffuse micronodular encephalitis presents as a subacute dementia difficult to differentiate from HAD. MRI has low sensitivity for CMV encephalitis. The most characteristic finding is periventricular contrast enhancement, with or without hydrocephalus. CSF may show normal findings or pleocytosis. Detection of CMV DNA in CSF by PCR is the diagnostic test of choice for neurological CMV disease [64, 73]. CMV CNS disease is usually fatal in a few weeks [71]. Antiviral drugs against CMV are not effective in most cases, but a combined regimen with foscarnet and ganciclovir may produce clinical improvement or stabilization in a high proportion of cases [74], until immune reconstitution with HAART.

Herpes simplex virus (HSV) encephalitis in AIDS patients can show identical presentation as that of immunocompetent patients [75] or can present with atypical clinical or pathological presentations due to immune suppression. HSV-2 encephalitis, and concomitant HSV-1 or HSV-2, and CMV encephalitis have been reported in HIV-infected patients [76]. The demonstration of HSV DNA in CSF by PCR has high diagnostic value for HSV encephalitis [76]. Acyclovir is the treatment of choice, although resistant strains may cause disease in AIDS. A bad response is the rule in cases with severe immune depression, usually associated with CMV encephalitis [76].

The risk of herpes zoster complications increases with immune depression [77]. They can present months after cutaneous lesions or even without them. VZV encephalitis or leukoencephalitis is considered to represent actually a vasculopathy

caused by the virus [78]. Large artery vasculopathy causes cerebral infarction. Small artery vasculopathy produces demyelination or necrotizing leukoencephalitis with a multifocal distribution and sometimes with hemorrhages. This condition manifests clinically with a progressive encephalopathy with variable impairment of consciousness and focal signs, which may take a chronic course. Sometimes the encephalitis is limited to the brainstem. Demyelinating lesions can be seen in CT or MRI. The association of multiple ischemic and hemorrhagic lesions is highly suggestive of VZV vasculopathy. Cerebral angiography may show arterial narrowing indicative of vasculitis. CSF usually contains high proteins without pleocytosis. Demonstration of VZV DNA in CSF may be useful for the diagnosis of VZV neurological complications. Intrathecal synthesis of IgG antibodies against VZV is more sensitive than PCR for the diagnosis [78]. Treatment with acyclovir may improve VZV encephalitis. Steroids are indicated as coadjutant therapy for vasculitis.

Stroke in Patients with HIV Infection

The frequency of stroke is highly increased in HIV-infected patients compared to an age-matched population, after controlling for traditional risk factors [79]. Patients with HIV infection may suffer a stroke due to a wide spectrum of mechanisms and etiologies [80–82]. Ischemic stroke may be caused by infections, most of them associated with immune depression, such as vasculitis associated with opportunistic meningitis (bacterial, including tuberculous, cryptococcal, or candidal), VZV, or CMV infection. Meningovascular syphilis should also be considered. Cardioembolic stroke may be related to AIDS-related cardiomyopathy, nonbacterial thrombotic endocarditis, and, particularly, infectious endocarditis in intravenous drug users. Between hematological causes, the high frequency of antiphospholipid antibodies and protein S deficit should be borne in mind, although it is sometimes difficult to establish a causal relationship. Acute stroke may occur also in the context of disseminated intravascular coagulation. Atherothrombotic stroke is also common, especially in older patients [80]. HIV per se may cause large vessel vasculopathy, sometimes with formation or large aneurysms, which may be the cause of up to 20% of strokes in these patients [82]. In many cases, stroke cause cannot be finally demonstrated.

In recent years, there has been concern about a possible risk of accelerated atherosclerosis associated with HAART, particularly with protease inhibitors, which may cause metabolic syndrome, with dyslipidemia and insulin resistance. The risk increases with the time of HAART exposure but also with the presence of vascular risk factors [83]. The incidence of ischemic stroke in HAART-treated patients is also increased with respect to the general population [81], and a substantial rise in patients hospitalized for stroke with coexisting HIV infection has been noticed in the United States [84]. However, the causes of the stroke in these patients are also multiple, and as yet it is not been shown that HAART increases the frequency of atherothrombotic strokes [80, 81].

Meningitis

Causes of meningitis among HIV-infected patients are multiple, including viral, bacterial, and fungal infections, together with carcinomatous meningitis. Clinical and CSF findings may be similar in all types of meningitis in HIV-infected patients. In some patients, CSF analysis can be entirely normal. Therefore, an exhaustive processing of CSF samples covering all the possible etiologies is warranted in cases with suspected meningitis. However, the low diagnostic yield of CSF microbiological studies forces empirical treatment in many patients. *Cryptococcus* and *Mycobacterium tuberculosis* meningitis are the most frequent etiological agents of meningitis in these patients. Aseptic lymphocytic meningitis may be caused by the HIV and herpesviruses, particularly VZV. The incidence of conventional bacterial meningitis is highly increased in comparison with the general population, even in the HAART era, and carries out a worse prognosis [85]. *Streptococcus pneumoniae* is the most frequent agent. *Listeria* meningitis may be increased in HIV-infected patients. *Staphylococcus aureus* causes meningitis in intravenous drug users, sometimes associated with endocarditis. Meningitis due to *Candida* spp. has been reported in HIV-infected patients usually in the presence of other predisposing factors, such as intravenous drug use and previous antibiotics [86].

The clinical manifestations of tuberculous meningitis are similar in patients with and without HIV infection [87]. Presentation is with subacute or chronic (occasionally acute) meningeal syndrome with fever, headache, and frequently altered mental status. Cranial nerve involvement is common, and focal neurological symptoms may be the consequence of vasculitic infarctions or granulomas. Most patients have extraneurological tuberculosis, and 50% have lung infiltrates. CT and MRI may reveal hydrocephalus, meningeal enhancement, and, occasionally, granulomas. CSF contains a variable pleocytosis, which is usually lymphocytic, but sometimes polymorphonuclear, elevated proteins, and low levels of glucose. Sensitivity of the Ziehl-auramine stain is low (20%), as is the yield of CSF cultures for mycobacteria. Adenosine deaminase activity in CSF has been considered useful in the early diagnosis of tuberculous meningitis but in HIV-infected patients has low sensitivity and specificity [88]. CSF PCR for *M. tuberculosis* in CSF may aid in the diagnosis because of its high sensitivity and specificity. Treatment for tuberculous meningitis is the same to that of people without HIV infection, including the use of dexamethasone. Meningitis caused by other mycobacteria is rare.

Cryptococcal meningitis is the leading cause of meningitis in sub-Saharan Africa, where it causes a high mortality compared to developed countries [89]. Cryptococcal meningitis may be indistinguishable from tuberculous meningitis on clinical grounds or in CSF findings [3]. A characteristic finding in MRI is dilatation of the Virchow–Robin spaces in the basal ganglia. CSF India ink can demonstrate the fungal capsule in 75% of cases. Cryptococcal antigen is positive in 90–100% of patients in CSF and in 75–99% in serum, always with high specificity. Treatment of choice is amphotericin B associated with 5-fluocytosine. A maintenance therapy with fluconazole is mandatory because of the high risk of relapse. In patients under HAART, maintenance therapy can be suppressed after 3 months with CD4 over 100/mm^3 and undetectable HIV viral load.

Myelopathies

Myelopathies affecting patients with HIV infection are best classified in segmentary myelopathies, which tend to present with an acute or subacute course, and diffuse myelopathies, usually with a progressive chronic or subacute presentation, as is the case with vacuolar myelopathy.

Vacuolar myelopathy is the most common cause of myelopathy in these patients [90]. It has been found in 50% of autopsies of AIDS patients, although only one-fourth of them were evident clinically. Pathological anomalies predominantly involve the lateral and dorsal columns of dorsal region, resembling subacute combined degeneration. It presents clinically as slowly progressive (along weeks or months) and symmetric spastic paraparesis. Gait ataxia or sensory symptoms are also common presentations. Sphincter symptoms are late. HAD is present in 60% of the patients. Neurological exam reveals that vibration and position senses are more severely affected than pain or light touch. There are symmetric pyramidal signs, but hyperreflexia might be absent in the case of associated peripheral neuropathy. Vacuolar myelopathy progresses slowly to spastic paraplegia. Diagnosis is mainly clinical, after other possible causes of myelopathy are excluded by means of spinal MRI and CSF studies. MRI shows atrophy of the spine and, occasionally, hyperintensities in the lateral or dorsal columns. There is no specific treatment. There have been reports of patients who improved after HAART. The other chronic diffuse myelopathy to consider in patients with HIV infection is tropical spastic paraparesis caused by HTLV-I, particularly in patients from countries where this infection is prevalent. Contrary to what happens with vacuolar myelopathy, this disease does not occur necessarily in patients with significant immune depression [91].

Among the segmentary myelopathies, viruses are the most frequent causes. HIV may cause transverse myelitis during primary infection. VZV myelitis develops more frequently in immunocompromised patients [92]. Weakness progresses in weeks but may show a chronic course over several months. MRI may be normal or show spinal hyperintensities in T2-weighted sequences, which may enhance after gadolinium. CSF may also be normal or demonstrate a variable inflammatory response. The HSV-1 and more frequently the HSV-2 in association with genital herpes are other possible causes of myelopathy. CMV can cause necrotizing myelopathy, sometimes concomitant with HSV-2. A case of human herpesvirus-7 mielitis has been reported recently [93]. Other causes of segmentary myelopathies are toxoplasmosis, tuberculous granuloma, epidural tumor or abscess, and vascular lesions due to syphilis or disseminated intravascular coagulation. Primary intramedullary tumors, as gliomas or lymphomas, are rare.

Neuropathies

Peripheral neuropathy is very common in HIV infection. In the pre-HAART era, the prevalence of symptomatic neuropathy was 35%, while 20% had asymptomatic neuropathy [94]. A similar prevalence has been found in HAART-treated patients, despite controlled HIV infection [95]. In naïve patients, polyneuropathy is present in 31% of cases after several years of treatment, but it is symptomatic

in only 5% [96]. For the clinical management of patients with suspected neuropathy, it is useful to classify neuropathies according to the clinical and electrophysiological pattern [97]. We will consider four groups: demyelinating neuropathies, axonal polyradiculopathies, mononeuritis multiplex, and distal symmetric polyneuropathy.

Distal symmetric polyneuropathy is the most frequent pattern. It is an axonal predominantly sensory polyneuropathy, caused most commonly by the HIV itself and by antiretroviral toxicity [97]. These two etiologies are practically indistinguishable from the clinical or electrophysiological point of view. Other causes of predominantly sensory distal neuropathy in these patients are alcoholism, malnutrition and vitamin deficits, diabetes, and uremia. A clinical picture similar to distal sensory polyneuropathy may occur with CMV nerve infection. HIV-associated distal sensory polyneuropathy characteristically presents with symmetric distal painful paresthesias and affects mainly the legs. Only occasionally a motor deficit exists. Examination may disclose hypesthesia with a stocking and glove distribution and distal hyporeflexia. Treatment is only symptomatic. Tricyclic antidepressants and antiepileptic drugs as gabapentin and lamotrigine are widely used, but unfortunately only topic capsaicin and *Cannabis* have demonstrated efficacy in controlled studies [97]. Antiretroviral toxic neuropathy is caused by the nucleoside reverse transcriptase inhibitors didanosine, zalcitabine, and stavudine. Combined therapy has a synergistic toxic effect. It affects between 15 and 30% of treated patients. Treatment consists in drug suppression and symptomatic treatment as used for VIH-associated neuropathy. Other drugs used in HIV-infected patients may cause toxic neuropathy: vincristine, isoniazid, dapsone, metronidazole, and thalidomide. Autonomic nervous system dysfunction can be demonstrated in a high percentage of HIV-infected patients in advanced stages, frequently in association with distal neuropathy, but it is rarely symptomatic.

Demyelinating inflammatory neuropathies are an uncommon cause of neuropathy in HIV-infected patients. Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy in HIV-infected patients have the same clinical, electrophysiological, and pathological characteristics as in uninfected patients [98]. CSF may contain mild pleocytosis, but not in all cases. Both present in patients without significative immune depression or in primary HIV infection.

Acute lumbosacral polyradiculitis, or cauda equina syndrome, is a well-defined clinical syndrome in AIDS patients with multiple causes [99, 100]. Most cases are caused by CMV infection. Tuberculosis is the second most frequent cause. Other reported etiologies are VZV and HSV, often associated with myelitis, cryptococcal or bacterial meningitis, syphilis, and meningeal lymphomatosis. All these causes have similar clinical presentation and CSF findings. CMV polyradiculitis presents with acute or subacute progressive leg weakness, often accompanied with paresthesias and radicular pain and urinary retention. Encephalopathic symptoms are frequent in final stages due to associated encephalitis. CSF contains variable pleocytosis, which may be polymorphonuclear in the most typical cases, increased proteins, and normal or low glucose. CSF PCR for CMV is the diagnostic test of

choice. Lumbar MRI is needed to exclude other causes of cauda equina syndrome. It may show normal results or demonstrate contrast enhancement in the roots and conus medullaris. This disease is fatal in most untreated cases. Treatment with ganciclovir or foscarnet has been successful in many patients. Therefore, rapid initiation of empirical antiviral treatment is mandatory when the disease is suspected.

Mononeuritis multiplex in HIV-infected patients is due mainly to two causes: the HIV itself and CMV infection. Less common causes are cryoglobulinemia associated with HCV, peripheral nerve infiltration by lymphoma, and diffuse infiltrative lymphocytosis syndrome. Mononeuritis multiplex associated with HIV is caused by peripheral nerve vasculitis and presents in early stages, whereas CMV neuropathy presents in severely immunocompromised patients [101]. The latter is a multifocal sensory and motor neuropathy with a subacute or chronic course, which often presents with patchy areas of dysesthesia and paresthesia. CSF is usually normal. It may improve with ganciclovir or foscarnet.

Myopathies

Two myopathies, difficult to differentiate form each other, may present in HIV-infected patients. One is HIV-associated myopathy, and the other is AZT myopathy. HIV-associated myopathy may present at any moment in the course of HIV infection [102]. Clinical and pathological findings are similar to those of polymyositis. The patient experiences symmetric limb weakness, with a predominantly proximal distribution, progressing in months. Patients improve with steroids. AZT myopathy has a similar clinical presentation but has a distinctive pathological pattern [103], probably related with mitochondrial dysfunction caused by the drug. Cases of severe rhabdomyolysis caused by other antiretroviral drugs, such as didanosine and raltegravir, have been reported. Other causes of myopathy in HIV-infected patients include focal myositis caused by toxoplasma and pyomyositis of diverse etiologies, frequently associated with venous puncture in drug addicts.

Neurosyphilis and HIV

Neurosyphilis may occur in any stage of HIV infection. However, the prevalence is higher than in patients without HIV infection and greater in patients with CD4 counts under 350/mm^3 [104]. In HIV-infected patients, neurosyphilis appears mainly in early stages of the syphilitic infection. For this reason, some authors have recommended CSF analysis in every patient with syphilis and HIV infection. However, CSF analysis is not considered necessary in cases of primary, secondary, or early latent syphilis, if neurological, visual, or auditory symptoms are not present. In HIV-infected patients, neurosyphilis may be asymptomatic or present the usual range of presentations in the general population that include lymphocytic meningitis, cranial neuropathies (VIII nerve), optic neuropathy, meningovascular syphilis, meningomyelitis, meningoradiculitis, cerebral gummas, general paresis, or tabes dorsalis. Some difficulties for the diagnosis of neurosyphilis may be present in these patients. CSF pleocytosis is one of the clues for the diagnosis of

neurosyphilis, but it is common in HIV infection. Occasionally non-treponemal tests for syphilis, VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma reagin), are negative in CSF. Treatment is the same as for patients without HIV infection. Reports of HIV-infected patients correctly treated for primary syphilis who had meningovascular relapse have induced some authors to recommend treating with doses for neurosyphilis every HIV-infected patient with syphilis.

Neurological Complications Associated with HAART

Neurological Immune Reconstitution Inflammatory Syndromes

Following the initiation of HAART, there is a rapid fall in plasma levels of HIV RNA and an increase in T lymphocytes, accompanied by significant functional improvement. Due to the restoration of the capability to develop an inflammatory response against infectious and noninfectious antigens, some patients may suffer clinical deterioration. This phenomenon is designated as immune reconstitution inflammatory syndrome (IRIS) [105]. Some autoimmune diseases presenting after initiation of HAART may be considered part of this entity. IRIS may represent the debut of a previously unknown disease (unmasking IRIS) or a paradoxical clinical deterioration of a known disease (paradoxical IRIS) after the beginning of HAART. IRIS affects between 15 and 35% of patients receiving HAART, and 1% suffer neurological IRIS, but the frequency is higher in patients with known opportunistic infections. Risk factors for IRIS are a higher immune depression before HAART and a more rapid immunological response [105]. IRIS usually presents in the first weeks or months of therapy but may be retarded for more than 1 year. In CNS–IRIS, there is infiltration of the CNS with activated T-cells. Recognizing this clinical entity is essential for the appropriate management of the patient, without compromising antiretroviral or anti-infective treatment.

The most common causes of CNS–IRIS are tuberculosis, cryptococcosis, and PML. IRIS presents in 30% of all patients with a diagnosis of tuberculosis who initiate HAART, and 12% of them may be neurological syndromes [106]. Intracranial tuberculomas, meningitis, or myeloradiculitis may appear or deteriorate, after a mean of 14–43 days. Similarly, IRIS may present in 17% of cryptococcal meningitis [107]. Latent meningitis may be unmasked. In addition to the clinical deterioration of the patient, there is increased inflammatory reaction in CSF and meningeal enhancement in neuroimaging studies, and granulomas may appear. Steroids improve the inflammation and clinical course of CNS–IRIS associated with tuberculosis and cryptococcosis. In patients with tuberculosis or cryptyococcal meningitis, HAART initiation must be retarded after several weeks [108].

IRIS occurs in up to 30% of PML patients treated with HAART [109]. After the clinical deterioration produced by IRIS, the patient may improve spontaneously, but occasionally the course is fatal. Thus, while effective HAART initiated early is essential for the improvement of PML patients, this treatment may result in death for some patients. Global mortality of PML patients with or without IRIS is similar, but patients with paradoxical IRIS have higher mortality than those with unmasking IRIS. In

neuroimaging studies, the inflammatory component can be demonstrated as contrast enhancement of the lesions in 31–60% of cases. CSF may also show inflammatory signs, something unusual in PML. CSF PCR for JCV is frequently negative because the host immune response can control JCV replication. Treatment with steroids may be beneficial in PML-IRIS if initiated before major neurological deterioration occurs [109].

The incidence of herpes zoster increases up to five times in patients with HAART. Most cases (86%) present between the second and fourth months of treatment [110]. VZV myelitis and encephalitis have also been reported as IRIS [105]. Other neurological IRIS reported are associated with TE, *Candida* meningitis, CMV ventriculoencephalitis, PCNSL, and primary cerebral lymphomatoid granulomatosis [105, 111, 112]. The HIV itself might be the triggering antigen of a neurological IRIS, causing encephalitis with multiple or diffuse lesions and CD8 lymphocyte infiltration in pathological studies (Fig. 15.5) [113, 114]. It is important to recognize this entity because it may improve with steroids. Chronic form of CNS–IRIS induced by persistent HIV replication within the CNS might be an important component of HAND [105]. Indeed, patients with HAART failure may suffer a severe form of diffuse encephalitis with an important inflammatory reaction [115] and predominant basal ganglia involvement when associated with cocaine abuse [116].

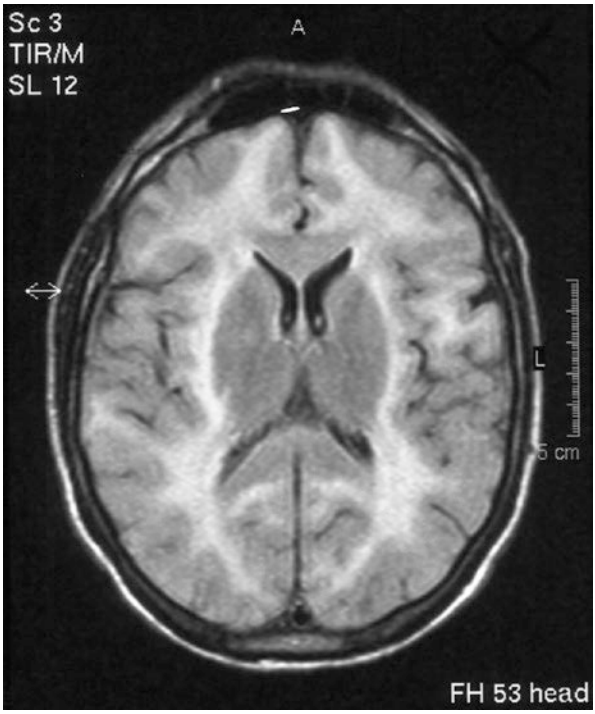


Fig. 15.5 Diffuse leukoencephalopathy in a patient with CD8 encephalitis. MRI FLAIR sequence showing bilateral symmetrical subcortical and periventricular white matter hyperintensities

After the initiation of HAART, the possible appearance of autoreactive T-cells might trigger autoimmune diseases, such as Guillain–Barré syndrome and demyelinating leukoencephalopathies [105].

Neuromuscular Weakness Associated with HIV

Patients undergoing HAART may present a syndrome of acute or subacute neuromuscular weakness associated with lactic acidosis [117]. In most cases, an axonal neuropathy is demonstrated in electrophysiological and pathological studies, but some patients have a myopathy (15%) or both. This picture resembles axonal Guillain–Barré syndrome. One-third of patients have sensory symptoms, and some have cranial nerve involvement. Hyperlactacidemia causes systemic symptoms, vomiting, and abdominal pain. Mortality of this syndrome is 13%. It has been related to nucleoside reverse transcriptase inhibitors, particularly stavudine, the antiretrovirals most frequently associated with lactic acidosis. The pathogenesis is not known, but it is considered to be probably caused by mitochondrial dysfunction.

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Neuropathies of Infectious Origin

16

Aida Rodriguez Sainz and Amaia Martinez Arroyo

Abstract

Peripheral neuropathies can be caused by a variety of infectious agents, including viruses, bacteria, and parasites. Infectious neuropathies are potentially treatable, and thus their recognition is crucial. In some developing countries, they constitute the main cause of peripheral neuropathy, with leprosy being the most relevant. The presentation of infectious neuropathies encompasses a wide range of peripheral nervous system disorders, including peripheral neuropathy, radiculopathy, radiculomyelopathy, cranial neuropathy, and motor neuropathy. This chapter describes the most frequent neuropathies of infectious origin. While some of them represent well-known clinical syndromes, there are other recently reported neuropathies caused by emergent viruses, an example of which is illustrated by the association between Zika virus infection and Guillain-Barré syndrome.

Keywords

Infectious neuropathy • Radiculopathy • Cranial neuropathy • Herpesviruses Dengue • Rabies • Zika • Chikungunya • Diphtheria • Brucella • HIV *Trypanosoma cruzi* • Leprosy

Different microorganisms can result in damage of peripheral nerves either by direct infection or by immune-mediated mechanisms. Early diagnosis and treatment help reduce chronic nerve damage, usually associated with deformities, chronic pain, and disability. We review the most important forms of infectious neuropathies;

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some of them are described in other sections of this book, to which the reader will be referred when pertinent.

Viral Neuropathies

Herpesviruses

Herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV) are double-stranded DNA viruses belonging to the *Herpesviridae* family and can cause peripheral nervous system (PNS) disorders. HSV-1, HSV-2, and VZV are neurotropic viruses that may remain latent in the dorsal root ganglia or trigeminal ganglia after primary infection. PNS damage occurs more frequently during viral reactivation.

Herpes Simplex Virus Types 1 and 2

HSV-1 and HSV-2 infect mucocutaneous surfaces and cause orofacial (herpes labialis or cold sores, HSV-1) and genital infections (herpes genitalis, HSV-2). After invasion of the nerve endings within the mucocutaneous surfaces, the virus is transported to the dorsal root ganglia, where it remains latent. A variety of triggers, including sunlight exposure, menses, fever, or stress, reactivate the virus to travel through the axon to the skin causing the classical labialis or genitalis cutaneous eruption.

HSV primary infections are usually asymptomatic. Reactivation of HSV can occur many times during a lifetime and decreases with age. The resulting skin lesions are focal, do not involve the entire dermatome, and associate transient local burning or tingling.

HSV-1 has been implicated in the etiology of Bell's palsy, a facial nerve palsy of unknown etiology. However, the lack of motor impairment after HSV-1 reactivation and the multiple recurrences of cold sores contrast with the often single episode of Bell's palsy. Furthermore, acyclovir therapy does not add benefit to prednisolone alone [1].

HSV-2 reactivation may result in a lumbosacral polyradiculitis with pleocytosis, manifested by radicular pain, hypoesthesia, leg weakness, and urinary retention and constipation [2]. A few cases of Guillain-Barré syndrome (GBS) have been described following both primary and reactivated HSV infections [2, 3].

Varicella Zoster Virus

Varicella zoster virus primoinfection causes varicella (chickenpox), and its reactivation causes herpes zoster (shingles), which can lead to several PNS complications. VZV remains latent predominantly in neurons within the dorsal root ganglia and trigeminal ganglia. During reactivation, the virus replicates and spreads to the ganglion, where it infects many neurons resulting in PNS damage. Herpes zoster is a disease of elderly people, with an incidence that increases 8–10 times in people over 60 years [4] and immunocompromised patients (AIDS, organ transplants, patients

treated with immunosuppressive therapy or lymphoma) [5]. Herpes zoster usually presents as a single episode; the incidence of recurrent herpes zoster is less than 5% in immunocompromised patients [6]. This could be explained by the fact that during latency few VZV nucleic acids are detected in dorsal root ganglia, considerably less than in HSV latent infection. Therefore, the local cell-mediated immune response inhibits cell-to-cell spread more easily, thus preventing VZV reactivation. Advanced age and immunocompromised states impair the cellular immune response and facilitate viral reactivation [4].

Herpes zoster starts with sensory symptoms, including paresthesia, itching, dysesthesia, or neuropathic pain with dermatomal distribution. Then an erythematous rash follows and evolves to a vesicular eruption that affects the skin of the same dermatome, although in 20% of cases, it spreads to the adjacent dermatome or crosses the midline at the same spinal level. The trigeminal and thoracic nerves are most commonly involved. Herpes zoster ophthalmicus, affecting the first branch of the trigeminal nerve, can result in visual complications, particularly when the nasociliary branch is involved (cutaneous lesions within the lateral nose, Hutchinson's sign). Keratitis, conjunctivitis, anterior uveitis, or oculomotor ophthalmoplegia can also occur. Herpes zoster oticus, also called Ramsay Hunt syndrome, appears when the virus involves the geniculate ganglia. The clinical triad consists of facial paralysis, vesicular eruption in the external auditory canal, and ear pain. Thoracic, cervical, or lumbosacral herpes zoster can associate signs of radiculomyelitis, such as myotomal weakness and ileus paralytic or neurogenic bladder. Mild signs of aseptic meningitis appear in up to 50% of patients, and cerebrospinal fluid (CSF) analysis shows a mild lymphocytic pleocytosis with increased proteins [5].

Postherpetic neuralgia is the most common and fearful complication. There is a severe burning or lancinating pain involving the affected dermatome that persists for 4–6 weeks following shingles. Age over 50 years and prodromic sensory symptoms represent predisponents. Postherpetic neuralgia is difficult to treat. A combination of tricyclic antidepressants (amitriptyline, nortriptyline), serotonin and norepinephrine reuptake inhibitor antidepressants (duloxetine and venlafaxine), anticonvulsants (gabapentin, pregabalin), and anesthetics (topic lidocaine) may reduce pain.

Zoster sine herpete is a typical herpes zoster pain without cutaneous lesions but with positive VZV antibodies and positive PCR of the viral DNA in cerebrospinal fluid [6].

Varicella zoster virus and Guillain-Barré syndrome (GBS) association is rare but has been described. Whether this association is coincidental or causal is a matter of discussion [6]. A Taiwanese population-based study of 1,262,380 patients revealed that the risk for GBS was 18 times greater when herpes zoster was present [7].

The treatment for herpes zoster should be administered within the first 72 h following the cutaneous rash to shorten skin healing and reduce pain intensity. There are three approved oral drugs: aciclovir (800 mg five times daily for 7–10 days), famciclovir (500 mg 3 times daily for 7 days), and valaciclovir (1000 mg 3 times daily for 7 days). In immunocompromised patients with disseminated herpes zoster, intravenous acyclovir is recommended [8].

A live-attenuated vaccine in adults over 60 years reduces the incidence of herpes zoster in 51% and postherpetic neuralgia in 67% [9]. It seems to confer protection during 3 years and is well tolerated [10].

Epstein-Barr Virus (EBV)

Primary infection with EBV produces fatigue, fever, cervical lymphadenopathy, sore throat, and splenomegaly and is referred to as infectious mononucleosis. Peripheral nervous system disease secondary to EBV infection is rare.

Occasional single cases of acute inflammatory demyelinating polyradiculoneuropathy, lumbosacral radiculopathy, brachial radiculopathy, and acute autonomic neuropathy have been described [11].

Cytomegalovirus (CMV)

Primary infection with CMV is usually asymptomatic. Between 50 and 80% of adult population have been infected. Reactivation occurs in severely immunosuppressed patients (i.e., AIDS patients) and can affect the PNS. CMV produces acute lumbosacral polyradiculitis, mononeuritis multiplex, acute or chronic demyelinating inflammatory neuropathies, and distal symmetrical polyneuropathy. For a detailed description, see Chap. 15 of this book.

Dengue Virus

Dengue virus (DENV) is an RNA virus from the family *Flaviviridae*. There are four serotypes, and the infection with one of them does not provide long-term immunity against the others. All of them can affect the nervous system [12]. DENV is transmitted by *Aedes* mosquitoes, and 50–100 million people are infected worldwide every year. The classical infection, or dengue fever, is self-limited and is characterized by fever, headache, myalgias, arthralgias, abdominal pain, and rash. Hemorrhagic complications can be severe and are known as dengue hemorrhagic fever. The incidence of neurological complications ranges between 0.5 and 21% [13]. Encephalopathy and encephalitis are the most common. PNS complications represent 5% of the neurological complications. Occasionally, dengue is associated with Guillain-Barré syndrome, amyotrophic neuralgia, acute mononeuropathies, and myositis [14, 15].

The majority of the cases of GBS due to DENV have occurred after dengue fever, suggesting a post-infectious, immune-mediated disorder [14]. However, a few reports of GBS concomitant with dengue fever suggest a direct infection. All cases made a good recovery after intravenous immunoglobulin therapy.

Myositis due to DENV has a wide range of severity, from myalgias with mild muscle weakness and mild elevation of serum CPK levels to acute pure motor quadriparesis with respiratory muscle involvement and high CPK levels [12]. Hypokalemic paralysis presented as acute motor quadriparesis and hypokalemia with complete recovery after potassium supplementation in dengue patients has also been reported [16]. Amyotrophic neuralgia in dengue fever often involves the

brachial plexus. Acute phrenic or oculomotor mononeuropathies have also been described in patients with dengue fever.

Rabies

Rabies is caused by exposure to rabies virus type I, typically transmitted by bat bites in America and dog bites in the rest of the world [17]. There are two presentation forms, both usually fatal. The most frequent is the encephalitic form and is described in Chap. 6, together with viral transmission, CNS symptoms, and treatment options.

The second presentation, the paralytic form, is seen in approximately 20% of the cases. Initially, there is a loss of small and large fiber axons in the bitten site of the body that will spread in the following days to involve other limbs, resulting in a diffuse flaccid paralysis. As other axonal diseases, the EMG may be initially normal, since the typical axonal changes need some time to develop. A lymphocytic pleocytosis is typically revealed in CFS samples. The diagnosis can be made by detecting rabies virus RNA in the saliva, skin, CSF, and urine [5].

Chikungunya Virus (CHIV)

Chikungunya is caused by a togavirus and is transmitted by different mosquitoes, as explained in Chap. 6. CHIV rarely affects the nervous system but sometimes can cause meningoencephalitis, myelopathy, and neuropathy. The typical form of Guillain-Barrè syndrome has also been reported [18, 19]. In a series of 74 patients neurologically affected by CHIV in India, two types of neuropathy were described [20]. Early neuropathy was observed in 32 (43.2%) patients. The neuropathy developed within a few days after the onset of fever was frequently accompanied by encephalopathy or myelopathy. It was a sensory motor neuropathy with accompanying CSF pleocytosis and poor response to plasmapheresis or intravenous immune globulins. Late neuropathy occurred in 11 cases and presented a few weeks after the onset of fever. It resembled a classical GBS and improved with treatment (steroids/plasmapheresis). Ten patients showed a carpal tunnel syndrome, but it was likely due to a severe wrist synovitis rather than to viral penetration in the PNS. Detailed information about chikungunya virus is also provided in Chap. 6.

Zika Virus (ZIKV)

Although Zika virus was first isolated in Africa in 1947 with a distinct lineage isolated in Malaysia in 1966 [21], the first human epidemic became apparent on the Micronesian island of Yap in 2007. Zika virus is maintained primarily in a cycle between humans and *Aedes aegypti* mosquitoes. The virus spreads across the Pacific to Easter Island, and in 2015 it emerged in South and Central America and the Caribbean [22]. The symptomatic illness is nearly always a mild, self-limiting

illness with fever, rash, joint pain, maculopapular rash, joint and muscle pain, headache, and non-purulent conjunctivitis. In 2016 several reports linked the infection with microcephaly and fetal deaths in the Americas and with serious neurological disease, particularly Guillain-Barré syndrome, leading the WHO to declare the outbreak a global emergency [23, 24]. There is real concern that the Zika virus outbreak currently concentrated in Latin America and the Pacific Islands will spread to a global epidemic. Recently, two cases of myasthenia gravis occurring 8–10 weeks after ZIKV infection have been described [25].

The risk of Guillain-Barré syndrome was estimated to be 0.24 per 1000 infections [26]. The clinical picture has been extracted from the Indonesia and Colombia series [26–29]. Ascending paralysis (74–82%) and bilateral facial palsy (50–60%) were the most prominent features. In the Colombian population, 6 out of 68 presented a GBS variant (4 Miller Fisher syndrome, 1 facial diplegia with areflexia, and 1 sensory GBS). The majority of patients had symptoms of ZIKV infection in 4 weeks preceding the onset of neurologic symptoms, and the median duration of symptoms of ZIKV infection was 4 days. Most patients (82–93%) had raised CSF protein. The need of mechanical ventilation and prognosis was similar to GBS from other causes.

The electrophysiological findings in Zika-associated GBS provide conflicting results. A recent large series reported from Colombia has demonstrated acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in the majority of patients (78%), but the series from French Polynesia and from Cucuta (Colombia) described an axonal neuropathy [26, 27, 29]. A recent review concludes that most cases are consistent with a primary demyelinating neuropathy with predominant involvement of distal nerve segments typically represented by reduction in the mean terminal latency index [30]. Antiglycolipid (mainly asialo GM1) antibodies are present in 31% of Zika-associated CBS patients, but their pathogenic role is unclear [26, 30]. Therapy in these patients has included intravenous immunoglobulins (IV) and plasmapheresis.

Regarding the pathogenesis of Zika-induced GBS, several mechanisms have been proposed. First, molecular mimicry against nervous system antigens induced by the virus; second, an immune dysregulation created by other mechanisms not related to molecular mimicry; third, a viral-induced hyperacute immune response; and finally, direct neural damage induced by the virus, a phenomenon not previously seen in classical GBS [29].

The detection of ZIKV nucleic acids by real-time reverse transcriptase polymerase-chain reaction (RT-PCR) in the blood, CSF, or urine offers the most reliable diagnosis. Urine seems the most useful diagnostic fluid, since the virus is eliminated during several days after the viral syndrome is over [29, 31].

Bacterial Neuropathies

Diphtheria

Diphtheria is the result of an infection with *Corynebacterium diphtheriae*, a gram-positive bacillus transmitted via aerosol droplets. The bacillus releases a toxin that

affects mostly the nasopharynx but can spread systemically damaging the skin, heart, and peripheral nerves. Diphtheria represented a major cause of morbidity and mortality in children, but after vaccination, its incidence decreased dramatically; in 2014, only 7321 cases were reported worldwide to the World Health Organization.

The incidence of diphtheritic polyneuropathy is directly proportional to the severity of intoxication, and up to 75% infections represent severe cases. Since the toxin damages the Schwann cells, diphtheritic polyneuropathy is mainly demyelinating.

Diphtheria usually starts with membranous exudates in the nasopharynx. It can also produce cervical lymphadenopathies and swelling of the neck soft tissue, known as "bull neck." Diphtheritic polyneuropathy is usually biphasic. Cranial nerves are first affected due to local spread of the toxin and followed by peripheral nerve damage due to the hematogenous dissemination and axonal transmission of the toxin [32]. Symptoms of bulbar palsy appear 3–6 weeks after initial infection and include dysphagia, dysphonia, palatal paralysis, or numbness of the tongue. Other cranial nerves such as oculomotor or facial nerves can also be affected. Severe respiratory weakness may appear (usually during weeks 3–4) and requires respiratory support. Limb weakness appears between weeks 5 and 8 since initial infection. Proximal motor weakness of the four extremities is seen in 60–90% of patients. Its severity ranges from mild to severe. Sensory symptoms such as paresthesia, hypoesthesia, loss of joint position or vibration in distal extremities, and loss of tendon reflexes are seen in nearly all patients. Autonomic neuropathy with arterial hypotension, bladder dysfunction, blurred vision, or hyperhidrosis has been reported. Myocarditis is also common in patients with severe infection [33].

Throat culture of *C. diphtheriae* or serum antitoxin antibodies can be performed to diagnose the illness. CSF studies for diphtheritic polyneuropathy can be normal or show elevated proteins. Nerve conduction studies show typical signs of demyelinating polyneuropathy such as slow conduction velocities, prolonged distal motor or F-wave latencies, and conduction blocks.

Treatment should be initiated with the clinical suspicion. It consists of antitoxin and antibiotics, and patients should be placed in isolation during the first 48 h of therapy. The recommended antibiotic treatment is oral erythromycin 40 mg/kg/day for 14 days or intramuscular procaine penicillin G 600,000 units/12 h for 14 days. Clindamycin and rifampicin are other alternatives. Close contacts should receive erythromycin for 7–10 days. Diphtheria vaccination is recommended for all babies, children, and adults. There are four vaccines against diphtheria (www.cdc.gov/diphtheria).

Leprosy

Leprosy continues to be an important health problem worldwide, with the highest prevalence in India (64% of cases worldwide), Brazil, Indonesia, and Nigeria. In Southeast Asia, Africa, and South America, leprosy represents the most common cause of peripheral neuropathy [34]. Yet, the incidence of leprosy in developed countries is increasing owing to emigration from underdeveloped countries [35]. In

Spain, for example, there are a few cases involving immigrants as well as natives [36, 37].

Leprosy is caused by *Mycobacterium leprae*, an intracellular gram-positive acid-alcohol-fast bacillus. It is morphologically indistinguishable from *Mycobacterium tuberculosis* and has tropism for macrophages and Schwann cells [38]. It is transmitted by nasal secretions and the skin from untreated bacillary patients and disseminates hematogenously. The incubation period ranges between 5 and 7 years but can be as long as 10–20 years. The bacillus has a high affinity for Schwann cells of the peripheral nerves, binding to the laminin-2 receptor and then to other membrane proteins, thus facilitating cell penetration where they multiply slowly. At a certain point, T lymphocytes will recognize the bacilli and will trigger an inflammatory reaction [39], resulting in peripheral nerve demyelination and axonal atrophy [40].

Nutrition, hygiene, and crowded housing play an important role as risk factors and influence disease presentation [41]. Recently, much attention has been focused on genetic factors. Multiple genes and loci have been identified as risk factors, expanding the understanding of disease susceptibility [42].

The current classification for leprosy, established by Ridley and Jopling in 1966 taking into account clinical, histological, and immunological criteria, divides presentation into tuberculoid leprosy (patients with good immune response), lepromatous leprosy (patients with poor response), and borderline leprosy.

The clinical manifestations of the disease are determined by the immune response of the host. The most common clinical presentations of leprous neuropathy are mononeuropathies and multiple mononeuropathies [43]. The most commonly involved nerves (in order) are the ulnar, median, posterior auricular, superficial radial, common peroneal, superficial peroneal, and posterior tibial [40]. The upper limb nerves are more often affected than those of the lower limbs. Since bacilli replicate at 27–30 °C, the cooler regions of the body will be most affected (distal limbs, ears). On examination, sensory and motor deficits can be observed, and peripheral nerves are usually thickened and painful. In cases of single nerve involvement, most often the ulnar nerve, sonography can be helpful to differentiate from ulnar nerve entrapment [44]. Symptoms are predominantly sensitive and autonomic, with thermalgesic hypoesthesia, anhidrosis, and local loss of the skin hair. In tuberculoid leprosy, there are focal inflammatory responses to the bacteria within the affected areas of the skin and nerves, resulting in typical hypopigmented patches and plaques with raised erythematous borders. In the lepromatous form, hematogenous dissemination and extensive infiltration of the bacilli produce more extensive manifestations in the nerves, skin, and other organs [45]. In lepromatous leprosy, clinical manifestations tend to be more severe.

A slowly progressive symmetric sensorimotor polyneuropathy develops with preferential small-fiber involvement and relative sparing of large myelinated fibers. Later in the disease, motor weakness may appear; tendon reflexes are long maintained. Nerve thickening is present in 40–75% of patients with polyneuropathy and up to 94% in multibacillary series [39]. After therapy, nerves may gradually shrink but remain abnormally firm [35]. Cranial nerve involvement in leprosy appears in 18% of patients, involving most often the fifth and seventh nerves [46].

Facial involvement leads to the loss of eyelashes and eyebrows, giving rise to the so-called leonine facies appearance. In some patients, there are no skin lesions, thus representing the pure polyneuritic form; nerve biopsy is the only way to establish a diagnosis of leprosy in these cases [47]. Regional signs and symptoms autonomic dysfunction, particularly involving sweating, are also seen in leprosy [48].

The main diagnostic aids in leprosy are the presence of cutaneous hypopigmented lesions with loss of sensation, peripheral nerve thickening, and skin-smear positive for the acid-fast bacilli. Nerve biopsy is the gold standard in those cases without skin involvement.

Treatment for leprosy includes a combination of multiple drugs, including dapsone, rifampicin, and clofazimine. In multibacillary leprosy, the standard regimen includes rifampicin 600 mg once a month, dapsone 100 mg daily, and clofazimine 300 mg once a month and 50 mg daily for 12 months. Some patients require treatment for up 24 months [49]. In paucibacillary leprosy, the standard regimen includes rifampicin 600 mg once a month and dapsone 100 mg daily for 6 months [50]. Second-line drugs are minocycline and fluoroquinolones such as pefloxacine and ofloxacine.

Two types of reactions may appear during therapy due to and increased cell-mediated immune response. The leprosy reaction type I is a hypersensitivity reaction type IV called reversal reaction, which appears during the first months of treatment producing a peripheral neuritis.

The leprosy reaction type II is a hypersensitivity reaction type III called erythema nodosum leprosum, where the typical erythematous skin lesions appear accompanied by uveitis, iridocyclitis, episcleritis, neuritis, arthritis, dactylitis, lymphadenitis, and orchitis [51, 52].

Treatment of the adverse reactions in nerves usually requires immunosuppressive or immune modulating drugs. Therapy with a higher dose of steroids is useful in type I reaction (RR). Dosages for prednisone or prednisolone vary from 30–40 mg/day to 60–80 mg/day in severe cases. There is some evidence of benefit for prednisolone, thalidomide, and clofazimine use in type II reactions [52].

Parasitic Neuropathies

Chagas Disease

Chagas disease, or American trypanosomiasis, is caused by *Trypanosoma cruzi*. It represents a zoonosis transmitted by triatomine insects with reservoir in humans, dogs, cats, rodents, and other mammals. Triatomine bugs release the *Trypanosoma cruzi* in feces and enters the body through a scratch on mucosal membranes of the mouth or the conjunctiva. Human infection can also be acquired via blood transfusion, organ transplantation, and vertical transmission.

Chagas disease is endemic in Central and South America. The disease runs into three phases: acute, indeterminate, and chronic. Patients in the acute phase develop fever, inflammation in the inoculation site, or "Chagoma," unilateral palpebral

edema (the "Romaña sign"), hepatosplenomegaly, and lymphadenopathy. Less than 1% develop meningoencephalitis and myocarditis [53]. In untreated patients, the acute phase resolves spontaneously after 4–8 weeks and enters in the indeterminate phase where the infection remains latent. Between 10 and 40% would progress to the chronic phase in the next 20–30 years. Most patients in the chronic phase develop cardiomyopathy manifested as arrhythmias, cardiac failure, sudden death, or thromboembolic events. Twenty percent of patients develop gastrointestinal lesions such as megaesophagus and megacolon. Finally, around 10% of patients with chronic Chagas disease present a mild sensorimotor polyneuropathy characterized by distal paresthesias or limb hypoesthesia and diminished tendon reflexes [54].

Trypanosoma cruzi can be detected by direct methods (microscopy) in the blood or CSF during the acute phase. In contrast, chronic disease is diagnosed by serological assays, since parasites are no longer present in the blood. The diagnosis requires the presence of IgG against *Trypanosoma cruzi* antigens in at least two different serological tests.

There are two drugs to treat Chagas disease: benznidazole and nifurtimox. Benznidazole is considered the first choice treatment because it has better tissue penetration, better tolerability, and probably a better safety and efficacy profile. Treatment should be given in both the acute and chronic phases during 60 days. Benznidazole can produce a toxic neuropathy as adverse effect, often mild with symptoms of formication, numbness, and pain [55].

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