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Neurological Complications of Infectious Diseases

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Preface

Primary infections of the central nervous system (CNS) such as meningitis or encephalitis typically present with fever and obvious neurologic impairment, facilitating management. In contrast, when neurologic disease occurs secondary to a systemic infection or with an insidious presentation, diagnosis and treatment may be delayed, often with catastrophic results. The goal for this book is to highlight uncommon causes of neurologic dysfunction that may not be easily recognized.

The first part reviews the general diagnostic approach for any patients presenting with suspected CNS infection. Molecular diagnostic testing has revolutionized the ability to rapidly identify CNS pathogens without an invasive procedure; however, understanding the strengths and limitations of available assays is crucial in interpreting results and guiding additional testing and treatment. When diagnostic evaluation is unrevealing, it is important to consider the possibility of antimicrobial-induced neurotoxicity, which paradoxically may mimic infection of the central nervous system.

Parts II to IV highlight specific pathogens causing CNS infection. These chapters include updated discussions of common neurotrophic pathogens, such as HSV or VZV, as well as neurologic manifestations of systemic infections, such as bacterial endocarditis and HIV. International travel and immigration have broadened the spectrum of infections seen domestically. Infectious disease physicians, neurologists, and neuro critical care providers need to consider not just endemic pathogens but also imported infections such as neurocystercercosis or neurobrucellosis if there is a compatible travel history.

Diseases of the spinal cord are discussed in Part V. This includes both bacterial processes, such as epidural abscesses and myelitis, typically seen with viral infections. Importantly, this part includes a chapter on post-infectious encephalomyelitis, an autoimmune sequela of systemic infection.

The final part includes miscellaneous infections. The chapter on tick-borne infections highlights the broad spectrum of infections caused by bacteria, viruses, and protozoa transmitted through tick bite. Whipple's disease is a diagnostic challenge, particularly when infection is limited to the CNS. Prion disease remains a

uniformly fatal syndrome, with early consideration of this diagnosis key in prevention of secondary cases through neurosurgical procedures or tissue donation.

As new pathogens are identified, new diagnostic techniques introduced, and new antimicrobials developed, it is likely that causes of neurologic complications associated with infectious diseases will continue to expand. Recognition of these uncommon and less easily identified syndromes has the potential to expedite treatment and improve neurocognitive outcomes.

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Series Editor's Introduction

This volume on *Neurological Complications of Infectious Diseases* edited by and with contributions from Drs. Rodrigo Hasbun, Karen Bloch, and Adarsh Bhimraj appears at an opportune time amidst the current rapidly evolving recognition of the myriad ways in which systemic infection is associated with central nervous system (CNS) complications. Initial reports regarding the current worldwide COVID-19 pandemic have emphasized the widespread systemic pathologies which involve upper and lower respiratory, cardiovascular, gastrointestinal, and hematologic systems. More recently, various attacks on the central and peripheral nervous system have become increasingly appreciated, including stroke due to small vessel thrombosis, acute encephalitis, encephalopathy, myelitis, and Guillain Barre Syndrome. As with other neurological complications of infectious disease, these include direct infectious as well as immunologically mediated complications. As outlined by the editors in their preface, this volume begins with a clinical and molecular approach to diagnosis in patients with suspected CNS infection including consideration of antimicrobial-induced neurotoxicity. Subsequent parts include discussions of the specific infectious pathogens which cause CNS infection, various spinal cord complications, and post-infectious encephalomyelitis. In view of the Corona-caused pandemics of recent years, the importance of travel- and immigration-derived infectious illness is also given appropriate emphasis.

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Part I
Diagnosis and Evaluation of the Patient with a CNS Infection

Chapter 1
Diagnostic Approach to a Patient with Suspected CNS Infection

Adarsh Bhimraj, Karen C. Bloch, and Rodrigo Hasbun

A diagnostic hypothesis for a suspected CNS (Central nervous system) infection has two components: an anatomic and a microbiologic or etiologic diagnosis. The anatomic diagnosis localizes the inflammation to a specific part of the CNS. The microbiologic or etiologic diagnosis identifies the pathogen or etiology that is causing the CNS inflammation. An accurate anatomic and microbiologic hypothesis requires a detailed history (including symptoms, duration, exposure & epidemiologic risk factors), a complete physical exam including a thorough neurologic exam, and an appropriate diagnostic work-up including imaging, labs and cerebrospinal fluid (CSF) testing (in meningitis and encephalitis but not in focal suppurative intracranial lesions). Prognosis and management depend on a rapid and accurate diagnostic hypothesis and testing.

A practical approach to the patient with suspected CNS infection would be to answer the following questions, to make a diagnostic and prognostic hypothesis:

1. Where is the "itis" or inflammation (anatomic site)?
2. How long has it been going on (duration of illness)?
3. Is it community acquired or healthcare acquired?
4. What is the exposure or epidemiological history?

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5. Is the patient a “normal host” or an “immuno-compromised host”?
6. Is it an acute severe infection or a chronic stable infection?
7. What is the type of CSF inflammatory response on routine CSF analysis?

1: Where Is the Inflammation?

Microorganisms have tropism to certain anatomic sites in the CNS, and outside the CNS. So anatomic localization helps identify the etiology or organism. *S. pneumoniae* and *Neisseria meningitidis* have tropism to the leptomeninges or pia-arachnoid [1]. Herpes simplex virus-1 (HSV-1) has tropism to the medial temporal lobe, and West Nile virus and Japanese encephalitis have tropism for the basal ganglia [2]. At a cellular level, poliovirus and West Nile virus infects the anterior horn cells causing an acute flaccid paralysis, and JC virus infects the oligodendrocytes, which produce myelin in the central nervous system causing white matter lesions caused by demyelination on magnetic resonance imaging (MRI). Anatomic localization can be done based on history, neurologic exam, imaging especially with MRI of the CNS, and CSF analysis. A patient with meningitis can have headache, meningeal signs, leptomeningeal enhancement on a T1 post contrast MRI of the brain, and increased white blood cells, with a low glucose on routine CSF analysis. The patient with HSV-1 encephalitis can present with amnesia, and temporal lobe changes on brain MRI [2]. Often clues to the diagnosis can be present at anatomic sites outside the CNS. *Nocardia* causes brain abscesses and also causes lung nodules. Sarcoidosis causes a chronic basilar leptomeningeal meningitis resembling tuberculosis, sometimes with bilateral hilar lymphadenopathy [3, 4]. Classifying the patient into the following anatomic syndromes can be helpful as it gives clues about the possible etiology.

- *Meningitis:* Leptomeningeal meningitis is inflammation of the pia-arachnoid and pachymeningitis is inflammation of the dura.
- *Encephalitis:* This is inflammation within the brain parenchyma.
- *Myelitis or Myelo-radiculitis:* This is inflammation of the spinal cord with or without involvement of the spinal nerve roots. Myelitis can happen with or without concomitant encephalitis.
- *Space occupying ring enhancing lesions* in the brain on post contrast CNS imaging.
- *Stroke or stroke-like syndromes* involving vascular territories of the brain.

2: How Long Has It Been Going on?

Meningitis can be divided into acute, subacute or chronic if the duration of symptoms is less than 5 days, 6–30 days, or > 30 days, respectively [5]. Etiologies such as bacterial meningitis (e.g., *S. pneumoniae* or *N. meningitidis*) causes severe acute meningitis [1], but indolent slow-growing organisms like fungi and *Mycobacterium*

tuberculosis cause subacute or chronic meningitis [3–5]. A patient can also have recurrent acute CNS infections such as meningococcal meningitis due to terminal complement deficiencies or due from reactivation of a latent virus such as HSV-2, which can cause a benign recurrent lymphocytic meningitis (Mollaret's meningitis) [1].

3: Is It Community Acquired or Healthcare Acquired?

In the CNS, healthcare acquired ventriculitis or meningitis (HCAVM) usually occur after neurological trauma or neurosurgical procedures [6]. Once the skull and dura are breached by trauma or surgery, do hospital acquired pathogens like *Pseudomonas aeruginosa*, *E. coli* and *Staphylococcus aureus* find a portal of entry into the CNS [6]. These organisms, unlike organisms that cause community acquired bacterial meningitis like *S. pneumoniae* or *N. meningitidis,* lack the capacity to directly invade the CNS.

4: What Is the Exposure or Epidemiological History?

The following three factors are essential for the pathogenesis of a CNS infection:

- The organism should be able to infect the human host and also have CNS tropism.
- The host should be susceptible to an infection by a particular organism. *S. pneumoniae* is a highly virulent organism capable of causing an infection even in a normal host and is also neurotropic. On the contrary *Listeria monocytogenes* usually causes meningitis in the elderly and hosts with deficient T cell immunity [1].
- A conducive environment and host behavior for transmission (exposure or epidemiology) is necessary, in addition to the host and pathogen factors. A mosquito bite in an endemic area could place the patient at risk for West Nile virus, Japanese encephalitis or even cerebral malaria [1]. On the contrary anyone can sporadically get HSV encephalitis.

Obtaining a tailored exposure history is very important in establishing the etiology, and ordering appropriate diagnostic tests. A few examples are as below.

- **Travel:** Travel to Arizona puts the patient at risk for chronic meningitis from Coccidioidomycosis [7].
- **Insect bites:** Tick bites are a risk factor for neuroborreliosis, and mosquito bites for arboviral infections [1].
- **Animal bites:** Raccoon bites or bat contact puts one at risk for rabies [2].
- **"Sick contacts":** Close contact with someone with meningococcal meningitis (in a college dorm or military barrack) increases risk for acquiring it [1]. Health care workers and prison inmates are at a higher risk for chronic meningitis from tuberculosis [4].

- **Sexual history:** An acute lymphocytic meningitis in a patient with recent unprotected sexual intercourse could be acute retroviral syndrome or neurosyphilis [1].

5: Is the Patient a "Normal Host" or an Immunocompromised Host?

The susceptibility of a patient to different infections depends on which arm of the immune system is compromised and the net state of immunosuppression. Opportunistic pathogens are organisms that are usually nonpathogenic in a normal host, but are pathogenic in an immunocompromised host. Hematopoietic stem cell transplant patients, are at a higher risk for opportunistic infections pre-engraftment, and subsequently if they need to be treated with immunosuppressive medications for graft versus host disease. Solid organ transplant patients, are at highest risk immediately after transplantation, and subsequently if they need to be treated for transplanted organ rejection.

The differential diagnosis for the same anatomic syndrome, changes significantly based on the host. For example, ring enhancing lesions or abscesses on brain imaging (post contrast MRI or CT) in an immunocompetent host are usually bacterial abscesses. However in a HIV patient with a CD4 count of less than 100/μL, cerebral toxoplasmosis should be considered. In a solid organ transplant recipient, invasive molds are higher on the differential.

6: Is It an Acute Severe Infection or a Chronic Stable Infection?

Differentiating an urgent treatable condition from a chronic stable infection is vital. Risk factors associated with an urgent treatable cause include: (1) abnormal host (immunosuppressed or elderly), (2) abnormal neurological exam (seizures, focal neurological findings, abnormal mental status), and (3) abnormal laboratory values (CSF glucose<45 mg/dl, CSF protein >100 mg/dl or Serum WBC >12,000) [8]. Clinicians should act fast if a patient has acute worsening of mental status or rapidly progressive neurological deficits within hours. Antibiotic delay in the treatment of bacterial meningitis can increase mortality [1]. A patient with a spinal epidural abscess who develops sudden lower extremity weakness and incontinence needs emergent surgery [9]. On the contrary, there is no rush to treat a patient who presents with headaches for weeks and no focal neurological features from chronic stable lymphocytic meningitis.

7: What Is the Type of CSF Inflammatory Response?

Routine cell counts and chemistry analysis of the CSF can be done quickly and can provide valuable diagnostic information. CSF can be obtained either by lumbar puncture from the subarachnoid space or from the cerebral ventricles via an external ventricular drain or ventricular shunt.

- **CSF total nucleated cell count (WBC count) and differential**- If the CSF WBC count/μL is in the thousands and is predominantly neutrophilic, it is suggestive of a bacterial meningitis from a virulent organism like *S. pneumoniae.* If the CSF WBC count/μL is close to 100,000 and is neutrophilic, it is suggestive of intra-ventricular rupture of a brain abscess. The differential diagnosis for a mild to moderate lymphocytic CSF pleocytosis is very broad, including viral, fungal, mycobacterial, neoplastic and immune mediated meningitis or encephalitis. The differential diagnosis for a predominantly eosinophilic CSF pleocytosis (greater than 10%) is very narrow and includes parasitic worm infections, Coccidioidomycosis, or an adverse reactions to intrathecally administered drugs. Certain CNS infections like Creutzfeldt-Jakob disease (CJD) and progressive multifocal leukoencephalopathy (PML) do not usually cause CSF pleocytosis.
- **CSF: Blood glucose ratio** is another discriminatory test. A very low ratio (0.4 or less) is suggestive of a bacterial, fungal, mycobacterial or neoplastic meningitis. It is important not to rely just on the CSF glucose level, and to obtain a blood glucose level at 30–45 min around the time of CSF sampling. CSF glucose levels usually equilibrate with blood levels in less than an hour. CSF glucose of 60 mg/dl is "normal", but the CSF: blood glucose ratio would be very low if the patient's blood sugar were 600 mg/dl.

Diagnostic Testing in a Patient with a CNS Inflammatory or Infectious Syndrome

It is beyond the scope of this chapter to go into the details of diagnostic testing, but we will briefly discuss general principles of testing. Diagnostic imaging especially MRI brain with and without contrast is not just useful for anatomic localization, but the radiographic pattern on different sequences can give clues about etiology. For example, a ring enhancing lesion on T-1 post contrast MRI with restricted diffusion in the center on diffusion weighted images, is more suggestive of an abscess than a tumor.

Tests for organism detection can be performed in the blood, serum, CSF or tissue from a biopsy of the brain or meninges. Traditional stains and cultures for bacteria,

fungi, and mycobacteria still play an important role, though the yield might be low especially when the CSF or tissue sample is of an inadequate volume. There are newer CSF molecular diagnostic tests like Multiplex PCR's, universal 16S or 18S ribosomal RNA PCR's, and unbiased meta-genomic sequencing available for organism detection. The same principles of diagnostic testing that apply to traditional stains and cultures are also relevant when interpreting molecular diagnostic tests. There could be false positive tests from contamination during specimen collection both with traditional and molecular tests. An example would be of a single colony of *Staphylococcus epidermidis* that grows from the CSF bacterial culture, or is detected by a molecular test. Both these "positive CSF tests" are suggestive of a contamination. Latent viruses like EBV, CMV and HHV-6, can reactivate in the context of another CNS inflammatory disease and a positive test from the CSF does not necessarily mean they are the cause.

Serum and CSF antibodies, both for infectious and immune mediated etiologies, are also problematic to interpret. Antibodies to infectious organisms often remain positive for months and years after the resolution of the infection, and a positive test doesn't always mean that the patient has an active infection. Borderline positive antibody tests are often false positive. The clinician should be extremely cautious in interpreting these "positive" tests especially in the workup of chronic meningitis and chronic encephalitis, as the false positive rate increases with the number of tests ordered.

A Clinical Syndrome Based Approach to CNS Infections

Acute Meningitis

This is inflammation of the meningitis which occurs rapidly within hours to days. Acute neutrophilic meningitis in adults is usually from community acquired bacterial pathogens like *S pneumoniae, N. meningitidis* and *Listeria.* Acute lymphocytic meningitis is usually from enteroviruses or arboviruses like West Nile. In the post craniotomy patient, virulent pathogens like *E. coli* and *Staphylococcus aureus* can cause an acute meningitis or cerebral ventriculitis. It is also important to note that post craniotomy meningitis from indolent pathogens like *Staphylococcus epidermidis* can present as chronic meningitis.

Recurrent Acute Meningitis

The differential diagnosis depends on the type of CSF pleocytosis. The causes of recurrent lymphocytic meningitis are:

- Mollaret's meningitis from recurrent HSV-2 reactivation in the pia-arachnoid.

- Intermittent leaking into the subarachnoid space from epidermoid cysts or craniopharyngiomas.
- Recurrent episodes of autoimmune disease (Bechet's, sarcoid, or granulomatous polyangiitis), medication (NSAID's, Trimethoprim, or IVIG).

The causes of recurrent neutrophilic meningitis are:

- Recurrent bacterial meningitis secondary to anatomic communication of the subarachnoid space with a non-sterile surface (mucosa or skin). This could be secondary to congenital defects or from trauma to the face, head or spine. If the patient has clear rhinorrhea or otorrhea, then test the fluid for beta-2 transferrin. It's presence in the fluid is highly suggestive that it is CSF.
- Immunoglobulin deficiency or asplenia can lead to recurrent infections from encapsulated organisms like *S pneumoniae, N. meningitidis and Haemophilus influenzae*. These organisms are neurotropic and cause meningitis.

Chronic Meningitis

This is meningitis that has an indolent presentation and lasts weeks to months [3]. Often an etiologic diagnosis is difficult, requiring multiple lumbar punctures and extensive testing. A few of the causes to consider in the differential diagnosis are:

- *Cryptococcus neoformans*
- Coccidiodomycosis, Histoplasmosis, Blastomycosis
- Spirochetes (Syphilis, Lyme, Leptospirosis)
- Acanthamoeba
- *Mycobacterium tuberculosis*
- Leptomeningeal carcinomatosis (adenocarcinomas of the lung, breast and melanoma)
- Lymphomatous leptomeningitis (NHL, ALL)
- Leptomeningeal gliomatosis

The differential diagnosis for chronic meningitis that predominantly involves the basilar leptomeninges includes fungal meningitis, tuberculous meningitis, neoplastic meningitis and neurosarcoidosis. If there is concomitant uveitis (inflammation of the iris, ciliary body or choroid of the eye) then consider the following etiologies

- Sarcoidosis.
- Bechet's syndrome, which can also involve the brainstem.
- Vogt-Koyanagi-Harada syndrome which presents with meningitis, deafness, granulomatous uveitis, alopecia, vitiligo, poliosis of eyelashes, eyebrows and hair.
- Wegner's granulomatosis
- Sjogren's syndrome
- *Tropheryma whippeli.*

Encephalitis

This is inflammation of the brain parenchyma. An etiologic diagnosis is unknown in more than half of the patients [10]. Most common known etiologies are either infections (usually viral) or immune mediated encephalitis. The most common infectious etiology for acute sporadic encephalitis is Herpes simplex virus, which has a predilection to involve the medial temporal lobes. Episodes of encephalitis involving deep gray matter (basal ganglia) during the summer and fall in the US is suggestive of West Nile viral infection. Japanese B encephalitis, which is more common in Asia, can have a presentation similar to West Nile encephalitis.

> Autoimmune encephalitis has to be considered as quickly as the most common viral causes have been ruled out [2]. It was initially described as a paraneoplastic syndrome, but is now reported without any association with tumors as well. It is either associated with antibodies against neuronal cell surface synaptic proteins, or with antibodies against intracellular proteins [2].

Myelitis or Myelo-Radiculitis

Myelitis is inflammation of the spinal cord and myelo-radiculitis is inflammation of both the spinal cord and spinal nerve roots. The causes are infectious, post infectious or post vaccination, or autoimmune. Symptoms can include weakness, paresthesias, and/or bowel, bladder or sexual dysfunctions. Infectious organisms that usually cause extensive transverse and vertical myelitis are herpes simplex and vascular zoster (VZV). CMV usually causes myeloradiculitis in immunocompromised patients especially in HIV patients with CD4 counts of 100/μL or less. Certain viruses have a predilection to infect anterior horn cells and cause acute flaccid paralysis. These viruses are West Nile virus, nonpolio enterovirus like enterovirus D68, and Japanese B encephalitis virus. Among the noninfectious etiologies of extensive myelitis, the most important is Neuromyelitis optica, which can cause significant CSF pleocytosis and can mimic an infectious myelitis.

Space Occupying Rim Enhancing Lesions in the Brain

Space occupying rim enhancing lesions in the brain on post contrast T-1 MRI can be caused by brain abscesses, demyelinating lesions, tumors or hematomas. Multiple brain abscesses in different vascular territories of the brain are usually from heamatogenous spread, and are caused by a single organism like *Staphylococcus aureus* or *Streptococcal* species. Solitary brain abscesses are usually infections that spread from a contiguous focus like mastoiditis or paranasal sinusitis and are polymicrobial with gram-positive cocci, anaerobes, and sometimes gram-negative rods. “Complete” ring enhancement of the lesions is usually seen in brain abscesses and tumors, whereas “incomplete” ring enhancement or the letter “C” shaped enhancement is usually seen in demyelinating lesions like acute demyelinating encephalomyelitis (ADEM) or in tumefactive demyelinating lesions.

Stroke or Stroke Like Syndromes from Infectious and Inflammatory Etiologies

Infections of the central nervous system can cause ischemic strokes either by direct invasion of the vessel wall to cause vasculitis, or when meningeal inflammation in meningitis spreads to the Virchow Robin-spaces surrounding the blood vessels, and eventually to cerebrovascular arterial wall to cause strokes. Infectious and inflammatory causes of stroke are:

- Varicella Zoster vasculitis
- Meningovascular syphilis
- Basilar meningitis from yeasts like Cryptococcus, Candida & dimorphic fungi, or *Mycobacterium tuberculosis*
- Secondary to systemic vasculitis like granulomatous polyangiitis, giant cell arteritis, or Takayasu's arteritis.
- Primary CNS angiitis, which is a diagnosis of exclusion of other secondary causes
- Intravascular lymphoma

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Chapter 2
Molecular Diagnostics in Central Nervous System Infections

Tamara Nawar, Anna Kaltsas, and Yi-Wei Tang

Central nervous system (CNS) infections are a major cause of morbidity and mortality worldwide. During the last decade, one million cases were reported with almost 100,000 deaths, mostly from the sub- Saharan African region, prompting the World Health Organization to create the "Defeating meningitis by 2030" project (https://www.who.int/immunization/research/Defeating_meningitis_2030_TTFJuly2018_report.pdf).

CNS infections can become life threatening particularly if not diagnosed early. Hence, timely and accurate diagnosis is essential in guiding early interventions [1, 2]. In addition, the unique anatomic characteristics of the CNS play a major role in the pathogenesis of infections. Although protected by the blood brain barrier, the CNS remains susceptible to microbial invasion [3].

CNS infections can be classified depending on their anatomic location: meningitis, encephalitis and myelitis represent infections of the meninges, brain, and spinal cord, respectively. Although the classic triad of fever, neck stiffness and altered mental status has a sensitivity of only 40% for diagnosing adults with bacterial meningitis, most infections present with at least one of these symptoms [4]. These symptoms, however, may be subtle or completely absent in the immunocompromised or elderly patients.

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The brain, spinal fluid, and spinal cord may function as a milieu for infections by various environmental or commensal organisms including viruses, bacteria, fungi, protozoa or parasites. Time to treatment is vital in decreasing morbidity and mortality related to these infections.

Conventional techniques including direct examination, culture and antigen/antibody detection can have major limitations. Patients are usually kept on broad spectrum antibiotics for a prolonged period until cultures result [5]. Furthermore, these techniques have reduced sensitivity, specifically for the detection of viral infections. For instance, using the example of enteroviruses, one of the most frequent pathogens causing meningitis, direct microscopic examination has a sensitivity between 65% and 75% with a mean retrieval time of 3.7–8.2 days [6]; while in other cases, viruses such as Coxsackievirus A are difficult to culture [7].

To overcome these diagnostic limitations, molecular methods are becoming one of the mainstays of detecting CNS infections, and their use has been associated with reduced length of hospital stay in some studies [8]. When compared to culture and other microscopic examinations,16S ribosomal ribonucleic acid (rRNA) PCR detected meningitis pathogens in 65% of CSF analytes compared to only 35% when using conventional methods [9]. In another study which compared broad-range bacterial PCR combined with DNA sequencing to culture-based methods for examining CSF, the specificity was high for both study arms, but the sensitivity of PCR vs culture was 59% vs 43%, respectively [9].

Conventional Techniques

Microscopic Examination

CSF gram stain has a 60–90% sensitivity and 97% specificity [10] for the diagnosis of bacterial meningitis. Rarely, false positive results have been described in the literature [11, 12].

Multiple variables can alter the sensitivity of gram stain. The sensitivity of gram stain can be as high as 80% in patients who have not been treated with antimicrobial therapy and as low as 40% in those who have already received some treatment. The sensitivity is also highly related to the pathogen, as gram stain can detect as many as 90% of *Streptococcus pneumoniae* [13, 14], but can be significantly lower in Listeria monocytogenes, the third most common cause of bacterial meningitis [15]. In tuberculous meningitis, modified Ziehl-Neelsen staining was highly sensitive in patients with probable or definite tuberculosis infection but had a low specificity with high false positive rates [16].

In cryptoccocal infections of the CNS, India ink examination is positive in 50–75% of patients with cryptococcal meningitis and the yield can increase to

almost 90% in patients with AIDS [2, 17]. In some studies, the sensitivity of India ink stain was as high as 93% and the specificity was almost 100% [18]. In addition, amoebae such as *Naegleria fowleri* are best diagnosed by direct observation of the trophozoites in the CSF by trichome or Giemsa staining [19].

Although microscopic examination is of limited value in viral infections, pathologic examination of brain tissue revealing the cytopathic effect of the virus can be highly suggestive of certain diagnoses. For instance, detection of Negri bodies in the CNS is pathognomonic of Rabies infection. Intranuclear eosinophilic bodies surrounded by halos usually suggest HSV infection.

Unfortunately, while microscopic examination and culture remains the gold standard for certain infections, its role in other infections remain marginal. For instance, in patients with infections caused by *Treponema pallidum*, *Borrelia burgdorferi* or *Toxoplasma* encephalitis, there are no highly effective stains to identify these organisms and other studies are needed to aid in the diagnosis [2]. Finally, obtaining brain tissue for culture and special stains is invasive and challenging and not often easily obtained.

Culture

CSF culture aids in the diagnosis of bacterial, mycobacterial and fungal infections [11] and allows for subsequent antibiotic susceptibility testing and targeted therapy (Table 2.1). However, the yield of culture growth is greatly impacted by the prior use of antibiotics. Current guidelines recommend a CT scan prior to a lumbar puncture in patients with meningitis and altered consciousness or focal neurological deficits, which in most instances delays culture collection and administration of directed therapy [91]. In practice, most patients receive antibiotics prior to lumbar puncture [5].

The volume of CSF collected also alters culture sensitivity. In one study, optimal results for fungal and mycobacterial infection were reported if >10 cc of fluid was cultured [80, 92]. Although it remains the gold standard for diagnosing bacterial and fungal infections, the role of culture remains limited for viral infections.

Some viruses grow poorly in culture; examples include cytomegalovirus, varicella zoster and adenovirus as suggested by Polage et al. In a study comparing nucleic acid amplification testing to culture in diagnosing viral infection, only <0.1% of viral cultures were positive [93]. The same applies to other viruses such as West Nile virus, which are also poorly recovered from conventional microbiologic cultures [94–96]. Moreover, the sensitivity of enterovirus culture in another study was only 65 to 75% and required up to a week for detection of the viral cytopathic effect [97].

Table 2.1 Laboratory methods in detecting common pathogens causing CNS infections

Organism	Diagnostic methodology	Advantages	Limitations	References
Viruses				
Adenovirus	Viral culture, Viral PCR	Viral culture remains the gold standard for diagnosis	Cultures do not detect types 40 and 41 and take 2–7 days to diagnose PCR sensitivity 96% and specificity 100% with faster results	[20, 21]
Japanese encephalitis virus	Viral Serology IgM ELISA, Viral Antigen	Viral serology has a sensitivity of 65–85% and specificity 89–100% Antigen detection is most useful during the first week of illness "window period"	Serology have Cross reactivity with other viruses which might alter the results	[22–24]
Powassan virus	Viral serology IgM in CSF and serum		False negative results in CSF Cross reactivity with other viruses alters specificity Cross reactivity with Lyme serology has been reported	[25, 26]
St Louis encephalitis virus	Viral serology IgM, Duplex microsphere-based immunoassay, metagenomics next-generation sequencing has been used	Results can be as fast as 4 h in immunoassay	Viral serology can also have cross reactivity with other viruses which may alter the specificity of the test	[27, 28]
Zika virus	Viral serology IgM, PCR	PCR results quickly within 4 h of testing with high sensitivity up to 96%	Serology have cross reactivity with other viruses alters specificity	[29, 30]
West Nile virus	Viral serology IgM in serum and CSF, Plaque reduction neutralizing test (PRNT), PCR	PCR is most helpful in immune compromised patients who do not have sufficient amounts of antibodies	Viral serology can have cross reactivity with other viruses that can alter the specificity of the test which is not seen with PRNT	[31–33]

Table 2.1 (continued)

Organism	Diagnostic methodology	Advantages	Limitations	References
Rabies virus	PCR, Serology, Pathology with cytopathic effect; Negri bodies	PCR has a high sensitivity and specificity up to 98% for both	Caution while interpreting serology results in patients who have received the rabies vaccine	[34, 35]
Rubella virus	Viral serology IgM, PCR	Both have high sensitivity and specificity Serology (Sensitivity 84.2–96.5%, Specificity 96.8–99.9%) and PCR (Sensitivity 83–95% and Specificity 100%)	Serologic testing can have false positive results in presence of rheumatoid factor or other viral infections (CMV, EBV or parvovirus B19)	[36, 37]
Measles virus	Viral serology IgM, PCR	Serology can detect and infection as early as 3 days	There has been false positive mostly when cross reacting with other viruses such as Parovovirus B19 and false negative results	[38, 39]
Mumps virus	Viral serology IgM, PCR and culture		Serology should be interpreted cautiously in patients who have received the vaccine. Cultures are rarely since they are positive in only 17–58% of cases	[40, 41]
Enterovirus	PCR	Sensitivity almost 100% Specificity almost 100%	Difficulty in identifying enterovirus D68 and enterovirus A71	[42, 43]
HIV	Viral serology and PCR	The sensitivity of serology is as high 83–98% and the specificity can be as high as 100% PCR is useful in quantifying viral load and monitor treatment response	Serologic testing cannot detect HIV2 infection	[44, 45]
CMV	PCR	Sensitivity 82–100% Specificity 95–100%		[46, 47]

(continued)

Table 2.1 (continued)

Organism	Diagnostic methodology	Advantages	Limitations	References
EBV	Viral serology and PCR	Serology can help distinguish between acute and past infection	Caution when interpreting serologic testing in immune compromised patients PCR can have false positive results and should be interpreted clinically	[48, 49]
HSV1 and HSV2	PCR	Rapid turnaround time Sensitivity >95% Specificity 100%	Rarely false positive results False negative results early in the disease	[50–52]
HHV6	PCR	discrimination between HHV-6A and HHV-6B	Hard to distinguish between active infection, latent infection and chromosomally integrated viral DNA	[53, 54]
VZV	Viral Serology and PCR	Serology is mostly valuable in detection of VZV vasculitis. PCR has a specificity as high as 95%		[55, 56]
JC virus	PCR and brain biopsy	Both have a high specificity up to 100%	PCR in patients with AIDS on ART can have a low positive predictive value (58%)	[57, 58]
Bacteria				
Streptococcus pneumoniae	CSF Culture, Antigen testing and PCR	Cultures has a sensitivity of almost 100% and can predict the susceptibility of the organism. Antigen testing may have a high specificity (96%) but lower sensitivity PCR is most widely used and permits rapid detection	The time to culture is longer than PCR testing	[5, 42, 59]