Chapter 12

CSF in acute and chronic infectious diseases

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Abstract

Infections of the nervous system are an important and challenging aspect of clinical neurology. Immediate correct diagnosis enables to introduce effective therapy, in conditions that without diagnosis may leave the patient with severe neurological incapacitation and sometimes even death. The cerebrospinal fluid (CSF) is a mirror that reflects nervous system pathology and can promote early diagnosis and therapy. The present chapter focuses on the CSF findings in neuro-infections, mainly viral and bacterial. Opening pressure, protein and glucose levels, presence of cells and type of the cellular reaction should be monitored. Other tests can also shed light on the causative agent: serology, culture, staining, molecular techniques such as polymerase chain reaction. Specific examination such as panbacterial and panfungal examinations should be examined when relevant. Our chapter is a guide-text that combines clinical presentation and course with CSF findings as a usuaful tool in diagnosis of neuroinfections.

INTRODUCTION

In this chapter we will try to represent and summarize the alterations of cerebrospinal fluid (CSF) during various central nervous system (CNS) infections. These are grouped into acute and chronic infections regarding their time course and we will cover the chemical and cellular CSF changes associated with viral, bacterial, fungal, and parasitic infections. The CSF alterations and findings caused by prion proteins are covered in a separate chapter.

ACUTE INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

Acute infections of the nervous system are as diverse in their clinical consequences for the patient as the variety of infectious agents causing them: from mild headaches to long-term morbidity and a threat to life. Therefore, the earliest possible diagnosis is absolutely essential. Central here stands the examination of the CSF. The correct diagnosis is often dependent on this rather simple procedure to allow diagnosis and focused antimicrobial and adjunctive therapy. This chapter deals with acute infectious diseases of the nervous system and the importance of the lumbar puncture (LP) in the diagnostic process.

ACUTE VIRAL DISEASES OF THE NERVOUS SYSTEM

Introduction

Viral pathogens

Viruses are the ultimate hitchhikers. They carry a minimal necessary amount of information with them, replicated, packaged, and preserved by the host cells. A single nucleic acid type – either DNA or RNA; single- or double-stranded – contains all the information needed. The genome is packaged in a protein coat, which in some viruses is further enclosed by a lipid envelope. All parts of the central and peripheral nervous system, even arteries and muscles, may be the target of viral pathogens. Importantly, besides the classic diseases, viruses may behave differently under immunosuppression or in immunocompromised states, potentially leading to

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Table 12.1

Viruses causing meningitis

Herpes simplex virus type 2	Tick-borne encephalitis virus
Epstein–Barr virus	
Varicella-zoster virus	West Nile virus
Human herpesvirus-6	Japanese encephalitis virus
Coxsackieviruses A and B	St. Louis encephalitis virus
Echoviruses	La Crosse virus
Enteroviruses	Western equine encephalitis virus
Human immunodeficiency virus (acute)	Colorado tick fever virus
Mumps virus	Dengue viruses
Lymphocytic choriomeningitis virus	Zika viruses
	Adenoviruses
Filoviridae	Arenaviruses
	Rubella

more acute or progressive disease. Secondary diseases of the nervous system (postvaccine or parainfectious) will not be covered in this chapter.

EPIDEMIOLOGY

Most viruses involved in acute CNS diseases can be acquired worldwide. The relationship between the host and the agent is of major importance and factors influencing the spread and epidemiology are listed in Table 12.1 (Mandell et al., 2010). How the virus spreads is another important determinant for its epidemiology: directly by respiratory droplets, kissing, touching, sexual intercourse, or through animal bites. Alternatively, it may be spread via vehicle transmission through an intermediate, e.g., by food, water, blood, or urine or as in vector-borne infections by mechanical spread. Echovirus, enterovirus, measles, mumps, coxsackievirus, herpesvirus, human immunodeficiency virus (HIV), and papovavirus are found in most areas of the world. Viruses transmitted by a vector are usually geographically limited to the vector's host environment: mosquitos or ticks show a clear-cut regional or continental occurrence (e.g., West Nile virus, tick-borne encephalitis virus, Japanese encephalitis virus). Some viruses today only exist in very circumscribed areas due to eradication efforts (e.g., poliomyelitis virus, smallpox) (Duintjer Tebbens et al., 2013).

PATHOGENESIS AND PATHOPHYSIOLOGY

The penetration of the CNS is achieved by several mechanisms (Craighead, 2000; Thompson and Green, 2012). Commonly, replication occurs outside the CNS and invasion by hematogenous spread (enterovirus). Via the vascular route, viral particles pass across the blood–brain barrier, or cross into the brain via infected leukocytes

(e.g., mumps, measles, or herpesviruses). Other viruses probably invade through peripheral nerves (rabies). The invasion and spread of the herpes simplex virus (HSV) in the CNS are probably mediated by the latent virus in the ganglion but there is room for speculation if the encephalitis is not due to a primary HSV infection (Steiner et al., 2007; Steiner, 2011, 2012). Toll-like receptor 3 (TLR3) mutations seem to be responsible for the failed immune response to prevent the invasion of HSV in some herpes simplex encephalitis (HSE) patients (Lim et al., 2014; Mørk et al., 2015). Once within the CNS, viruses spread through the subarachnoid space, leading to an inflammatory response. Then, inflammatory cells (lymphocytes) specifically targeting the infecting virus accumulate in the CNS. This is accompanied by the release of inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α as well as local immunoglobulin production by plasma cells (Kothur et al., 2016). Viruses such as varicella-zoster virus (VZV) may cause disease through cerebral vasculitis, with immunocompetent patients usually developing a large-vessel vasculitis.

CLINICAL FEATURES

Viral meningitis, meningoencephalitis, and encephalitis

Infection of the meningeal structures with an endogenic inflammatory response results in meningitis. Clinically, the typical presenting symptoms are headache, fever, and stiff neck. Additional clinical features can help to distinguish common headaches (migraine, tension-type headache, etc.) from those possibly caused by a viral infection: photophobia and pain on eye movements. The general accuracy of the clinical signs is under debate (Khatib et al., 2017) and thus clinical suspicion has to be high and threshold low to perform necessary procedures (LP) excluding an infectious origin of the symptoms (McGill et al., 2017). As a rule of thumb, we recommend to our residents covering the emergency room to perform LP when any combination of at least two out of the three principal symptoms of meningitis exist (headache, fever, neck stiffness) and no other cause can be determined.

Viral meningitis in its pure form has a very good prognosis and mortality rates are trending towards zero, but the prognosis is dependent on additional spread of the viral infection to the brain (encephalitis), to the spinal cord (myelitis), or to nerve roots (radiculitis). Viruses causing aseptic meningitis are listed in Table 12.1 (Chadwick, 2005; Harvala and Simmonds, 2016; Nesher et al., 2016; McGill et al., 2017). The viral involvement of the meninges can involve the cortex and brain itself, leading to meningoencephalitis and encephalitis. By definition,

encephalitis is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction (Steiner et al., 2010). In many cases the association with fever, headache, and general malaise and brain dysfunction is conveyed as behavioral changes, confusion, focal neurologic deficits, somnolence, stupor, and epileptic seizures (focal and generalized). The dramatic clinical picture needs rapid identification, symptomatic support and treatment (antiepileptic drugs) and specific treatment when available (e.g., acyclovir). Long-term survival and morbidity depend on the host immune status, treatment administered, and on the virus itself. HSV-1, VZV, Epstein–Barr virus, mumps, measles, and enteroviruses are responsible for most cases of viral encephalitis in immunocompetent individuals (Jellinger, 2009; Stahl et al., 2011; Beckham et al., 2016) but other viruses are listed in Table 12.2. Additionally, a viral infection of the CNS can be limited to the spinal cord resulting in myelitis. More common in clinical practice than the direct invasion of the myelon by the virus is a postinfectious inflammation (transverse myelitis). The direct invasion of the gray matter in the myelon is typically seen with enterovirus infections (poliovirus) but has been described in West Nile Virus and tick-borne encephalitis virus.

DIAGNOSTIC FEATURES

The history can be extremely helpful to assess a patient with suspected viral meningitis or encephalitis. If the patient is confused, agitated, or disoriented, relevant information has to be obtained from an accompanying person. History of exposure (HIV, mumps, measles) and the typical clinical syndrome of certain viral infections like measles, varicella, and shingles can be extremely helpful to determine the infective agent. The geographic location as well as recent travel history could be of relevance (examples from recent outbreaks include acute respiratory syndrome, severe acute respiratory syndrome, Nipah

Table 12.2

Viruses causing meningoencephalitis

Enteroviruses	La Crosse virus
Herpes simplex 1	St. Louis encephalitis virus
Herpes simplex 2 (neonates)	Japanese encephalitis virus
Varicella-zoster virus	Yellow fever
Epstein–Barr virus	Dengue virus
Cytomegalovirus	Equine encephalitis viruses
West Nile virus	Nipah virus
Tick-borne encephalitis virus	Zika virus
Colorado tick fever virus	Rabies viruses
Measles virus	

virus, avian H5N1 influenza A infection, Zika virus) (Peiris et al., 2004; Sing, 2014; Halpin and Rota, 2015). The seasonal occurrence (polio and West Nile virus) as well as occupation may well be important. A history of insect or other animal bites can be relevant for arbovirus infection as well as rabies. On general examination, skin rashes should be noticed as well as bite marks or insect bites. In pure meningitis, neuroimaging is not indicated but is frequently performed before LP to exclude any rare contraindications.

If the neurologic exam is abnormal in any way (including papilledema on fundoscopy as part of the neurologic exam), or a seizure has occurred, neuroimaging is recommended (Archer, 1993; Gopal et al., 1999; Hasbun et al., 2001). In suspected encephalitis, neuroimaging is essential, both in ascertaining and confirming the neurologic syndrome and helping to establish the appropriate diagnosis and prognosis. This should be performed before the LP. Initially computed tomography is used frequently but most important is the more sensitive magnetic resonance imaging and this should be the imaging study of choice in suspected viral encephalitis (Jordan et al., 2016; Piquet and Cho, 2016; Koeller and Shih, 2017).

Electroencephalography (EEG) is generally regarded as a nonspecific investigation in encephalitis and mostly slow activity is seen. However, the sensitivity for brain changes by EEG makes it a useful tool to demonstrate cerebral involvement during the early state of the disease. Specific EEG features can however give clues as to the diagnosis: In HSE, in addition to background slowing, there is a temporary temporal focus showing periodic epileptiform discharges. The EEG in subacute sclerosing panencephalitis (SSPE) shows a typical generalized periodic EEG pattern repeating with intervals between 4 and 15 seconds and synchronized with myoclonus of the patient (Westmoreland, 1987; Gaspard et al., 2015; Martins and Palmini, 2015; Cag et al., 2016; Pessa et al., 2016; Saini et al., 2016). Due to the strong separation of blood and brain by the blood–brain barrier, the peripheral blood results in viral meningitis and encephalitis can be normal or only slightly abnormal and nonspecific. Possible minor alterations of blood tests pointing to liver or kidney involvement can be found and are mostly due to a viral infection also of those peripheral organs (typically seen in Epstein–Barr virus and cytomegalovirus infections).

CEREBROSPINAL FLUID

CSF analysis: cells and chemistry

The presence of inflammation in the CNS is confirmed by CSF analysis. No clear difference can be made using

CSF analysis between meningitis and encephalitis. Leukocytes (white blood cells) are elevated (mostly not above 250/μL). The differential diagnosis shows a predominance of lymphocytes but in early infection neutrophils can be present (Feigin and Shackelford, 1973; Whitley et al., 1989; Cunha, 2013). If the clinical presentation is highly suspicious for encephalitis, a spinal fluid analysis returning with only borderline elevated cells should be repeated as, especially in HSE, a normal CSF can be seen in the first hours of infection. This can cause a treatment delay, worsening the prognosis of the encephalitis or leading to an alternative wrong diagnosis (de Toledo et al., 2001; Benninger et al., 2013; Desena et al., 2014; Saraya et al., 2016). In HSE at least 10% have normal cell counts within a week of onset of illness, usually, but not always, increasing later (Koskiniemi et al., 1984). This has been also shown for enterovirus encephalitis and in one study 36% had CSF with normal protein and/or cell count (Tavakoli et al., 2008). CSF protein is usually mildly elevated (<150 mg/dL) in viral encephalitis. In HSE it is normal in 50% of cases early in the illness (Koskiniemi et al., 1984). If a bloody tap is obtained through trauma at LP, the protein level should be adjusted down by 0.1 mg/dL for every 1000 red cells/μL (Dennett et al., 1991).

CSF: plasma glucose ratio in healthy adults is about 0.6 and thus an abnormal level is less than this, generally 0.5 or less. In most viral CNS infections, glucose levels are in the normal range but a low level (hypoglycorrhachia) has been reported in some cases of mumps, varicella-zoster, and herpes simplex infection (Davis et al., 2004). Hypoglycorrhachia has also been described in HIV-infected patients with cytomegalovirus meningoencephalitis and West Nile virus infection (Farinelli et al., 1989; Unzek et al., 2006; Steiner et al., 2007). Even if CSF parameters are in the "viral" range, we recommend caution and a high level of suspicion for possible bacterial meningitis. This is even more true in cases of previous antibiotic treatment and empiric antibiotics as in bacterial meningitis should be considered in addition to a CSF smear and culture, particularly because partially treated bacterial meningitis can be present with CSF findings similar to viral meningitis.

VIRUS ISOLATION AND CULTURE

The causative agent in clinical viral meningitis and encephalitis will remain unknown in the majority of patients. Virus isolation in cell culture is possible, but unfortunately the yield is very low and today cultures are rarely performed for diagnostic purposes. Depending on the virus to be isolated the diagnostic yield ranges from 4% in HSE to 40% in enterovirus-mediated encephalitis (Nahmias et al., 1982; Chonmaitree et al., 1989; Leland and Ginocchio, 2007). A reasonable place for cell cultures for the isolation of viruses still exists in the identification of unusual agents. The isolation of Nipah virus in Malaysian pig farmers was important in an outbreak from February to April 1999 (Chua et al., 1999). The virus produces syncytia in Vero cell cultures 5 days after inoculation with CSF.

INTRATHECAL ANTIBODIES

The identification of specific intrathecal antibodies is still a frequently used method for reaching a diagnosis. Oligoclonal antibody production (oligoclonal bands) exclusively intrathecally can occur in CNS infection. The diagnosis of SSPE can be helped by the detection of oligoclonal bands in the CSF. SSPE is a progressive, debilitating, and deadly brain disorder related to measles (rubeola) infection. Demonstration of intrathecal production of antibody requires demonstration of IgG, IgA, or IgM antibody, which is regarded as diagnostic of CNS infection in the absence of evidence of breakdown of the blood–brain barrier. Both serum and CSF must be tested (Sharief and Thompson, 1990). The origin of antibodies detected in the CSF must be determined to differentiate between peripheral blood-derived antibodies having crossed the blood–brain barrier into the CSF from those produced intrathecally against the background of a brain-derived pathology.

Calculating the ratio between the amount of antibodies in the CSF and serum for specific antibodies and total IgG, the antibody specific index helps to discriminate the origin of the antibody production and has been shown to be useful in several infectious and inflammatory disorders (e.g., multiple sclerosis, HIV, cytomegalovirus, VZV, and others) (Reiber, 1998; Reiber et al., 1998; Jarius et al., 2012). Diagnosis using capture immunoassays to detect IgM antibody has proved useful for arbovirus diagnosis but has been extended nowadays to detect intrathecal IgM in mumps encephalitis, varicella-zoster encephalitis, HSE, and measles in SSPE (Sharief and Thompson, 1990). An IgM assay for St. Louis encephalitis virus and Wile Nile virus exists. The detection of IgM in serum alone is generally not sufficient to implicate the virus as the cause of a suspected encephalitis. With regard to, for example, Japanese encephalitis virus as the cause of encephalitis in a highly endemic area where many infections occur in the rainy season, only very few cause CNS infection (Grossman et al., 1973).

PCR AND REAL-TIME PCR (RT-PCR)

For nucleic acid detection, polymerase chain reaction (PCR) technology provides the most convenient test.

Assays for HSV-1, HSV-2, VZV, human herpesviruses 6 and 7, cytomegalovirus, Epstein–Barr virus, JC virus of progressive multifocal leukoencephalopathy, dengue virus, enteroviruses, and respiratory viruses as well as HIV can be performed from CSF samples or brain tissue. Reports are available routinely in less than 24 hours and, if suspected, empiric antiviral treatment can thus be stopped early in the clinical course. PCR offers the advantages of high sensitivity and specificity and this holds true for even very small amounts of viral DNA or RNA. The minimum volume of CSF needed is determined more by the nucleic acid extraction system than the amplification process itself, with a typical minimum extraction volume of 100–300 μL. In CSF, nucleic acid is relatively stable. Stability is enhanced if mononuclear cells are present and DNA is stable up to 30 days even at room temperature; however, RNA is less stable and advised to be stored at low temperatures (–70°C) until PCR (Wiedbrauk and Cunningham, 1996). Especially HIV RNA seems to degrade rapidly and shows significant decline after 24 hours, making detection difficult. With storage at 4°C, however, there is no significant loss of HIV RNA by 96 hours (stability is enhanced in ethylenediaminetetraacetic acid plasma in comparison to serum) (Rotbart et al., 1985; Ginocchio et al., 1997; Ahmad et al., 1999).

Detection of specific nucleic acid from the CSF is dependent on the timing of the CSF sample. In HSE, the sensitivity is 96% and the specificity 99% when CSF is studied between 48 hours and 10 days from symptom onset. Thus, in the early hours often the first CSF analysis can be negative for HSV-1 and should be repeated if clinically suspected (Adler et al., 2011; Steiner, 2012; Kennedy and Steiner, 2013). A high viral load has been suggested in some, but not all studies, to be correlated with a worse outcome (Nahmias et al., 1982). On the other hand, no relationship between CSF viral load and severity of clinical symptoms or outcome was detected in 23 HSE patients (Revello et al., 1997). A long duration of genome detectability (>20 days) is probably more important in predicting poor outcome than initial level (Schloss et al., 2009). Information on correlation between viral load and outcome is scarce in other encephalitides. The HIV viral load in CSF seems not to be correlated with the viral load in the blood and in late infection behaves as if in a separate compartment (with the possibility of different antiviral resistance patterns) (Stingele et al., 2001). Progressive multifocal leukoencephalopathy associated with HIV infection and JC polyomavirus load in the CSF is correlated with a shorter survival if not treated (Bossolasco et al., 2005).

High-throughput techniques enable the detection of currently unknown viruses (Wommack et al., 2015; Paez-Espino et al., 2016). This might not be limited to the discovery of infectious agents regarding encephalitis. Other neurologic and neurodegenerative diseases might be associated with a viral origin that is unknown today (Amor et al., 2014; Manghera et al., 2014; Pecho-Vrieseling et al., 2014; Mechelli et al., 2015; Christensen, 2016).

TREATMENT

In general, patients with viral meningitis do not need any specific treatment and supportive analgesic control and fluid input are usually enough. Occasionally, LP-induced low-pressure headache adds to the headache complaints but resolves in most cases rapidly. Prognosis of viral meningitis is very good. Once HSV is suspected as the causative virus for meningoencephalitis, treatment should be initiated immediately. HSE is treated with acyclovir 10 mg/kg intravenously every 8 hours for 2 weeks (Solomon et al., 2012). Treatment should be prolonged in case of relapse and reexamination of the CSF may indicate the need for an additional 1–2 weeks of acyclovir therapy (Cinque et al., 1996; Ito et al., 2000).

PROGNOSIS

Simple lymphocytic meningitis has an excellent prognosis with almost zero mortality. Long-term morbidity and mortality are increased in encephalitis. Following myelitis or encephalitis, more than 10% of patients suffer from severe neurologic deficits, e.g., seizures, para- or tetraplegia, cognitive deficits. Untreated HSV encephalitis has a mortality rate of 70% and makes initial treatment such an important prognostic indicator (Jouan et al., 2015). TLR3 is a pattern recognition receptor triggered by viral double-stranded RNA and leading to the activation of specific transcription factors, which stimulate the production of cytokines that induce a complex program of innate immune responses facilitating viral, including HSV, clearance. In children with genetic defects that shared the common feature of encoding proteins involved in TLR3 interferon signaling pathways, mutations in TLR3 were associated with recurrent HSE (Zhang et al., 2007; Lim et al., 2014; Steiner and Tyler, 2014). Whether the defect in the TLR3 receptor reduces inflammation-mediated epileptogenesis as shown in animal models needs to be established in future clinical studies (Benninger et al., 2014; Gross et al., 2017). Regarding autoimmune-mediated encephalitis, reports suggest that the most commonly recognized cause of antibody-mediated autoimmune encephalitis, anti-N-methyl-D-aspartate receptor encephalitis, may in some cases be triggered by and follow HSE (Armangue et al., 2013, 2015). Thus, in the

context of recurrent encephalitis following HSE, the possibility of autoimmune encephalitis has to be ruled out.

Acute bacterial meningitis

INTRODUCTION AND EPIDEMIOLOGY

Acute bacterial meningitis (Table 12.3) is one of the most severe acute inflammatory diseases of the CNS, leading to severe morbidity and death. Even with appropriate antibiotic therapy the mortality rate is extremely high (13–27%) (Aronin et al., 1998; van de Beek et al., 2006; Weisfelt et al., 2006). Neurologic disabilities occur frequently in surviving patients. The appropriate approach to deal with the worldwide health problem caused by bacterial meningitis is twofold: prevention and treatment. Despite decreases in the occurrence of meningitis brought about by vaccination programs against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* in the developed world, the incidence of bacterial meningitis is still unacceptably high, ranging between 3 and 10 per 100,000 people (Thigpen et al., 2011; Liu et al., 2012). The demographics of bacterial meningitis has shifted due to vaccination programs (Daza et al., 2006), but acute treatment and thus prevention of neurologic deficits and death as a consequence of bacterial meningitis remain the first priority. Immediate early diagnosis and appropriate antibiotic treatment as well as critical care management are the basis of management but may not be sufficient to approach the inflammatory response and its consequences in patients with bacterial meningitis.

Table 12.3

Common bacteria causing meningitis

Bacteria	Age of patient
Group B streptococci	< 1 month
Enterobactericeae (Gram-negative)	
Listeria monocytogenes	
Streptococcus pneumoniae	1–12 months
Haemophilus influenzae type B	
Neisseria meningitidis	
Group B streptococci	
Escherichia coli	
Haemophilus influenzae type B	1–18 years
Streptococcus pneumoniae	
Neisseria meningitidis	
Streptococcus pneumoniae	<50 years
Neisseria meningitidis	
Streptococcus pneumoniae	>50 years
Neisseria meningitidis	
Enterobactericeae	
Listeria monocytogenes	

PATHOGENESIS AND PATHOPHYSIOLOGY

Bacterial invasion of the brain in meningitis and encephalitis is only one part of the pathogenesis. The inflammatory response triggered by the bacterial assault is tolerated by the brain and spinal cord very poorly, leading directly to damage of nervous tissue (Fitch et al., 1999; Hasbun et al., 2001). The inflammatory response to bacterial infection in the CSF has substantial clinical impact with associated morbidity and mortality (Koedel et al., 2002, 2010a; Weisfelt et al., 2006). Death is the result of systemic and/or intracranial complications such as brain edema with cerebral or cerebellar herniation (Nau et al., 1999; Koedel et al., 2002, 2010a; Scheld et al., 2002). Neutrophils and cytokines migrating to the site of infection can prevent invading pathogens but the mechanisms used against the pathogen can be harmful to the host tissue. Experimentally it has been shown that the cell wall components of bacteria cause the production of a wide range of cytokines. These cytokines, such as interleukins and TNF-α, contribute to the accumulation of leukocytes in the CSF, to brain edema, blood–brain barrier damage, and damage of cells within the CNS (Saukkonen et al., 1990; Sharief et al., 1992). The crossing of the blood–brain barrier is a sophisticated mechanism (Coureuil et al., 2017) and viable bacteria cause meningeal inflammation via cell membrane components and induce clinical symptoms and even death in animal models (Weber and Tuomanen, 2007; Koedel et al., 2010b). The presence of cell wall components in the CSF was correlated with neurologic sequelae and mortality (Schneider et al., 1999). There is evidence that treatment of bacterial meningitis with antibiotics alone has the capability to increase CSF cytokine concentrations, most likely because antibiotic-induced bacterial lysis releases large amounts of harmful bacterial products into the CSF (Mustafa et al., 1989; Van Furth and Roord, 1996).

CLINICAL AND DIAGNOSTIC FEATURES

Patients with bacterial meningitis have to be identified fast and early in the course of the disease. In order to accomplish this difficult task, the level of suspicion cannot be high enough. As in most parts of medicine, the physician has to conjecture to initiate the right diagnostic steps due to missing signs and symptoms in a significant proportion of patients with bacterial meningitis. Classically, bacterial meningitis presents fulminantly with rapidly developing fever, altered consciousness, and headaches, but this classic triad is present in only 50% of all patients (van de Beek et al., 2004). As we described in the section on viral meningitis, headache, fever, neck stiffness, and altered consciousness should encourage the

Table 12.4

Differential diagnosis of bacterial meningitis

Bacterial abscess
Viral meningitis
Meningitis caused by fungi and parasites
Autoimmune-mediated meningitis
Medications: trimethoprim and nonsteroidal anti-inflammatory drugs (NSAIDS)
Malignancy
Subarachnoid hemorrhage (SAH)
Migraine
Peripheral viral illnesses
Pneumonia

physician to consider bacterial meningitis until ruled out (present in 95% of patients). The commonly known signs of Kernig and Brudzinski have to be viewed with caution as their sensitivity (up to 95%) depends very much on the examiner and their specificity is rather low (~5%) (Sakushima et al., 2011). The differential diagnosis is broad (Table 12.4), but as the gold standard to rule out bacterial meningitis is the CSF investigation, we encourage its broad use after ruling out contraindications for LP. Helpful clinical additional signs should be identified by the medical exam: purpura fulminans is typical for meningococcal meningitis. Septicemia (Waterhouse–Friderichsen syndrome) is seen in about 10% of patients with meningococcal meningitis: septic shock, hemorrhages leading to multiorgan failure, and disseminated intravascular coagulation. Focal signs on neurologic examination are seen in about 10% of patients, suggestive for a brain abscess, stroke, or venous thrombosis (Alvis-Miranda and Castellar-Leones, 2013a, b). Seizures are present in up to 30% on presentation.

CSF ANALYSIS

Opening pressure

CSF examination begins with the measurement of the opening pressure and we recommend that measurement of the opening pressure is incorporated in the routine of all LP, independent of the indication. The usual range of opening pressure is around 50–200 mm CSF. Pressures over 180 mm CSF are considered to be abnormal. The causes of intracranial hypertension are manifold, ranging from pseudotumor cerebri to intracranial neoplasms. Subarachnoid hemorrhage, elevated central venous pressure, and a host of other conditions raise CSF pressure. Meningitis, bacterial as well as viral, can increase the CSF opening pressure substantially (Lee and Lueck, 2014).

Gross examination

As the normal CSF is crystal clear, any change in clarity can point to a certain direction regarding the diagnosis: the occurrence of pleocytosis is the usual reason for cloudy fluid. At least 200 white cells/µL can be present without altering the clarity. Over 500 white cells per cubic millimeter usually produces cloudiness. Red cell concentrations between 500 and 6000/µL can cause the fluid to appear cloudy, while concentrations of over 6000/µL give a grossly bloody appearance. A markedly elevated protein can also alter the clarity of the CSF. The presence or absence of color, usually xanthochromia, in the CSF is a crucial observation. Xanthochromia commonly indicates spontaneous subarachnoid hemorrhage.

Direct CSF microscopy

Microscopic examination of the CSF should be done rapidly. Gram stain and the detection of bacterial antigens by latex agglutination can help diagnose bacterial meningitis rapidly, especially regarding *S. pneumoniae* or *H. influenzae*. *Listeria monocytogenes* or Gram-negative bacilli are much more difficult to detect on microscopic CSF examination. In particular, *Listeria* has the ability to evade the immune system and can spread via phagosomes from cell to cell without encountering the host's immune cells (Pamer, 2004; Hamon et al., 2006; de Noordhout et al., 2014). Thus, microscopy may not be informative in 20–40% of cases (van de Beek et al., 2004; Viallon et al., 2011).

Bacterial culture of the CSF

The CSF culture is the gold standard for the diagnosis of bacterial meningitis. The results of CSF cultures are positive in 70–85% of patients who have not received prior antimicrobial therapy, but cultures may take up to 48 hours for organism identification (Spanos et al., 1989). Multiple studies have shown that prior antibiotic therapy should not significantly alter the CSF cell count or the glucose and protein concentrations. Antibiotics can, however, affect the results of CSF Gram stain and culture. In the presence of antibiotics, the sensitivity of CSF Gram stain and culture drops to 40–60% and to less than 50%, respectively. The rate at which antibiotics clear bacteria from the CSF of humans has not been established, but animal studies of pneumococcal meningitis show that penicillin produces a 2-log drop in CSF bacterial concentration every hour, such that sterilization is achieved by 8 hours (Sande et al., 1981; Blazer et al., 1983; Lebel and McCracken, 1989). The diminished sensitivity of the CSF culture in the patients who received antibiotics before the LP and the 72-hour test period

hinder clinicians from reaching a prompt diagnosis and starting the treatment in the ideal period.

PCR and rt-PCR

Detection of bacteria in CSF can be done using rt-PCR. The bottleneck of traditional rt-PCR is the extraction of DNA. Direct rt-PCR allows the detection of bacterial pathogens directly from CSF specimens without DNA extraction, thereby reducing processing time, cost, labor, and risk of cross-contamination. Direct rt-PCR improves testing throughput and provides a more robust method for laboratories with high volume of specimens. With the elimination of DNA extraction, there is no DNA loss and thus, lower numbers of bacteria are detected compared to traditional rt-PCR, well within the range detected by culture (Wu et al., 2013; Bloch and Tang, 2016; Vuong et al., 2016). In addition, direct rt-PCR conserves precious CSF specimens as it only requires 2 µL of CSF per reaction (Bianchi et al., 2015; Bhagchandani et al., 2016; Vuong et al., 2016).

Quantitative CSF analysis: cells and chemistry

Cytologic parameters in bacterial meningitis include high cell numbers associated with predominant polynuclear neutrophils (>80%). However, these parameters are often misleading, with an absence of pleocytosis (1–12% of cases) or predominant mononuclear cells (Bratlid and Bovre, 1977; Koutroumanidis et al., 2000; Hase et al., 2014). In one study, out of 645 patients with bacterial meningitis 7% of patients did not have pleocytosis (van de Beek et al., 2004; Lin et al., 2014; Mentis et al., 2016). Furthermore, these two parameters have low discriminatory power between bacterial versus viral meningitis. Spanos et al. (1989) showed in 205 episodes of viral and 217 episodes of bacterial meningitis that polynuclear cells could be identified in only 40% of cases and that even for total CSF cell numbers the large overlap between the two etiologies made the differentiation difficult. The range of CSF protein lies between 1 and 5 g/L (Lindquist et al., 1988; Viallon et al., 2000).

The use of CSF protein levels for the diagnosis of bacterial meningitis is helpful but needs to be viewed with caution. Sensitivity and specificity were examined regarding bacterial meningitis and varied from 60% to 86% with specificity between 60% and 100%. In various studies, 1–10% of patients with bacterial meningitis had normal CSF protein concentration, while for 5–25% of patients with proven viral meningitis the protein level was significantly increased (Donald and Malan, 1986; Coll et al., 1994). The CSF glucose levels are dependent on serum glucose levels. The normal CSF:serum glucose ratio lies in the region of 0.6. The normal glucose level in CSF varies from 2.6 to 4.2 mmol/L. CSF glucose is low

in several conditions of increased glucose consumption, depending on the amount of pleocytosis (Hegen et al., 2014). Glucose levels can be undetectable in bacterial meningitis and ratios below 0.4 are very indicative of bacterial origin of low CSF glucose. The sensitivity however is rather low and CSF glucose level performance remains inadequate for diagnosing bacterial meningitis. Durand et al. (1993) showed that only 50% of patients had a CSF glucose level of <2.2 mmol/L. While bacterial meningitis probably is the most common diagnosis associated with hypoglycorrhachia, several studies showed low CSF glucose in only one-fourth of overall cases. One-third of hypoglycorrhachia episodes were associated with noninfectious causes such as strokes, carcinomatosis, lymphomatosis, and neurosarcoidosis. Subjects with a recent history of neurosurgery and hypoglycorrhachia most often had bacterial meningitis, while HIV-infected subjects with hypoglycorrhachia most often had fungal meningitis followed by cerebral toxoplasmosis and neurosyphilis. Surprisingly, the most common diagnoses associated with hypoglycorrhachia in subjects without HIV infection or neurosurgical history were noninfectious (Chow and Troy, 2014).

Hypoglycorrhachia, especially in children with seizures, should raise the suspicion for glucose transporter type 1 deficiency syndrome. The classic phenotype is characterized by seizures, delayed neurologic development, and microcephaly as well as movement disorders. Seizures begin before age 2 years in approximately 90% but can present later in life in approximately 10% (Nakamura et al., 2015). CSF lactate level can be useful in diagnosing bacterial meningitis. The normal level of lactate in the CSF is 2 mmol/L and not different from that in the blood. Increase in lactate above 4 mmol/L is a more specific indicator for bacterial meningitis than other CSF markers in immediate evaluation (CSF cell count, CSF glucose, and protein concentration) (Donald and Malan, 1986; Giulieri et al., 2015; Julián-Jiménez and Morales-Casado, 2016; Slack et al., 2016; Xiao et al., 2016).

Acute fungal infections of the central nervous system

INTRODUCTION AND EPIDEMIOLOGY

Fungal infections of the CNS are mainly seen in immunocompromised patients. This includes patients post organ transplantation, acquired immunodeficiency syndrome (AIDS), immunosuppressive chemotherapy, chronic corticosteroid therapy, autoimmune diseases, and chemotherapy. Some fungal diseases are also observed in immunocompetent patients (meningitis with *Coccidioides immitis*, *Histoplasma, Cryptococcus*). The estimated annual incidences of invasive fungal infections

caused by opportunistic pathogens per million of the population are 72–228 infections for *Candida* species, 30–66 for *Cryptococcus neoformans*, and 12–34 for *Aspergillus* species (Pfaller et al., 2006).

ETIOLOGY AND PATHOGENESIS

CNS fungal pathogens can be separated into three groups: yeasts, molds, and dimorphic fungi (Table 12.5). Of these fungal pathogens the true neurotropic fungi are *Cryptococcus neoformans* and *C. bantiana* as well as *Coccidioides immitis,* which commonly infects the brain. Most fungi are found worldwide but a specific distribution is typical for *C. immitis* (Mexico, South America, and southwest United States) and *Blastomyces dermatitidis,* which is endemic in Africa and in continental North America. *Histoplasma capsulatum* is found in certain areas in Ohio, United States, and Latin America. Most fungal infections occur in immunocompromised hosts (Table 12.6); in addition patients with intact immune systems are being infected. Risk factors for particular fungal infections are known and include long-term antibiotic therapy and very young age in *Candida* infections, bird feces contamination for *Cryptococcus* and *Histoplasma,* ketoacidosis and renal failure in *Zygomycetes* (Black and Baden, 2007). Fungi are found in the ground and vegetations, on the skin of birds, and in bat feces. Fungal spores enter the body through inhalation into the lungs but CNS fungal infections are usually secondary to infections elsewhere in the body by hematogenous spread, most commonly from the lung. CNS invasion can be by direct extension from the adjacent structures: sinuses, nose, and ear canal. The brain is usually resistant to fungal infections and it needs special conditions to breach the protective blood–brain barrier.

CLINICAL FEATURES

Most common nervous system presentation with most of the yeasts are meningitis and meningoencephalitis, commonly caused by *Candida albicans*. In infants,

Table 12.5

Fungal infections of the central nervous system

Yeasts	Molds	Dimophic fungi
Candida, Cryptococcus neoformans	*Aspergillus, Mucor, Rhizopus, Rhzomucor, Absidia, Cunninghamella*	*Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis*

Table 12.6

Fungal infections of the central nervous system

Patient group	Fungus	Presentation
Healthy	*Blastomyces, Histoplasma, Coccidioides*	Meningitis
AIDS, HIV	*Histoplasma, Cryptococcus*	Meningoencephalitis
Neurosurgery	*Candida*	Abscess
Neutropenia	*Candida, Aspergillus*	Meningitis, abscess
Steroid treatment	*Aspergillus, Mucorales, Scedosporium*	Abscess
Organ transplant	*Candida, Aspergillus, Cryptococcus*	Meningitis, meningoencephalitis

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

meningitis is more common than in older patients. *Candida* meningitis is rarely but occasionally described in healthy people or after neurosurgical procedures (Nguyen and Yu, 1995; Borha et al., 2009).

Cryptococcus neoformans is the most common causative agent for chronic lymphocytic fungal meningitis. The incidence of cryptococcal infection emerged as an important opportunistic infection in persons with HIV infection and is one of the AIDS-defining illnesses, typically occurring when the blood CD4 cell count is below 200 cells/mL (Currie and Casadevall, 1994; Gottfredsson and Perfect, 2000; Cox et al., 2001). About 5–10% of patients with HIV develop cryptococcal meningitis. Cryptoccoal meningitis usually has a subacute or chronic course. The most typical presentation is excruciating headaches without fever. Elevated intracranial pressure in the absence of ventricular dilatation may cause visual and hearing loss and on examination papilledema is found frequently (Gottfredsson and Perfect, 2000; Bicanic et al., 2009a, b, 2012; Greene et al., 2017; McCarthy and Walsh, 2017). Focal mass lesions, abscesses, or granulomas are seen with some fungal infections of the CNS. *Candida*, *Zygomycetes,* and, rarely, *Aspergillus* can form abscesses. Intracranial granuloma is seen more frequently with *Aspergillus* infections. Spread from the nasal sinuses can cause symptoms at the base of the skull (Sharma et al., 1997; Sundaram and Murthy, 2011; Naik et al., 2015). Rarely, fungal infections can lead to angiitis causing ischemic stroke (Martins et al., 2010; Chatterjee et al., 2016).

CSF AND SERUM ANTIGENS AND ANTIBODIES

White blood cells in the CSF in fungal meningitis depend on the infectious agent. In *Cryptococcus neoformans* a predominant lymphocytic pleocytosis is detected while monocytes and neutrophils are seen in *Candida, Aspergillus,* and blastomycosis meningitis (Saccente and Woods, 2010). Eosinophilia is relatively exclusive in *Coccidioides* infection. If the *Candida* meningitis is device-related (e.g., neurosurgical procedures) pleocytosis may be absent (Sánchez-Portocarrero et al., 2000; Satishchandra et al., 2007). Glucose is low with elevated CSF protein as typical finding. As with other opportunistic infections, HIV-positive patients may have fewer cells in the CSF then expected (e.g., cryptococcal meningitis). The cryptococcal organism is found by India ink preparations in more than 50% of HIV-negative patients and 90% of patients with AIDS (Black and Baden, 2007; Satishchandra et al., 2007). Antigen assays in the CSF show different sensitivities: *Cryptococcus* 90%, *Histoplasma* 38% (Guimarães et al., 2006; Opota et al., 2015). Although not commonly used, the cell wall component 1,3-beta-D-glucan can be used as a preliminary screening tool in the case of invasive fungal disease (negative in *Zygomycetes*).

Protozoal and helminthic infections and infestations of the nervous system

INTRODUCTION AND EPIDEMIOLOGY

Morbidity and mortality caused by parasitic infections of the CNS are still considered major problems in most of the world. The majority of patients are found in low- and middle-income countries and correlate with the hygienic surrounding, but parasitic infections of the nervous system are being recognized in rising numbers also in the developed world due to international air travel and tourism, HIV infections, and posttransplant immune suppression. The parasites infecting the nervous system are divided into two groups depending on their cell number (Table 12.7): protozoa (Greek: *protos* "first" and *zoion* "animal"), a term coined by Georg August Goldfuß describing parasites with only one cell (Langer, 1970), and metazoa (multicellular organisms) or helminthes. Pathophysiologically, multicellular helminthes have the ability to destroy tissue and cross physical barriers (e.g., skin), migrating and causing an inflammatory response, which is often eosinophilic. The protozoa on the other hand are mainly seen in immune-compromised hosts, explaining the fact that most of the severe opportunistic infections in patients with HIV are caused by protozoan parasites (Walker and Zunt, 2005). Some

Table 12.7

Parasitic infections of the central nervous system

Protozoa		Trypanosomiasis
		Malaria
		Toxoplasma
		Leishmaniasis
		Amebiasis
		Microsporidiasis
Metazoa	Flatworms	Schistosomiasis
		Cysticercosis
		Paragonimiasis
		Hydatidosis
		Coenurosis
		Sparganosis
	Roundworms	Gnathostomisasis
		Angiostrongyliasis
		Filariasis
		Toxocariasis
		Strongyloidiasis

parasites regularly cause symptomatic disease, while others cause few, if any, symptoms. Regarding the CNS, the most common parasite is cysticercosis and only secondary in numbers echinococcosis, toxoplasmosis, and schistosomiasis. Vector-related parasites include malaria, onchocerciasis, toxocariasis, trypanosomiasis, and angiostrongyliasis and their occurrence is dependent on the geographic region (endemic areas).

CLINICAL FEATURES

Clinical presentations of the parasitic CNS diseases can be quite variable but have a certain common picture, making the differential diagnosis between the different infectious agents a challenge. Most parasites upon their CNS infection lead to seizures or encephalopathy, eosinophilia (in blood or CSF), and fever. Neurocysticercosis most frequently is associated with headache, focal neurologic deficits, and seizures, depending on the location of the cysts (Carabin et al., 2011; Arora et al., 2017; Nash et al., 2017). Interestingly, it has been shown in intracranial electroencephalographic recordings that seizure onset does not necessarily correlate with the neurocysticercosis cyst location and in neurosurgical series of patients a robust association between neurocysticercosis and hippocampal sclerosis was shown, theorizing that hippocampal sclerosis could result from recurrent seizure activity due to a distant focus or from chronic recurrent inflammation (Del Brutto et al., 2016).

Toxoplasmosis is caused by *Toxoplasma gondii,* which develops into cysts in muscles (skeletal and cardiac), retina, and the brain. The infection itself is often

subclinical. Once a cyst ruptures, the tachyzoite released causes an acute illness with fever, lymphadenopathy, rash, and visual disturbances. CNS lesions are almost exclusively found in immune-compromised patients and 20% of HIV-infected patients infected with *Toxoplasma* develop encephalitis. Transplacental infection occurs and the consequences are devastating, causing seizures, microcephaly, and chorioretinitis (Brooks et al., 2015; Ngoungou et al., 2015; Cabral et al., 2016; Sinai et al., 2016).

Clinical manifestation in echinococcosis can be quite variable depending on the strain: cystic echinococcosis is caused by *Echinococcus granulosus,* while alveolar echinococcosis is caused by *E. multilocularis.* Cerebral lesions occur in 1–4% of individuals with systemic cystic echinococcosis, with nonspecific clinical findings related to those of space-occupying lesions, increased intracranial pressure, and seizure activity.

Schistosomiasis (*Schistosoma mansoni* and *S. haematobium*) as a neurologic entity caused spinal infections while *S. japonicum* affects the brain. Eggs cause granuloma formation. The acute form is called Katayama syndrome with fever, urticarial rash, cough, and pulmonary infiltrates, often accompanied by a moderate peripheral eosinophilia. This is caused mainly by migrating larvae. In 3% of cases, encephalopathy develops. If the CNS infection is not in the frame of acute infection, cerebral schistosomiasis is asymptomatic but depending on the size can cause focal symptoms. The CNS evaluation for eosinophils is helpful here.

Malaria is the most common parasitic disease worldwide and the cerebral form is always caused by *Plasmodium falciparum,* usually resulting in acute encephalopathy with fever, seizures, and coma. Vascular damage is the usual mechanism of cerebral malaria and depends on the amount of parasitemia. Early symptoms are fatigue, headaches, irregular fever (nonspecific), followed by vomiting, apathy, and then seizures and coma.

Toxocariasis infests the brain rarely but these patients may present with seizures, eosinophilic meningitis, optic neuritis, and meningomyelitis (Graeff-Teixeira et al., 2009; Nicoletti, 2013; Pittella, 2013).

Onchocerciasis or river blindness is caused by *Onchocerca volvulus* and the common symptoms include itching, skin bumps, and blindness. Epidemiologically suspected to be linked to nodding disease, Avindra Nath's group recently showed that nodding syndrome is an autoimmune epileptic disorder caused by molecular mimicry, with *O. volvulus* antigens possibly suggesting immunomodulatory therapies (Johnson et al., 2017).

Trypanosomiasis is divided in the American and African form. The name is derived from the Greek *trypano*- "borer" and *soma* "body" because of their corkscrew-like motion. *Trypanosoma cruzi* is endemic in Latin America and causes Chagas disease (Kennedy, 2004). CNS involvement in Chagas disease may occur in a small percentage of patients in the acute phase. The African form (sleeping sickness) infects the brain parenchyma by early seeding in the choroid plexus and secondary passage into the CSF, or by direct passage into the cerebral capillaries. Symptoms range from meningitis to meningoencephalitis with brain edema and arachnoiditis and seizures and death occur without treatment (Grab and Kennedy, 2008; Pittella, 2009; Ferrins et al., 2013).

CSF ANALYSIS

Microscopic CSF analysis

By examining CSF and blood samples using a microscope, malaria, toxoplasmosis, and human African trypanosomiasis can be identified directly (no staining required). However, direct observation is time consuming and labor-intensive, and proper diagnosis depends on qualified laboratory technicians. This is unfortunately not true for most other parasitic diseases. Eosinophilia is common but very nonspecific (mostly seen in helminthic infections). The antiparasite antibody assays are most frequently used but limitations remain (especially in endemic areas of old, nonacute infection). Both serum and CSF samples are commonly used for the detection of these antibodies. Detection in the CSF or serum of products that are secreted by viable parasites is also possible in some conditions.

PCR

The detection of parasite DNA by PCR is an experimentally simple approach and is currently receiving much more attention than serologic detection of secreted products of viable parasites. Unfortunately, parasite DNA can originate from both the live and dead organism and thus, a positive PCR is not necessarily definitive proof of a viable parasite infection. The strengths of the PCR, however, are its sensitivity and exquisite specificity, which are characteristics that provide a powerful tool for the differential diagnosis of parasite subtypes and polymorphisms and for molecular epidemiologic investigations. Additional specific tests can be useful.

Specific tests

For cysticercosis the detection of the HP10 antigen can identify secreted metacestode glycoprotein. This assay is useful for the long-term follow-up of patients, both during and after treatment. The card agglutination test for trypanosomes (antibody-mediated agglutination of

fixed trypanosomes) is often used initially in the diagnosis of CNS trypanosomiasis, and is followed by direct visualization of the parasite in CSF. Various PCR-based methods and immunodiagnostic tests are used to detect antibodies to parasite proteins of *Plasmodium* to diagnose malaria.

CHRONIC INFECTIOUS DISEASES OF THE CNS

Human immunodeficiency virus infection

Thirty-five million people have died from AIDS-related illnesses since the start of the epidemic. Today, an estimated 36.7 million people globally live with HIV and 2.1 million people have become newly infected. The access to antiretroviral therapy is improving (~18.2 million) and remains the strongest and most important tool to fight AIDS (Fettig et al., 2014; UNAIDS, 2016). Two viral subtypes, HIV-1 and HIV-2, exist, of which HIV-1 is by far the most common. The improved efficacy of today's treatment has turned HIV into a chronic disease with life expectancy approaching population norms for patients who comply with an appropriate antiretroviral treatment (Teeraananchai et al., 2017). Despite the achievements in the management of HIV infection, the virus persists in the latency organs of the host for the host's entire life. Most obvious association with the CNS is via opportunistic infections, discussed above. Without antiretroviral treatment, the progressive decline of CD4+ cells leads to the development of CNS opportunistic infections (cryptococcosis, tuberculosis, toxoplasmosis). Besides this, HIV enters the brain directly and is detectable in the CSF.

The direct advanced HIV infection of the CNS is associated with cognitive impairment independent of opportunistic infections (Snider et al., 1983). AIDS dementia complex, a subcortical dementia, was characterized as a disabling disorder of progressive loss of attention and concentration, notable motor slowing, and various behavioral components, and generally led to death within a year (Navia et al., 1986). The complex was termed HIV-associated dementia (Antinori et al., 2007) and the term HIV-associated neurocognitive disorders (HAND) is most commonly used today (Carroll and Brew, 2017). Compared to the general population, about a half of patients with HIV infection have lower cognitive performance levels, categorized as a mild neurocognitive disorder. The main difference between CNS infections and HIV-associated neurocognitive disorders is their response to antiretroviral therapy.

While CNS opportunistic infections and the prevalence of HIV-associated dementia have significantly decreased in the era of effective antiretroviral therapies, still about half of all treated patients with HIV have cognitive impairment. HIV RNA has been found in CSF from patients regardless of CSF involvement, but the viral load in CSF is usually lower than in plasma. Virus load does not seem to correlate with the severity of the HIV-associated dementia nor with abnormal quantitative neurologic performance (Kaul, 2009). On the other hand, lower HIV DNA levels in monocytes are associated with highly active antiretroviral therapy initiation within the first year of infection, suggesting that the early commencement of highly active antiretroviral therapy may improve outcomes in HAND (Murray et al., 2012; Dahl et al., 2014). In recent studies a negative correlation of the amount of CSF interferon-α and cognitive performance was found, strengthening the hypothesis that it is not direct viral infiltration but rather inflammatory responses that may be responsible for HAND (de Almeida et al., 2017). CSF pleocytosis, consisting mostly of lymphocytes and to a lesser extent of monocytes, is present early in the course of HIV infection even in neurologically asymptomatic subjects, suggesting that it is directly linked to HIV infection itself, rather than an undiagnosed opportunistic infection or neurologic complications (Ho et al., 2013).

Antiretroviral treatment also reduces initial pleocytosis. Interestingly, if untreated, CSF pleocytosis correlates with plasma and CSF HIV RNA levels and with levels of CSF and blood CD8+ cell activation. Despite stable and successful control of HIV-1 in the periphery, approximately 5–10% of individuals with HIV-1 still have detectable virus in the CSF, termed "CSF escape" (Edén et al., 2010). Disagreement between the HIV viral loads in the plasma and CSF is defined by detectable levels of HIV RNA in the CSF, indicative of a viral load of >200 copies/mL, when the viral load in the plasma is <50 copies/mL or by an HIV RNA viral load in the CSF that is ≥1 log higher than that in the plasma (Canestri et al., 2010). The appearance of new neurologic symptoms in the context of standard antiretroviral therapy regimens and well-controlled plasma HIV infection warrants an evaluation of the CSF to determine whether CNS isolated viral replication is occurring.

Neurosyphilis

Treponema pallidum causes syphilis and, if the CNS is involved, neurosyphilis. Three stages are usually seen in the course of the disease. In the early stage, the infection presents with painless genital ulcers and lymphadenopathy. After 3–5 weeks of primary infection, some patients progress to secondary syphilis, manifesting as meningitis. Meningitis in secondary syphilis only occurs in 25% of syphilis infections and may present with headache, vomiting, photophobia, and cranial nerve deficits

(most commonly of the seventh and eighth nerves). Late disease occurs >10 weeks later and is also termed latent syphilis. This form can ultimately lead to tertiary syphilis presenting as further neurologic dysfunction, including tabes dorsalis, dementia, and general paresis (Read and Donovan, 2012; Clement et al., 2014). Serologic testing with Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin is the gold standard for screening. Regarding the VDRL, although estimated specificity is high, sensitivity is lower, which is a major limitation of the test. The method for both the serum and CSF VDRL tests requires specialized glass plates and a light microscope. For CSF testing, the cardiolipin-lecithin-cholesterol antigen is diluted and a smaller volume of the antigen suspension is used compared to serum, adjusting for the much lower concentration of immuno-globulin in CSF compared with blood.

In contrast to the VDRL test, the rapid plasma reagin test for plasma or serum incorporates carbon particles, which enables the test to be performed on a disposable paper card and read with the naked eye, rather than a microscope (Marra et al., 2012). The main limitations of nontreponemal tests are their reduced sensitivity in pri-mary syphilis and late latent syphilis, and false-positive results due to cross-reactivity. After a positive initial screening, fluorescent treponemal antibody absorption (FTA-ABS) test or *T. pallidum* particle agglutination can be used to confirm infection (Janier et al., 2014).

The sensitivity of nontreponemal and treponemal tests for syphilis increases with duration of infection, and ranges from approximately 75% in the primary stage to virtually 100% in the secondary stage. In all patients with late latent syphilis, LP is recommended to exclude neurosyphilis. CSF testing is considered diagnostic when it demonstrates a mononuclear cell count greater than 5–10 cells/μL, protein concentration greater than 40 mg/dL, and a reactive CSF VDRL.

While CSF-VDRL is specific, the test lacks sensitiv-ity (as low as 27%: Davis and Schmitt, 1989) and cannot be used to exclude disease (Nayak and Acharjya, 2012). In general, we recommend that all CSF samples be tested for VDRL even if the indication for the LP was not related. PCR testing for CSF infection is controver-sial, with 50% of neurosyphilis patients testing negative (Castro et al., 2016). Appropriate treatment of neurosyphilis should reduce the CSF pleocytosis and protein by 6 months after treatment, but CSF VDRL test results may remain reactive for at least 2 years. Leuko-cyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months, or if the CSF cell count or protein is not normal after 2 years, retreatment should be considered (Marra et al., 2008).

Tuberculosis of the central nervous system

Tuberculous meningitis is often seen in immunocompro-mised individuals, most commonly as an HIV co-infection. In immunocompetent individuals, how-ever, tuberculous meningitis is not uncommon: of the 8.7 million incident cases in 2011, 1.1 million (1.0–1.2 million or 12–14%) were among people living with HIV (Glaziou et al., 2014). Clinically headache, fever, weight loss, vomiting, and cranial nerve palsies are com-mon. Focal symptoms from tuberculomas, miliary dis-ease, or cerebral infarction may also be seen (Brancusi et al., 2012; Pehlivanoglu et al., 2012).

Tuberculous meningitis is not easy to diagnose: LP typically reveals a nonspecific pattern of elevated intra-cranial pressure, lymphocytic pleocytosis, elevated protein, and low glucose. In HIV-positive individuals, it is important to note that CSF cell counts may not dem-onstrate lymphocytosis. Research suggests that large CSF volumes and longer microscopy examination times identified *Mycobacterium tuberculosis* using acid-fast stains with a sensitivity of 52%. CSF cultures on Lowenstein-Jensen medium are also effective in detecting *M. tuberculosis* in up to 90% of cases; how-ever, this technique is severely limited due to result times of several weeks. DNA detection in CSF by PCR assay may be a useful ancillary diagnostic test, with a nearly 100% specificity but a sensitivity that var-ies between 30% and 50%, thus limiting its usefulness. Empiric therapy should be started as soon as the diag-nosis is suspected, as confirmatory testing is typically delayed.

Subacute sclerosing panencephalitis

SSPE occurs in immunocompetent children who encounter natural measles infection at a young age. The risk of developing SSPE after childhood measles is estimated as 1/25,000 and vaccine coverage over 90% arrests the transmission of measles in a population and reduces markedly the incidence of SSPE. It is gener-ally accepted that the measles virus (MV) can reach the brain by infecting circulating lymphocytes or endo-thelial cells. Transneuronal and axonal spread is also considered. Viral antigens are expressed and induce an anti-MV immune response. Cognitive changes can be subtle. Myoclonus is the most common and frequently the first symptom bringing the child to medical attention.

In the beginning slow, brief blinking or head-dropping attacks, or asymmetric upper body jerks can be observed several times a day, more in the evening when the child is tired. Rare and less typical presenta-tions of SSPE include epileptic seizures, epilepsia partia-lis continua, acute encephalopathy, hemiparesis, acute

ataxia, unilateral dystonia, or psychiatric disturbances and dementia. CSF analysis, protein, and cell count are normal and pressure can be normal or, infrequently, elevated. Immunoglobulin index is high and oligoclonal bands reacting with MV antigens are seen in almost all patients. Antimeasles IgG and measles-specific IgG index are diagnostic. MV RNA can sometimes be detected by rt-PCR. No specific drug can clear the persistent MV from the CNS. Antiviral and immuno-modulatory treatments can achieve partial remission or stabilization rates exceeding those expected in the natural course (Steiner et al., 2014). Intraventricular interferon treatment has been shown to modify the course of SSPE and should be considered (Wirguin et al., 1988, 2005; Steiner et al., 2016).

Mollaret's meningitis

Mollaret's meningitis is characterized by recurrent self-limiting meningitis in otherwise healthy individuals (Mollaret, 1944). Recurrence takes place at intervals of several weeks to months and has been documented after up to 28 years, with attacks lasting for several days and then resolving (Tyler and Adler, 1983). CSF contains from 200 to several thousands of lymphocytes per cubic millimeter, and large endothelial cells, termed Mollaret cells, may be present. Protein levels in the CSF are elevated and glucose may sometimes be low. Complete recovery occurs within several days. Diagnosis is established after other causes of lymphocytic meningitis have been ruled out.

Mollaret originally suspected either a hypersensitivity condition or an infectious disease. In some patients the disorder has been associated with Epstein–Barr virus (Graman, 1987), HSV-1 (Steel et al., 1982), and histoplasmosis (Haynes et al., 1976), but the majority of cases are associated with HSV-2 infection (Bergström et al., 1990). In 1991 Berger reported 3 patients in whom Mollaret's meningitis followed recrudescence of genital herpes. The attacks responded to acyclovir in 2 patients, and in 1 the disorder did not recur following treatment. Prior to the introduction of PCR technology, the possibility that the disorder was due to an HSV infection was intriguing because of the recurrent, self-limiting nature of the condition and because of the CSF findings, which were compatible with viral infection. Indeed, PCR made it possible to identify the etiology of the disease in most, if not all, patients and to attribute it either to HSV-2 (Picard et al., 1993; Cohen et al., 1994; Jensenius et al., 1998), or to HSV-1 in selected cases (Yamamoto et al., 1991; Tedder et al., 1994). Cohen et al. (1994) reported the identification of HSV-2 DNA in the CSF of patients with Mollaret's meningitis associated with the presence of Mollaret cells in the CSF.

Whether to treat patients during the acute attacks remains an open question. Although some reports suggested either shorter episodes (Cohen et al., 1994; Jensenius et al., 1998) or resolution of the syndrome (Berger, 1991; Picard et al., 1993), one could argue that a short course of antiherpetic treatment does not affect the viral reservoir and is not associated with prevention of future mucocutaneous disease (Straus et al., 1984).

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