Current Clinical Neurology
Series Editor: Daniel Tarsy

Rodrigo Hasbun
Karen C. Bloch
Adarsh Bhimraj *Editors*

Neurological Complications of Infectious Diseases

Humana Press

Current Clinical Neurology

Series Editor

Daniel Tarsy
Beth Israel Deaconness Medical Center
Department of Neurology
BOSTON, MA
USA

More information about this series at http://www.springer.com/series/7630

Rodrigo Hasbun • Karen C. Bloch
Adarsh Bhimraj
Editors

Neurological Complications of Infectious Diseases

Humana Press

Springer

Editors
Rodrigo Hasbun
UT Health McGovern Medical School
Houston, TX
USA

Adarsh Bhimraj
Dept of Infectious Diseases, Apt 635
Cleveland Clinic Foundation
Cleveland, OH
USA

Karen C. Bloch
Div of Infectious Dis, MCN A-2200
Vanderbilt University
Nashville, TN
USA

ISSN 1559-0585 ISSN 2524-4043 (electronic)
Current Clinical Neurology
ISBN 978-3-030-56083-6 ISBN 978-3-030-56084-3 (eBook)
https://doi.org/10.1007/978-3-030-56084-3

© Springer Nature Switzerland AG 2021
This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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.

Houston, TX, USA Rodrigo Hasbun, MD, MPH
Nashville, TN, USA Karen C. Bloch, MD, MPH
Cleveland, OH, USA Adarsh Bhimraj, MD

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.

Daniel Tarsy, MD
Professor of Neurology, Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, MA, USA

Contents

Contributors

Brian S. Appleby, MD Department of Neurology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, OH, USA

Department of Pathology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Department of Psychiatry, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Ibne Karim M. Ali, PhD Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Maja Babic, MD Department of Infectious Disease, Cleveland Clinic, Cleveland, OH, USA

Madison K. Bangert, MD Section of Infectious Diseases, UT Health McGovern Medical School, Houston, TX, USA

Adarsh Bhimraj, MD Department of Infectious Diseases, Apt 635, Cleveland Clinic Foundation, Cleveland, OH, USA

Karen C. Bloch, MD, MPH Division of Infectious Disease, MCN A-2200, Vanderbilt University, Nashville, TN, USA

Michael J. Bradshaw, MD Department of Neurology, University of Washington; Rosalind Franklin University of Medicine and Science; Billings Clinic, Billings, MT, USA

Marie Cantier, MD Department of Neurology, Saint-Antoine University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France

INSERM U1148, Université Paris Diderot, Paris, France

Jennifer R. Cope, MD, MPH Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Rima El-Abassi, MD, ABPN, ABCN Department of Neurology, Louisiana State University, New Orleans, LA, USA

John England, MD, FAAN Department of Neurology, Louisiana State University, New Orleans, LA, USA

Önder Ergönül, MD, MPH Infectious Diseases and Clinical Microbiology Department, Koç University, Şişli, Istanbul, Turkey

Marc Fischer, MD, MPH Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, USA

Ourania Georgacopoulos, MSPH National Center for Emerging and Zoonotic Diseases, Waterborne Disease Prevention Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA

Eric A. Goethe, MD Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA

Maria Fernanda Gonzalez-Lara, MD, MSc Department of Infectious Diseases, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Mexico City, Mexico

Carolyn Gould, MD, MSCR Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, USA

Rodrigo Hasbun, MD, MPH UT Health McGovern Medical School, Houston, TX, USA

Anna Kaltsas, MD Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Joseph S. Kass, MD, JD, FAAN Department of Neurology, Baylor College of Medicine, Houston, TX, USA

Naomi R. Kass, BA Rice University, Houston, TX, USA

Murat Kutlu, MD Infectious Diseases and Clinical Microbiology Department, Pamukkale University, Denizli, Turkey

Setty M. Magaña, MD, PhD National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

A. Mailles, PhD European Study Group for the Infections of the Brain (ESGIB), Basel, Switzerland

Infectious Diseases Department, Santé Publique France, Saint Maurice, France

Christina Marra, MD Department of Neurology and Internal Medicine, University of Washington School of Medicine, Seattle, WA, USA

Mikael Mazighi, MD, PhD INSERM U1148, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Department of Neurology, Lariboisière University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France

Salam Nasralla, MD Department of Neurology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Tamara Nawar, MD Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Luis Ostrosky-Zeichner, MD, FACP, FIDSA, FSHEA, FECMM Department of Infectious Diseases, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Mexico City, Mexico

McGovern Medical School, Division of Infectious Diseases, University of Texas, Houston Health Science Center, Memorial Hermann Hospital, Texas Medical Center, Houston, TX, USA

Daniel D. Rhoads, MD Department of Laboratory Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA

Rohini D. Samudralwar, MD Department of Neurology, University of Texas Health Science Center, Houston, TX, USA

Deanna Saylor, MD, MHS Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Internal Medicine, John Hopkins Medicine, University Teaching Hospital, Lusaka, Zambia

M. Schilling, MD Department of Medicine, University of Texas Medical Branch, Galveston, TX, USA

Claus Simpfendorfer, MD Imaging Institute, Cleveland Clinic, Cleveland, OH, USA

Ariane G. Soldatos, MD, MPH National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Michael Soliman, MD Department of Neurology, Louisiana State University, New Orleans, LA, USA

Romain Sonneville, MD, PhD INSERM U1148, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France

J. P. Stahl, MD Department of Infectious Diseases, University and Hospital of Grenoble Alpes, Grenoble, France

European Study Group for the Infections of the Brain (ESGIB), Basel, Switzerland

M. B. Tanabe, MD Department of Medicine, Division of Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA

Yi-Wei Tang, MD, PhD Infectious Diseases Service, Clinical Microbiology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Nicole R. Villemarette-Pittman, PhD Department of Neurology, Louisiana State University, New Orleans, LA, USA

A. C. White Jr., MD Department of Internal Medicine, Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA

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?

A. Bhimraj
Department of Infectious Diseases, Apt 635, Cleveland Clinic Foundation, Cleveland, OH, USA

K. C. Bloch
Division of Infectious Disease, MCN A-2200, Vanderbilt University, Nashville, TN, USA
e-mail: Bkaren.bloch@vumc.org

R. Hasbun (✉)
UT Health McGovern Medical School, Houston, TX, USA
e-mail: Rodrigo.Hasbun@uth.tmc.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_1

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

References

1. Hasbun R, Brouwer MC, Van de Beek D, Tunkel AR. Acute meningitis. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 9th ed. Philadelphia: Churchill Livingstone Elsevier; 2020.
2. Venkatesan A, Michael BD, Probasco JC, Geocadin RG, Solomon T. Acute encephalitis in immunocompetent adults. Lancet. 2019;393:702–16.
3. Thakur KT, Wilson MR. Chronic meningitis. Continuum (Minneap Minn). 2018;24(5):1298–326.
4. Fitzgerald DW, Sterling TR, Hass DW. Chapter 246. Mycobacterium tuberculosis. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th ed; Philadelphia: Elsevier; 2020. p. 2985–3021.
5. Sulaiman T, Salazar L, Hasbun R. Acute versus subacute community-acquired meningitis in adults: an analysis of 611 patients. Medicine. 2017;96(36):e7984.
6. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017;64:e34–65.
7. Goralska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. Infection. 2018;46(4):443–59.
8. Hasbun R, Bijslma M, Brouwer MC, et al. Risk score for identifying adults with CSF pleocytosis and negative CSF gram stain at low risk for an urgent treatable cause. J Infect. 2013;67(2):102–10.
9. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61(6):e26–46.
10. Hansen MA, Samannodi MS, Castelblanco RL, Hasbun R. Clinical epidemiology, risk factors, and outcomes of encephalitis in older adults. Clin Infect Dis 2020;70 (11):2377–85.

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.

T. Nawar · A. Kaltsas
Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: nawart@mskcc.org

Y.-W. Tang (✉)
Infectious Diseases Service, Clinical Microbiology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: yi-wei.tang@cepheid.com

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_2

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]

Table 2.1 (continued)

Organism	Diagnostic methodology	Advantages	Limitations	References
Listeria monocytogenes	CSF Culture and PCR	PCR testing has a high sensitivity and specify	Cultures can have a low sensitivity	[15, 60, 61]
Mycobacterium tuberculosis	Culture Antigen testing PCR	Susceptibility testing Sensitivity as high as 88% Elevated titers can correlate with severity Sensitivity almost 80% Specificity almost 98% Detection of drug resistance Newer techniques can detect low levels DNA of the bacterium	False negative results Serial specimens are needed to increase the diagnostic yield Large volume of CSF required to improve sensitivity	[62–65]
Anaplasma phagocytophilum	Blood smear, morulae in neutrophils Serology PCR	Cost-effective Rapid	False negative results depending on granulocytes count	[66]
Ehrlichia chaffeensis	Serology Blood smear, morulae in neutrophils PCR	Rapid Cost-effective	False negative results in the acute phase of the illness Cross-reactivity with similar pathogens Low sensitivity 20–30%	[67, 68]
Rickettsia (Rocky Mountain spotted fever)	Serology PCR	High sensitivity 95%	False negative results in the acute phase of the illness Cross-reactivity with similar pathogens Treatment may blunt serologic response Low sensitivity	[69–71]
Borrelia burgdorferi	Serology (ELISA and Western Blot) PCR		False negative in the acute phase of the illness Low sensitivity	[26, 72]

(continued)

Table 2.1 (continued)

Organism	Diagnostic methodology	Advantages	Limitations	References
Treponema pallidum	Microscopic examination through dark field microscopy Serology VDRL FTA-ABS	Highly specific High specificity High sensitivity	Requires technical qualifications Low sensitivity Low specificity	[73–75]
Fungi				
Coccidioides	Culture Serology Antigen testing	High specificity High specificity Higher sensitivity compared to culture Higher sensitivity compared to culture	Only 15% positive results False negative results early in the disease	[76, 77]
Cryptococcus neoformans	Microscopic examination Antigen testing	Rapid Specificity almost 100% Sensitivity (93 ~ 100%) Specificity (93~98%)	Positive in 50–75% of patients Rarely false positive results and cross-reaction with other species	[18, 78, 79]
Histoplasma capsulatum	Culture Antigen testing Serology	High sensitivity	Time to culture 7 days Recovered in only 25–65% of specimens Cross-reactivity with other fungal infection Negative in the acute phase of the illness Cross-reactivity with other fungal infection Negative in immune suppressive states	[80, 81]
Protozoa				
Plasmodium falciparum	Microscopic examination Antigen testing PCR	Quantification of parasitemia Rapid High sensitivity High specificity Detection even in low levels parasitemia	Observer dependent False negative results in low parasitemia Prozone effect in high parasitemia	[82–84]

Table 2.1 (continued)

Organism	Diagnostic methodology	Advantages	Limitations	References
Toxoplasma gondii	Serology PCR	Sensitivity 83%	False negative results in immune suppressed states False positive results (IgM) have been reported Specificity 95%	[85–87]
Helminths				
Taenia solium	Serology		False negative results Positive results may demonstrate a prior infection	[88–90]

Antigen Testing

Although antigen testing in the setting of bacterial meningitis has a poor sensitivity [98] it can provide for rapid detection of some bacteria such as *Mycobacterium tuberculosis*. Antigen detection such LAM, ESAT, Ag 85 complex and the 65-kDa in the CSF have been used for the diagnosis of tuberculous meningitis with promising sensitivity and specificity [99]. Furthermore, in a study evaluating the value of ESAT-6 (Early Secreted Antigen test) in tuberculous meningitis, the sensitivity was as high as 88% and most importantly the authors were able to conclude that higher levels of antigens were associated with worse clinical severity [62].

Uni-Gold ICT has been used to detect pneumococcal antigen in CSF. When compared to PCR detection of Streptococcus pneumoniae in CSF, the test showed strong correlation results, with a specificity of up to 96% and a sensitivity of 86% [59].

Although the role of antigen detection has been limited in bacterial infections, its use has been more robust for diagnosis of CNS fungal infections.

Cryptococcal antigen testing in the CSF is widely used. The test relies on the detection of the fungus capsular polysaccharide antigen in the CSF [100]. Immuno-Mycologics Inc. (IMMY) lateral flow assay (LFA) and enzyme immunoassay (EIA) are commonly used antigenic tests [78] which have demonstrated high sensitivity (93~100%) and specificity (93~98%) [101]. In the setting of proper sample handling, these tests have low false positive rates if titers are greater than or equal to 1:4 [102]. Rarely, false positive rates have been reported when cross reactions occur with other fungal infections such as *Trichosporon asahii (beigelii) or non-neoformans Cryptococcus* [79]. Serum antigen has been used in indirectly diagnosing cryptoccocal meningitis in high risk AIDS patients where the prevalence of the infection is high and where ability to obtain CSF sampling is hindered [103, 104]. Furthermore, polysaccharide antigen titer (peak titer >1:1024) gives solid general prognostic information, with higher titers representing higher load of infection and a greater chance of therapeutic failure [69].

Aspergillus galactomannan antigen and 1,3-beta-D-glucan in the serum have also seen increased widespread use for the detection of possible invasive fungal infection. In 2012, Lyons et al. used these fungal markers to detect *Exserohilum rostratum* meningitis in patients who had received contaminated methylprednisolone injections [105]. The galactomannan antigen has also been used as an indirect marker of infections caused by aspergillosis or fusariosis [6]. CSF Beta-D-glucan has been used to detect CNS fungal infections [106]. Moreover, patients receiving antifungal therapy exhibit a reduction in CSF Beta-D-glucan which makes it a useful biomarker in monitoring treatment response [107].

Serology

Serologic diagnosis of CNS infections relies on the detection of antibodies against microorganism antigens. The "window" period until the seroconversion and a positive test results can sometimes delay the time of diagnosis, and a negative test does not necessarily rule out an infection. Furthermore, in certain populations such as immune compromised patients, such tests have a lower sensitivity due to lower antibody response, and nucleic acid amplification has largely replaced these assays [108, 109]. Although many of these tests have largely lost their appeal as diagnostic modalities, they remain valuable in certain types of infections. In Zika virus infection, antibodies (IgM followed by IgG) for Zika virus are positive within one week after the infection and can remain positive for up to 2 months. There are currently 5 FDA approved serologic assays for the detection of antibodies to Zika virus. These tests should be interpreted cautiously considering the cross-reactivity with other flaviviruses. False positive results have also been reported in patients who have received the Japanese encephalitis or Yellow fever vaccine. In a recent study, MMB Zika assays had 88–97% sensitivity [29].

The identification of IgM for West Nile virus in CSF can occur as early as 3 days after the infection but may persist for months. However, as seen in Zika virus infection, false positive results have been also reported in patients infected with other viruses and those who have received certain vaccines. This limitation is due to the structural similarity of the envelope E protein among Flavivirus genus members. As such antibodies produced against the E protein can be cross-reactive among viruses of the same genus and lead to false positive results [22]. Targeting the virus specific E protein have been suggested as a as solution in patients who have coinfection with other viruses or who were previously immunized [110]. False negatives may occur in immune compromised patients such as those who have received Rituximab [111], which is a limitation of serologic assays in diagnosing West Nile virus.

Although molecular testing using viral DNA have been widely used in the diagnosis of VZV encephalitis, antibodies to varicella zoster virus in the CSF still remain the most commonly used method to detect the infection [112]. Moreover, serological assays have been used to diagnose venereal infections affecting the CNS, including neurosyphilis which can be confirmed by VDRL testing (venereal disease research laboratory) [113].

Molecular Diagnostics

Molecular diagnostic tests rely on nucleic acid amplifications and detection of organisms' deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) in a sample. These means of diagnosis have dramatically impacted the management of certain infectious diseases [114, 115]. It has allowed the rapid detection of fastidious or previously uncultivable organisms. While traditional methods of culture have the advantages of phenotypic identification of organisms, allowing for antimicrobial susceptibility testing and strain characterization, they remain limited in strain differentiation, rapid detection, and as mentioned earlier, can fail to detect fastidious organisms and can be affected by prior antibiotic treatment [3, 116, 117].

Helpful in the diagnosis of CNS infections is the fact that CSF, spinal and brain tissue are naturally sterile specimens, which means that even the detection of minute concentration of microbes in them would be suggestive of an infection if not a contaminant. Molecular diagnostics have also allowed for the quantification of viral loads which guides the duration of therapy in certain infections. For certain infections and molecular tests, the sensitivity and specificity can approach 100 percent. These techniques have impacted the diagnosis and early treatment of multiple viral encephalitides and decreased some of the morbidity associated with more invasive testing. For instance, prior to molecular testing, brain biopsy was the gold standard for the diagnosis of HSV encephalitis [118] due to the lack of ability of different techniques to identify the pathogen in CSF [119]. Once obtained, the specimen was examined for HSV culture, antigen or DNA by in situ hybridization [120]. However, brain biopsy is obviously invasive and associated with serious complications including stroke, hemorrhage and neurologic deficits [121]. After the implementation of nucleic acid amplification, testing using this modality has proven to be the test of choice for the diagnosis of CNS infections due to herpes group viruses and enteroviruses [116, 122–124]. Indeed, several molecular diagnostic techniques have been implemented and have gained success in the past decades.

Monoplex Assays

This technique includes the three steps of sample extraction, target nucleic acid amplification and detection, in a "closed system" which overcomes the carryover contamination risk and has accelerated the transition to molecular testing. Multiple monoplex PCR tests have been approved for CNS infections:

Simplexa HSV-1&2 was FDA approved for the diagnosis of herpes infections in the CNS with a rapid turnaround time (~75 min sample to result) [50]. In March 2007, The Xpert EV assay (Cepheid, Sunnyvale, CA) was approved for the diagnosis of Enterovirus meningitis. This technique had a high sensitivity 94.69% and specificity 100% with a 100% positive predictive value [125]. CE marked NucliSens EasyQ Enterovirus assay is another monoplex assay approved for Enterovirus CNS infections with comparable sensitivity and specificity as previous tests, with results reported in almost 5 h [126].

Zika infection was first detected in Uganda in 1974 and today has become a public health emergency. In 2015, after the infection was identified in 24 patients in Brazil, it began to draw public attention. Due to the infrequency of Zika virus infection prior to 2015 (at least as far as was known), there were no commercially available assays for the detection of the virus at that point. After 2016, additional molecular testing was developed, in which highly conserved RNA regions in the virus genome, membrane junction and partial envelope regions were used as rRT-PCR primer and sequence targets [127, 128].

In 2016, the FDA approved Zika Virus Molecular Emergency Use Authorization (EUA) Assays; Trioplex Real-time RT-PCR Assay that simultaneously detects Chikungunya, Dengue and Zika viruses. It targets the Zika E gene and can detect the virus in the serum, CSF, amniotic fluid, blood and urine. This assay can detect as many as 2430 genomic copies equivalent/mL from a whole blood sample in 4 h turnaround time. The assay has the ability to detect the nucleic acid of the virus on potentially the day of symptom onset and throughout the first 7 days of the illness.

Real time PCR has also impacted the diagnosis of many bacterial infections. This technique has shown promising results in diagnosing neurobrucellosis when compared to cultures in a report of 6 patients [129].

Mycobacterium tuberculosis (MTB) infection of the CNS remains the most severe form of infection with tuberculosis. Children and HIV patients are at highest risk for the infection [63]. In light of the high morbidity and mortality associated with CNS infection, prompt diagnosis and treatment are key in managing the disease. Currently, nucleic acid amplification is the preferred diagnostic modality due to its rapid turnaround time and high specificity [63]. This innovation has revolutionized the global health challenge of TB management and the institution of early life saving therapy.

Xpert MTB/RIF is widely used in the United States for the diagnosis of TB meningitis. This test allows for the simultaneous detection of MTB complex and the presence of Rifampin resistance, a strong predictor of multi-drug resistant TB. The technique uses molecular-beacon technology to target the *rpoB* gene, which in turn predicts rifampin resistance. In addition, the gene is flanked by MTB specific DNA sequences, which makes it possible to detect, concurrently, the infection and drug resistance [130]. When compared to culture, in a meta-analysis of 18 studies Xpert MTB/RIF had a sensitivity of 81% and a specificity of 98% [131]. In another prospective study in a Sub-Saharan African population, Xpert MTB/Rif had a sensitivity of 62% (42–75%) and a specificity of 95% (87–99%). Although this test exhibits a lower sensitivity, it remained higher than the sensitivity of conventional culture or smear (30% and 12% respectively). The sensitivity of the test depends on the technique and the volume of CSF used. Centrifuged samples had a higher sensitivity when compared to non-centrifuged samples (28% sensitivity with 2 mL of uncentrifuged CSF vs 72% in 6 mL of centrifuged CSF) [63].

Due to the variable sensitivity in the Xpert MTB/RIF test, in 2017, the World Health Organization recommended the use of Xpert MTB/RIF Ultra assay as the initial diagnostic test for MTB meningitis. The Ultra assay has shown improved sensitivity when compared to Xpert MTB/RIF assay in an HIV cohort in Uganda (95% sensitivity Xpert MTB/RIF Ultra assay compared to 45% sensitivity for Xpert assay) [132].

Multiplex Assays and Syndromic Panel Testing

In 2015, the Film Array Meningitis/Encephalitis panel (MEP) (BioFire Diagnostics, LLC) received FDA approval as a diagnostic test [133]. It can detect up to 14 pathogens involved in CNS infections including viruses (Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2, human herpes virus 6, human paraechovirus and varicella-zoster virus), bacteria (*Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitides* and *Streptococcus pneumoniae*) and fungal infections (*Cryptococcus neoformans- C. gattii*). This multiplex assay is a closed system that performs nucleic acid purification, extraction, transcription and amplification. The results are reported within one hour. This novel technique demonstrates almost 100% sensitivity in Herpes simplex infection with a specificity close to 100% and similar results for Enterovirus and VZV [133]. When compared to Cepheid Xpert Enterovirus assay in a Children's Hospital Colorado study, the MEP identified 68/72 samples (94.4%) that were positive by the former assay. Moreover, MEP detected an additional sample that tested negative by the Cepheid Xpert Enterovirus assay, the results of which were confirmed by discrepancy analysis [134].

HSV encephalitis is the most common cause of encephalitis worldwide. While HSV2 is capable of causing encephalitis especially in neonates and infants, HSV1 is still responsible for almost 90% of these infections in adults [135]. If untreated, the mortality related to these infections can approach almost 70% [136] and patients can have severe permanent neurologic deficits as a result of this infection. Early recognition of HSV is critical as even patients who are treated can develop complications related to the infection such as behavioral changes, retrograde amnesia and lasting cognitive impairment [137, 138]. Moreover mortality from the virus has been reported as high as 30% [139, 140]. Molecular testing has allowed for the early diagnosis of HSV infections with a rapid turnaround time. In a recent study, CSF PCR for HSV has also decreased the overuse and duration of Acyclovir therapy [141].

Multiple PCR assays have been proven to be effective at diagnosing HSV infection. Simplexa™ HSV 1 & 2, FilmArray Meningitis/Encephalitis panel and MultiCode RTx HSV 1&2 kit have been FDA approved for the detection of these pathogens in the CNS [50, 133, 142]. Sensitivity and specificity of PCR in HSV encephalitis in adults has ranged between 96–98% and 95–99%, respectively [143]. In neonates and infants, the sensitivity was variable, ranging from 75% to 100% [144]. HSV PCR assays can have variable performance characteristics and results need to be interpreted cautiously.

False positive results for HSV encephalitis with MEP have also been reported. A recent study describes the case of a tuberculous meningitis that was misdiagnosed as HSV encephalitis with MEP panel [145]. False negative results have also been described in the literature. Usually these results have been reported early in the course of the disease. In a prospective analysis of 27 patients, 10 patients had HSE by positive PCR of CSF samples, 2 of which had negative results when obtained at time of admission. Samples that were later collected at day 4 and 7 tested positive for HSV [51]. Hence in patients with negative PCR results, the test should be

repeated 3–7 days after presentation for those who have a presentation that remains suggestive of herpetic encephalitis [55]. False negative results have been also associated with WBC count <10 leukocytes/mm^3 in the CSF. Other factors that could alter CSF results include the presence of hemoglobin and lactoferrin as well as large numbers of RBCs in the fluid that may inhibit the PCR [146]. Due to the limitations of the test results, all patients with suspected HSV encephalitis should be initiated on Acyclovir at time of diagnosis until further elucidation of test results. Moreover, in a recent Enterovirus encephalitis outbreak in Catalonia in 2016, the MEP detected 4 CSF samples positive Enterovirus that were negative on pan-Enterovirus real-time PCR assay [147].

CMV PCR testing in the CSF is the standard for diagnosis of CMV related neurologic disease. Prior studies have shown that in patients with biopsy proven CNS disease, 12/13 samples tested positive for CMV by PCR [46]. Several PCR techniques have been validated for the diagnosis of CMV in multiple specimens. EraGen Multicode, Focus Simplexa, Elitech MGB Alert CMV and Abbott CMV were compared in a study involving 200 specimens, of which 25 were from CSF. Although only 2 specimens were positive for CMV, EraGen and Focus Simplexa techniques demonstrated a 100% sensitivity [47]. In a recent study evaluating the FilmArray meningitis/encephalitis (ME) panel 3/3 specimens were true positives for CMV infection [148].

In a recent study in HIV infected patients, the FilmArray panel was 100% sensitive in patients with culture positive CSF *Cryptococcus neoformans;* it also demonstrated an excellent negative predictive value in patients with culture negative CSF. In this study, the sensitivity of the MEP was directly proportional to the amount of recovered organism in fungal culture [149]. False positive rates with this assay occurred mostly in bacterial meningitis, and then mostly due to *Streptococcus pneumoniae*. It is unclear if false positive results in this instance were related to handling or preparation of the specimen or cross reactivity. The overall positive agreement rate for *Streptococcus pneumonia* was close to 80% and the negative agreement rate closer to 100% between the meningitis encephalitis panel and conventional bacterial culture [150].

Next Generation Sequencing

Molecular assays have revolutionized the management and diagnosis of infections. With a shorter turnaround time, higher sensitivities and specificities, they have replaced more invasive and time-consuming methods. However, molecular methods do require a prior knowledge of the likely pathogenic organism. The primer independent next generation sequencing (NGS) technology led to its application for the diagnosis of infections when knowledge of the possible organism is lacking. Multiple reports have demonstrated its use in diagnostically challenging diseases. Due to the blood-brain-barrier, the CNS is considered a sterile environment which makes the interpretation of results easier. The role of NGS was demonstrated in a

case of a fourteen-year-old boy with immune deficiency who ultimately was diagnosed with meningoencephalitis due to Leptospirosis that was recovered from the patient's CSF but not serum [151]. In a recently published systematic review, NGS was used to diagnose 44 cases of CNS infections [152]. A more recent case report describes a woman who presented with recurrent bouts of headache and sensory deficit. NGS revealed *Taenia solium*-DNA that was later confirmed by serologic testing [88]. Moreover, this technique has also allowed for the identification of novel organisms. A recent study indicate that metagenomic NGS of CSF obtained from patients with meningitis or encephalitis improved diagnosis of neurologic infections and provided actionable information in some cases [153]. Recent cases outlining the usage of next generation sequencing in CNS infections are listed in Table 2.2.

Table 2.2 Representative cases of usage of next generation sequencing in CNS infections

Organism identified	Presentation	Specimen used	Reference
Astrovirus	42-year-old with chronic lymphocytic leukemia who underwent allogeneic bone marrow transplant presents with hearing loss, tinnitus and behavioral changes	Brain tissue	[154]
Brucella	Case series of four patients who presented with fever, headache, back pain and weigh loss	CSF	[155]
EBV	44-year-old female with facial paralysis and brain lesions	Brain tissue	[156]
Japanese encephalitis virus	16-year-old boy with fever, rigors, diarrhea and limb weakness	CSF	[157]
JC virus	52-year-old male with R sided hemiparesis and seizures	Brain tissue	[156]
Leptospira santarosai	14-year-old with severe combined immune deficiency presents with headache, fevers and seizures	CSF	[151]
Listeria monocytogenes	Case series of 3 patients who presented with nausea, vomiting, fever and headache One of the patients progressed to coma	CSF	[158]
Mycobacterial infections (*Mycobacterium immunogenum Mycobacterium ilatzerense)*	40-year-old female with headache, left sided vision loss, night sweats and right sided numbness with brain lesion noted on MRI	Brain lesion	[159]
Mycobacterium tuberculosis	67-year-old with multiple brain and spinal lesions	Brain tissue	[156]
Taenia solium (Neurocysticercosis)	44- year-old female with chronic headache and focal weakness	CSF	[88]
Taenia solium (Neurocysticercosis)	Case series of 4 patients who presented with fever, headache, seizures, loss of consciousness or visual impairment	CSF	[89]

Conclusion

The microbiologic diagnosis of CNS infections has seen a seismic shift in recent years away from traditional microbiologic techniques of culture, gram stain, and pathology looking for viral cytopathic changes, and towards molecular based techniques such as monoplex, multiplex PCRs, and next generation sequencing. These newer methods have allowed for more rapid and accurate diagnosis of previously difficult to identify viruses, fungi and bacteria, allowing for decreased associated mortality, morbidity, and hospital lengths of stays, as well as for decreased utilization of empiric antibiotics and antivirals. Finally, next generation sequencing may offer a tantalizing and exciting possible solution to making the diagnosis of rare or unexpected CNS infections from samples of brain tissue or CSF in particularly challenging cases.

References

1. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM. 2005;98(4):291–8. https://doi.org/10.1093/qjmed/hci1047. Epub 2005 Mar 1010.
2. Puges M, Gabriel F, Carrer M, et al. Puzzling mosaics in cerebrospinal fluid. Clin Microbiol Infect. 2018;24(11):1156–7. https://doi.org/10.1016/j.cmi.2018.1106.1019. Epub 2018 Jun 1122.
3. Bloch KC, Tang YW. Molecular approaches to the diagnosis of meningitis and encephalitis. In: Persing DH, editor. Molecular Microbiology: Diagnostic Principles and Practice. 3rd ed. Washington, DC: American Society for Microbiology Press; 2016. p. 287–305.
4. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849–59. https://doi.org/10.1056/NEJMoa040845.
5. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010;23(3):467–92. https://doi.org/10.1128/CMR.00070-00009.
6. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis. 2013;57(Suppl 3):S139–70.
7. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes. 2004;11(Suppl 2):57A–64A.
8. Dewan M, Zorc JJ, Hodinka RL, Shah SS. Cerebrospinal fluid enterovirus testing in infants 56 days or younger. Arch Pediatr Adolesc Med. 2010;164(9):824–30. https://doi.org/10.1001/archpediatrics.2010.1153.
9. Welinder-Olsson C, Dotevall L, Hogevik H, et al. Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. Clin Microbiol Infect. 2007;13(9):879–86. https://doi.org/10.1111/j.1469-0691.2007.01756.x. Epub 02007 Jun 01730.
10. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006;354(1):44–53. https://doi.org/10.1056/NEJMra052116.
11. Dunbar SA, Eason RA, Musher DM, Clarridge JE 3rd. Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. J Clin Microbiol. 1998;36(6):1617–20.
12. Musher DM, Schell RF. Letter: false-positive gram stains of cerebrospinal fluid. Ann Intern Med. 1973;79(4):603–4.

13. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med. 1998;129(11):862–9.
14. Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. Lancet Infect Dis. 2007;7(3):191–200. https://doi.org/10.1016/S1473-3099(1007)70050-70056.
15. Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Community-acquired Listeria monocytogenes meningitis in adults. Clin Infect Dis. 2006;43(10):1233–8. https://doi.org/10.1086/508462. Epub 502006 Oct 508410.
16. Walls T, McSweeney A, Anderson T, Jennings LC. Multiplex-PCR for the detection of viruses in the CSF of infants and young children. J Med Virol. 2017;89(3):559–61.
17. John MA, Coovadia Y. Meningitis due to a combined infection with Cryptococcus neoformans and Streptococcus pneumoniae in an AIDS patient. J Infect. 1998;36(2):231–2.
18. Saha DC, Xess I, Biswas A, Bhowmik DM, Padma MV. Detection of Cryptococcus by conventional, serological and molecular methods. J Med Microbiol. 2009;58(Pt 8):1098–105. https://doi.org/10.1099/jmm.1090.007328-007320. Epub 002009 Jun 007315.
19. Grace E, Asbill S, Virga K. Naegleria fowleri: pathogenesis, diagnosis, and treatment options. Antimicrob Agents Chemother. 2015;59(11):6677–81. https://doi.org/10.1128/AAC.01293-01215. Epub 02015 Aug 01210.
20. Buckwalter SP, Teo R, Espy MJ, Sloan LM, Smith TF, Pritt BS. Real-time qualitative PCR for 57 human adenovirus types from multiple specimen sources. J Clin Microbiol. 2012;50(3):766–71. https://doi.org/10.1128/JCM.05629-05611. Epub 02011 Dec 05614.
21. Buller RS. Molecular detection of respiratory viruses. Clin Lab Med. 2013;33(3):439–60.
22. Martin DA, Biggerstaff BJ, Allen B, Johnson AJ, Lanciotti RS, Roehrig JT. Use of immunoglobulin m cross-reactions in differential diagnosis of human flaviviral encephalitis infections in the United States. Clin Diagn Lab Immunol. 2002;9(3):544–9.
23. Desai A, Chandramuki A, Gourie-Devi M, Ravi V. Detection of Japanese encephalitis virus antigens in the CSF using monoclonal antibodies. Clin Diagn Virol. 1994;2(3):191–9.
24. Moore CE, Blacksell SD, Taojaikong T, et al. A prospective assessment of the accuracy of commercial IgM ELISAs in diagnosis of Japanese encephalitis virus infections in patients with suspected central nervous system infections in Laos. Am J Trop Med Hyg. 2012;87(1):171–8. https://doi.org/10.4269/ajtmh.2012.4211-0729.
25. Fatmi SS, Zehra R, Carpenter DO. Powassan virus – a new reemerging tick-borne disease. Front Public Health. 2017;5:342. https://doi.org/10.3389/fpubh.2017.00342. eCollection 02017.
26. Frost HM, Schotthoefer AM, Thomm AM, et al. Serologic evidence of powassan virus infection in patients with suspected lyme disease. Emerg Infect Dis. 2017;23(8):1384–8. https://doi.org/10.3201/eid2308.161971.
27. Chiu CY, Coffey LL, Murkey J, et al. Diagnosis of fatal human case of st. louis encephalitis virus infection by metagenomic sequencing, California, 2016. Emerg Infect Dis. 2017;23(10):1964–8. https://doi.org/10.3201/eid2310.161986.
28. Johnson AJ, Noga AJ, Kosoy O, Lanciotti RS, Johnson AA, Biggerstaff BJ. Duplex microsphere-based immunoassay for detection of anti-West Nile virus and anti-St. Louis encephalitis virus immunoglobulin m antibodies. Clin Diagn Lab Immunol. 2005;12(5):566–74. https://doi.org/10.1128/CDLI.1112.1125.1566-1574.2005.
29. Michelson Y, Lustig Y, Avivi S, Schwartz E, Danielli A. Highly sensitive and specific Zika virus serological assays using a magnetic modulation biosensing system. J Infect Dis. 2019;219(7):1035–43. https://doi.org/10.1093/infdis/jiy1606.
30. Theel ES, Hata DJ. Diagnostic testing for Zika virus: a postoutbreak update. J Clin Microbiol. 2018;56(4):(pii):JCM.01972-01917. https://doi.org/10.01128/JCM.01972-01917. Print 02018 Apr.
31. Barzon L, Pacenti M, Ulbert S, Palu G. Latest developments and challenges in the diagnosis of human West Nile virus infection. Expert Rev Anti-Infect Ther. 2015;13(3):327–42. https://doi.org/10.1586/14787210.14782015.11007044. Epub 14782015 Feb 14787212.

32. Busch MP, Kleinman SH, Tobler LH, et al. Virus and antibody dynamics in acute west nile virus infection. J Infect Dis. 2008;198(7):984–93. https://doi.org/10.1086/591467.
33. Johnson BW, Kosoy O, Martin DA, et al. West Nile virus infection and serologic response among persons previously vaccinated against yellow fever and Japanese encephalitis viruses. Vector Borne Zoonotic Dis. 2005;5(2):137–45. https://doi.org/10.1089/vbz.2005.1085.1137.
34. Dacheux L, Reynes JM, Buchy P, et al. A reliable diagnosis of human rabies based on analysis of skin biopsy specimens. Clin Infect Dis. 2008;47(11):1410–7. https://doi.org/10.1086/592969.
35. Noah DL, Drenzek CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. Ann Intern Med. 1998;128(11):922–30.
36. Dimech W, Panagiotopoulos L, Marler J, Laven N, Leeson S, Dax EM. Evaluation of three immunoassays used for detection of anti-rubella virus immunoglobulin M antibodies. Clin Diagn Lab Immunol. 2005;12(9):1104–8. https://doi.org/10.1128/CDLI.1112.1109.1104-1108.2005.
37. Mace M, Cointe D, Six C, et al. Diagnostic value of reverse transcription-PCR of amniotic fluid for prenatal diagnosis of congenital rubella infection in pregnant women with confirmed primary rubella infection. J Clin Microbiol. 2004;42(10):4818–20. https://doi.org/10.1128/JCM.4842.4810.4818-4820.2004.
38. Bellini WJ, Helfand RF. The challenges and strategies for laboratory diagnosis of measles in an international setting. J Infect Dis. 2003;187(Suppl 1):S283–90. https://doi.org/10.1086/368040.
39. Lerman SJ. The measles-mumps-rubella vaccination program in Finland. N Engl J Med. 1995;332(16):1103.
40. Rubin S, Eckhaus M, Rennick LJ, Bamford CG, Duprex WP. Molecular biology, pathogenesis and pathology of mumps virus. J Pathol. 2015;235(2):242–52. https://doi.org/10.1002/path.4445.
41. Studahl M, Lindquist L, Eriksson BM, et al. Acute viral infections of the central nervous system in immunocompetent adults: diagnosis and management. Drugs. 2013;73(2):131–58. https://doi.org/10.1007/s40265-40013-40007-40265.
42. Hanson KE. The first fully automated molecular diagnostic panel for meningitis and encephalitis: how well does it perform, and when should it be used? J Clin Microbiol. 2016;54(9):2222–4. https://doi.org/10.1128/JCM.01255-01216. Epub 02016 Jul 01213.
43. Messacar K, Burakoff A, Nix WA, et al. Notes from the field: enterovirus A71 neurologic disease in children - Colorado, 2018. MMWR Morb Mortal Wkly Rep. 2018;67(36):1017–8. https://doi.org/10.15585/mmwr.mm16736a15585.
44. Branson BM, Stekler JD. Detection of acute HIV infection: we can't close the window. J Infect Dis. 2012;205(4):521–4. https://doi.org/10.1093/infdis/jir1793. Epub 2011 Dec 1029.
45. Stafylis C, Klausner JD. Evaluation of two 4th generation point-of-care assays for the detection of human immunodeficiency virus infection. PLoS One. 2017;12(8):e0183944. https://doi.org/10.1371/journal.pone.0183944. eCollection 0182017.
46. Arribas JR, Clifford DB, Fichtenbaum CJ, Commins DL, Powderly WG, Storch GA. Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. J Infect Dis. 1995;172(2):527–31.
47. Binnicker MJ, Espy ME. Comparison of six real-time PCR assays for qualitative detection of cytomegalovirus in clinical specimens. J Clin Microbiol. 2013;51(11):3749–52. https://doi.org/10.1128/JCM.02005-02013. Epub 02013 Sep 02004.
48. De Paschale M, Clerici P. Serological diagnosis of Epstein-Barr virus infection: problems and solutions. World J Virol. 2012;1(1):31–43. https://doi.org/10.5501/wjv.v5501.i5501.5531.
49. Wang J, Ozzard A, Nathan M, et al. The significance of Epstein-Barr virus detected in the cerebrospinal fluid of people with HIV infection. HIV Med. 2007;8(5):306–11. https://doi.org/10.1111/j.1468-1293.2007.00475.x.
50. Kuypers J, Boughton G, Chung J, et al. Comparison of the Simplexa HSV1 & 2 Direct kit and laboratory-developed real-time PCR assays for herpes simplex virus detection. J Clin Virol. 2015;62:103–5.
51. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis. 2002;34(8):1154–7. https://doi.org/10.1086/339550. Epub 332002 Mar 339521.

52. Censullo A, Vijayan T. Using nuclear medicine imaging wisely in diagnosing infectious diseases. Open Forum Infect Dis. 2017;4(1):ofx011. https://doi.org/10.1093/ofid/ofx1011. eCollection 2017 Winter.
53. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev. 2015;28(2):313–35. https://doi.org/10.1128/CMR.00122-00114.
54. Messacar K, Breazeale G, Wei Q, Robinson CC, Dominguez SR. Epidemiology and clinical characteristics of infants with human parechovirus or human herpes virus-6 detected in cerebrospinal fluid tested for enterovirus or herpes simplex virus. J Med Virol. 2015;87(5):829–35.
55. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47(3):303–27. https://doi.org/10.1086/589747.
56. Nagel MA, Forghani B, Mahalingam R, et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. Neurology. 2007;68(13):1069–73. https://doi.org/10.1212/1001.wnl.0000258549.0000213334.0000258516. Epub 0000252007 Feb 0000258547.
57. Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R, De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. J Clin Microbiol. 2005;43(8):4175–7. https://doi.org/10.1128/JCM.4143.4178.4175-4177.2005.
58. Nakamichi K, Lim CK, Saijo M. New approach for JC virus detection and its application for PML diagnosis. Rinsho Shinkeigaku. 2014;54(12):1028–30.
59. Boulos A, Fairley D, McKenna J, Coyle P. Evaluation of a rapid antigen test for detection of Streptococcus pneumoniae in cerebrospinal fluid. J Clin Pathol. 2017;70(5):448–50. https://doi.org/10.1136/jclinpath-2016-204104. Epub 202016 Nov 204118.
60. Le Monnier A, Abachin E, Beretti JL, Berche P, Kayal S. Diagnosis of Listeria monocytogenes meningoencephalitis by real-time PCR for the hly gene. J Clin Microbiol. 2011;49(11):3917–23. https://doi.org/10.1128/JCM.01072-01011. Epub 02011 Sep 01014.
61. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine (Baltimore). 1998;77(5):313–36.
62. Song F, Sun X, Wang X, Nai Y, Liu Z. Early diagnosis of tuberculous meningitis by an indirect ELISA protocol based on the detection of the antigen ESAT-6 in cerebrospinal fluid. Ir J Med Sci. 2014;183(1):85–8.
63. Patel VB, Theron G, Lenders L, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study. PLoS Med. 2013;10(10):e1001536.
64. Thwaites GE, Chau TT, Farrar JJ. Improving the bacteriological diagnosis of tuberculous meningitis. J Clin Microbiol. 2004;42(1):378–9.
65. Yang J, Han X, Liu A, et al. Use of digital droplet PCR to detect Mycobacterium tuberculosis DNA in whole blood-derived DNA samples from patients with pulmonary and extrapulmonary tuberculosis. Front Cell Infect Microbiol. 2017;7:369. https://doi.org/10.3389/fcimb.2017.00369. eCollection 02017.
66. Rand JV, Tarasen AJ, Kumar J, Homan SM, Tobin E. Intracytoplasmic granulocytic morulae counts on confirmed cases of ehrlichiosis/anaplasmosis in the Northeast. Am J Clin Pathol. 2014;141(5):683–6. https://doi.org/10.1309/AJCP1306Q1302BOKYALDYZ.
67. Paddock CD, Childs JE. Ehrlichia chaffeensis: a prototypical emerging pathogen. Clin Microbiol Rev. 2003;16(1):37–64.
68. Thomas LD, Hongo I, Bloch KC, Tang YW, Dummer S. Human ehrlichiosis in transplant recipients. Am J Transplant. 2007;7(6):1641–7. https://doi.org/10.1111/j.1600-6143.2007.01821.x.
69. Kaplan JE, Vallabhaneni S, Smith RM, Chideya-Chihota S, Chehab J, Park B. Cryptococcal antigen screening and early antifungal treatment to prevent cryptococcal meningitis: a review of the literature. J Acquir Immune Defic Syndr. 2015;68(Suppl 3):S331–9.

70. Kato CY, Chung IH, Robinson LK, Austin AL, Dasch GA, Massung RF. Assessment of real-time PCR assay for detection of Rickettsia spp. and Rickettsia rickettsii in banked clinical samples. J Clin Microbiol. 2013;51(1):314–7. https://doi.org/10.1128/JCM.01723-01712. Epub 02012 Nov 01727.
71. McQuiston JH, Wiedeman C, Singleton J, et al. Inadequacy of IgM antibody tests for diagnosis of Rocky Mountain Spotted Fever. Am J Trop Med Hyg. 2014;91(4):767–70. https://doi.org/10.4269/ajtmh.4214-0123. Epub 2014 Aug 4264.
72. Avery RA, Frank G, Eppes SC. Diagnostic utility of Borrelia burgdorferi cerebrospinal fluid polymerase chain reaction in children with Lyme meningitis. Pediatr Infect Dis J. 2005;24(8):705–8.
73. Creegan L, Bauer HM, Samuel MC, Klausner J, Liska S, Bolan G. An evaluation of the relative sensitivities of the venereal disease research laboratory test and the Treponema pallidum particle agglutination test among patients diagnosed with primary syphilis. Sex Transm Dis. 2007;34(12):1016–8.
74. Monath TP, Frey SE. Possible autoimmune reactions following smallpox vaccination: the biologic false positive test for syphilis. Vaccine. 2009;27(10):1645–50. https://doi.org/10.1016/j.vaccine.2008.1610.1084. Epub 2008 Nov 1618.
75. Wheeler HL, Agarwal S, Goh BT. Dark ground microscopy and treponemal serological tests in the diagnosis of early syphilis. Sex Transm Infect. 2004;80(5):411–4. https://doi.org/10.1136/sti.2003.008821.
76. Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006;42(1):103–7. https://doi.org/10.1086/497596. Epub 492005 Nov 497529.
77. Kassis C, Zaidi S, Kuberski T, et al. Role of coccidioides antigen testing in the cerebrospinal fluid for the diagnosis of coccidioidal meningitis. Clin Infect Dis. 2015;61(10):1521–6. https://doi.org/10.1093/cid/civ1585. Epub 2015 Jul 1524.
78. Hansen J, Slechta ES, Gates-Hollingsworth MA, et al. Large-scale evaluation of the immunomycologics lateral flow and enzyme-linked immunoassays for detection of cryptococcal antigen in serum and cerebrospinal fluid. Clin Vaccine Immunol. 2013;20(1):52–5. https://doi.org/10.1128/CVI.00536-00512. Epub 02012 Oct 00531.
79. Tone K, Umeda Y, Makimura K. Cross-reactivity in Cryptococcus antigen latex agglutination test in two commercial kits. Med Mycol. 2016;54(4):439–43. https://doi.org/10.1093/mmy/myv1115. Epub 2016 Feb 1027.
80. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Infect Dis. 2005;40(6):844–52. https://doi.org/10.1086/427880. Epub 422005 Feb 427816.
81. Wheat LJ, Batteiger BE, Sathapatayavongs B. Histoplasma capsulatum infections of the central nervous system. A clinical review. Medicine (Baltimore). 1990;69(4):244–60.
82. Gitau EN, Kokwaro GO, Karanja H, Newton CR, Ward SA. Plasma and cerebrospinal proteomes from children with cerebral malaria differ from those of children with other encephalopathies. J Infect Dis. 2013;208(9):1494–503.
83. Moody A. Rapid diagnostic tests for malaria parasites. Clin Microbiol Rev. 2002;15(1):66–78.
84. Murray CK, Gasser RA Jr, Magill AJ, Miller RS. Update on rapid diagnostic testing for malaria. Clin Microbiol Rev. 2008;21(1):97–110. https://doi.org/10.1128/CMR.00035-00007.
85. Alfonso Y, Fraga J, Fonseca C, et al. Molecular diagnosis of Toxoplasma gondii infection in cerebrospinal fluid from AIDS patients. Cerebrospinal Fluid Res. 2009;6:2. https://doi.org/10.1186/1743-8454-1186-1182.
86. Liesenfeld O, Press C, Montoya JG, et al. False-positive results in immunoglobulin M (IgM) toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. J Clin Microbiol. 1997;35(1):174–8.
87. Montoya JG. Laboratory diagnosis of Toxoplasma gondii infection and toxoplasmosis. J Infect Dis. 2002;185(Suppl 1):S73–82. https://doi.org/10.1086/338827.

88. Liu P, Weng X, Zhou J, et al. Next generation sequencing based pathogen analysis in a patient with neurocysticercosis: a case report. BMC Infect Dis. 2018;18(1):113. https://doi.org/10.1186/s12879-12018-13015-y.
89. Fan S, Qiao X, Liu L, et al. Next-generation sequencing of cerebrospinal fluid for the diagnosis of neurocysticercosis. Front Neurol. 2018;9:471. https://doi.org/10.3389/fneur.2018.00471. eCollection 02018.
90. White AC Jr, Coyle CM, Rajshekhar V, et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2018;66(8):e49–75. https://doi.org/10.1093/cid/cix1084.
91. Cohen J. Management of bacterial meningitis in adults. BMJ. 2003;326(7397):996–7. https://doi.org/10.1136/bmj.1326.7397.1996.
92. Wu HM, Cordeiro SM, Harcourt BH, et al. Accuracy of real-time PCR, Gram stain and culture for Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae meningitis diagnosis. BMC Infect Dis. 2013;13:26. https://doi.org/10.1186/1471-2334-1113-1126.
93. Polage CR, Petti CA. Assessment of the utility of viral culture of cerebrospinal fluid. Clin Infect Dis. 2006;43(12):1578–9.
94. Huang C, Morse D, Slater B, et al. Multiple-year experience in the diagnosis of viral central nervous system infections with a panel of polymerase chain reaction assays for detection of 11 viruses. Clin Infect Dis. 2004;39(5):630–5. https://doi.org/10.1086/422650. Epub 422004 Aug 422611.
95. Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology. 2006;66(1):75–80. https://doi.org/10.1212/1201.wnl.0000191407.0000181333.0000191400.
96. Solomon T. Flavivirus encephalitis. N Engl J Med. 2004;351(4):370–8. https://doi.org/10.1056/NEJMra030476.
97. Gorgievski-Hrisoho M, Schumacher JD, Vilimonovic N, Germann D, Matter L. Detection by PCR of enteroviruses in cerebrospinal fluid during a summer outbreak of aseptic meningitis in Switzerland. J Clin Microbiol. 1998;36(9):2408–12.
98. Tarafdar K, Rao S, Recco RA, Zaman MM. Lack of sensitivity of the latex agglutination test to detect bacterial antigen in the cerebrospinal fluid of patients with culture-negative meningitis. Clin Infect Dis. 2001;33(3):406–8. https://doi.org/10.1086/321885. Epub 322001 Jun 321821.
99. Flores LL, Steingart KR, Dendukuri N, et al. Systematic review and meta-analysis of antigen detection tests for the diagnosis of tuberculosis. Clin Vaccine Immunol. 2011;18(10):1616–27. https://doi.org/10.1128/CVI.05205-05211. Epub 02011 Aug 05210.
100. Antinori S, Radice A, Galimberti L, Magni C, Fasan M, Parravicini C. The role of cryptococcal antigen assay in diagnosis and monitoring of cryptococcal meningitis. J Clin Microbiol. 2005;43(11):5828–9.
101. Ji S, Ni L, Zhang J, Huang J, Zhou Z, Yu Y. Value of three capsular antigen detection methods in diagnosis and efficacy assessment in patients with cryptococcal meningoencephalitis. Zhonghua Yi Xue Za Zhi. 2015;95(46):3733–6.
102. Wilson DA, Sholtis M, Parshall S, Hall GS, Procop GW. False-positive cryptococcal antigen test associated with use of BBL Port-a-Cul transport vials. J Clin Microbiol. 2011;49(2):702–3. https://doi.org/10.1128/JCM.01169-01110. Epub 02010 Dec 01115.
103. Jarvis JN, Percival A, Bauman S, et al. Evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated cryptococcal meningitis. Clin Infect Dis. 2011;53(10):1019–23.
104. Meya DB, Manabe YC, Castelnuovo B, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010;51(4):448–55. https://doi.org/10.1086/655143.

105. Lyons JL, Roos KL, Marr KA, et al. Cerebrospinal fluid (1,3)-beta-D-glucan detection as an aid for diagnosis of iatrogenic fungal meningitis. J Clin Microbiol. 2013;51(4):1285–7. https://doi.org/10.1128/JCM.00061-00013. Epub 02013 Jan 00030.
106. Lyons JL, Thakur KT, Lee R, et al. Utility of measuring (1,3)-beta-d-glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection. J Clin Microbiol. 2015;53(1):319–22.
107. Salvatore CM, Chen TK, Toussi SS, et al. (1-->3)-beta-d-Glucan in Cerebrospinal Fluid as a Biomarker for Candida and Aspergillus Infections of the Central Nervous System in Pediatric Patients. J Pediatric Infect Dis Soc. 2016;5(3):277–86. https://doi.org/10.1093/jpids/piv1014. Epub 2015 Mar 1019.
108. Landry ML, Tang YW. Immunologic and molecular methods for viral diagnosis. In: Detrick B, Schmitz JL, Hamilton RG, editors. Manual of molecular and clinical laboratory immunology. 8th ed. Washington, DC: American Society for Microbiology Press; 2016. p. 309–18.
109. Storch GA. Diagnostic virology. Clin Infect Dis. 2000;31(3):739–51.
110. Chabierski S, Barzon L, Papa A, et al. Distinguishing West Nile virus infection using a recombinant envelope protein with mutations in the conserved fusion-loop. BMC Infect Dis. 2014;14:246.
111. Morjaria S, Arguello E, Taur Y, et al. West Nile virus central nervous system infection in patients treated with rituximab: implications for diagnosis and prognosis, with a review of literature. Open Forum Infect Dis. 2015;2(4):ofv136. https://doi.org/10.1093/ofid/ofv1136. eCollection 2015 Dec.
112. Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system – prognosis, diagnostics and treatment. J Infect. 2015;71(3):281–93. https://doi.org/10.1016/j.jinf.2015.1006.1004. Epub 2015 Jun 1012.
113. Henao-Martinez AF, Johnson SC. Diagnostic tests for syphilis: new tests and new algorithms. Neurol Clin Pract. 2014;4(2):114–22. https://doi.org/10.1212/1201.CPJ.0000435752.0000417621.0000435748.
114. He T, Kaplan S, Kamboj M, Tang YW. Laboratory diagnosis of central nervous system infection. Curr Infect Dis Rep. 2016;18(11):35. https://doi.org/10.1007/s11908-11016-10545-11906.
115. Yang S, Rothman RE. PCR-based diagnostics for infectious diseases: uses, limitations, and future applications in acute-care settings. Lancet Infect Dis. 2004;4(6):337–48. https://doi.org/10.1016/S1473-3099(1004)01044-01048.
116. Smalling TW, Sefers SE, Li H, Tang YW. Molecular approaches to detecting herpes simplex virus and enteroviruses in the central nervous system. J Clin Microbiol. 2002;40(7):2317–22.
117. Tang YW. Laboratory diagnosis of CNS infections by molecular amplification techniques. Expert opin Med Diagn. 2007;1(4):489–509.
118. DeBiasi RL, Kleinschmidt-DeMasters BK, Weinberg A, Tyler KL. Use of PCR for the diagnosis of herpesvirus infections of the central nervous system. J Clin Virol. 2002;25(Suppl 1):S5–11.
119. Weisz RR. Brain biopsy in herpes simplex encephalitis. N Engl J Med. 1980;303(12):700. https://doi.org/10.1056/NEJM198009183031212.
120. Burns J, Redfern DR, Esiri MM, McGee JO. Human and viral gene detection in routine paraffin embedded tissue by in situ hybridisation with biotinylated probes: viral localisation in herpes encephalitis. J Clin Pathol. 1986;39(10):1066–73. https://doi.org/10.1136/jcp.1039.1010.1066.
121. Abdullah KG, Li Y, Agarwal P, et al. Long-term utility and complication profile of open craniotomy for biopsy in patients with idiopathic encephalitis. J Clin Neurosci. 2017;37:69–72. https://doi.org/10.1016/j.jocn.2016.1011.1013. Epub 2016 Dec 1012.
122. DeBiasi RL, Tyler KL. Polymerase chain reaction in the diagnosis and management of central nervous system infections. Arch Neurol. 1999;56(10):1215–9.
123. Sawyer MH, Holland D, Aintablian N, Connor JD, Keyser EF, Waecker NJ Jr. Diagnosis of enteroviral central nervous system infection by polymerase chain reaction during a large community outbreak. Pediatr Infect Dis J. 1994;13(3):177–82.

124. Tang YW, Mitchell PS, Espy MJ, Smith TF, Persing DH. Molecular diagnosis of herpes simplex virus infections in the central nervous system. J Clin Microbiol. 1999;37(7):2127–36.
125. Nolte FS, Rogers BB, Tang YW, et al. Evaluation of a rapid and completely automated real-time reverse transcriptase PCR assay for diagnosis of enteroviral meningitis. J Clin Microbiol. 2011;49(2):528–33.
126. Capaul SE, Gorgievski-Hrisoho M. Detection of enterovirus RNA in cerebrospinal fluid (CSF) using NucliSens EasyQ Enterovirus assay. J Clin Virol. 2005;32(3):236–40.
127. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016;29(3):487–524.
128. Waggoner JJ, Pinsky BA. Zika Virus: diagnostics for an emerging pandemic threat. J Clin Microbiol. 2016;54(4):860–7. https://doi.org/10.1128/JCM.00279-00216. Epub 02016 Feb 00217.
129. Colmenero JD, Queipo-Ortuno MI, Reguera JM, Baeza G, Salazar JA, Morata P. Real time polymerase chain reaction: a new powerful tool for the diagnosis of neurobrucellosis. J Neurol Neurosurg Psychiatry. 2005;76(7):1025–7. https://doi.org/10.1136/jnnp.2004.049411.
130. Lawn SD, Nicol MP. Xpert(R) MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol. 2011;6(9):1067–82. https://doi.org/10.2217/fmb.1011.1084.
131. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2014;44(2):435–46.
132. Bahr NC, Tugume L, Rajasingham R, et al. Improved diagnostic sensitivity for tuberculous meningitis with Xpert((R)) MTB/RIF of centrifuged CSF. Int J Tuberc Lung Dis. 2015;19(10):1209–15. https://doi.org/10.5588/ijtld.1215.0253.
133. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of biofire filmarray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol. 2016;54(9):2251–61. https://doi.org/10.1128/JCM.00730-00716. Epub 02016 Jun 00722.
134. Messacar K, Breazeale G, Robinson CC, Dominguez SR. Potential clinical impact of the film array meningitis encephalitis panel in children with suspected central nervous system infections. Diagn Microbiol Infect Dis. 2016;86(1):118–20. https://doi.org/10.1016/j.diagmicrobio.2016.1005.1020. Epub 2016 Jun 1012.
135. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics. 2016;13(3):493–508. https://doi.org/10.1007/s13311-13016-10433-13317.
136. Whitley RJ. Viral encephalitis. N Engl J Med. 1990;323(4):242–50. https://doi.org/10.1056/NEJM199007263230406.
137. Grydeland H, Walhovd KB, Westlye LT, et al. Amnesia following herpes simplex encephalitis: diffusion-tensor imaging uncovers reduced integrity of normal-appearing white matter. Radiology. 2010;257(3):774–81. https://doi.org/10.1148/radiol.10100179. Epub 10102010 Oct 10100178.
138. Hart RP, Kwentus JA, Frazier RB, Hormel TL. Natural history of Kluver-Bucy syndrome after treated herpes encephalitis. South Med J. 1986;79(11):1376–8.
139. Whitley RJ. Herpes simplex virus infections of the central nervous system. Continuum (Minneap Minn). 2015;21(6 Neuroinfectious Disease):1704–13.
140. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986;314(3):144–9. https://doi.org/10.1056/NEJM198601163140303.
141. Van TT, Mongkolrattanothai K, Arevalo M, Lustestica M, Dien Bard J. Impact of a rapid herpes simplex virus pcr assay on duration of acyclovir therapy. J Clin Microbiol. 2017;55(5):1557–65. https://doi.org/10.1128/JCM.02559-02516. Epub 02017 Mar 02558.
142. Gitman MR, Ferguson D, Landry ML. Comparison of Simplexa HSV 1 & 2 PCR with culture, immunofluorescence, and laboratory-developed TaqMan PCR for detection of herpes simplex virus in swab specimens. J Clin Microbiol. 2013;51(11):3765–9.

143. Tyler KL. Update on herpes simplex encephalitis. Rev Neurol Dis. 2004;1(4):169–78.
144. Kimberlin DW, Lakeman FD, Arvin AM, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis. 1996;174(6):1162–7.
145. Gomez CA, Pinsky BA, Liu A, Banaei N. Delayed diagnosis of tuberculous meningitis misdiagnosed as herpes simplex virus-1 encephalitis with the filmarray syndromic polymerase chain reaction panel. Open Forum Infect Dis. 2017;4(1):ofw245. https://doi.org/10.1093/ofid/ofw1245. eCollection 2017 Winter.
146. Al-Soud WA, Radstrom P. Purification and characterization of PCR-inhibitory components in blood cells. J Clin Microbiol. 2001;39(2):485–93. https://doi.org/10.1128/JCM.1139.1122.1485-1493.2001.
147. Launes C, Armero G, Anton A, et al. Molecular epidemiology of severe respiratory disease by human rhinoviruses and enteroviruses at a tertiary paediatric hospital in Barcelona, Spain. Clin Microbiol Infect. 2015;21(8):799.e795–7.
148. Liermann K, Schafler A, Henke A, Sauerbrei A. Evaluation of commercial herpes simplex virus IgG and IgM enzyme immunoassays. J Virol Methods. 2014;199:29–34.
149. Rhein J, Bahr NC, Hemmert AC, et al. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. Diagn Microbiol Infect Dis. 2016;84(3):268–73.
150. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. Clin Microbiol Rev. 2018;31(1):(pii):31/31/e00024-00017. https://doi.org/10.01128/CMR.00024-00017. Print 02018 Jan.
151. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. N Engl J Med. 2014;370(25):2408–17.
152. Gutierrez M, Emmanuel PJ. Expanding molecular diagnostics for central nervous system infections. Adv Pediatr Infect Dis. 2018;65(1):209–27. https://doi.org/10.1016/j.yapd.2018.1004.1005. Epub 2018 Jun 1020.
153. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med. 2019;380(24):2327–40. https://doi.org/10.1056/NEJMoa1803396.
154. Naccache SN, Peggs KS, Mattes FM, et al. Diagnosis of neuroinvasive astrovirus infection in an immunocompromised adult with encephalitis by unbiased next-generation sequencing. Clin Infect Dis. 2015;60(6):919–23.
155. Fan S, Ren H, Wei Y, et al. Next-generation sequencing of the cerebrospinal fluid in the diagnosis of neurobrucellosis. Int J Infect Dis. 2018;67:20–4. https://doi.org/10.1016/j.ijid.2017.1011.1028. Epub 2017 Nov 1028.
156. Salzberg SL, Breitwieser FP, Kumar A, et al. Next-generation sequencing in neuropathologic diagnosis of infections of the nervous system. Neurol Neuroimmunol Neuroinflamm. 2016;3(4):e251. https://doi.org/10.1212/NXI.0000000000000251. eCollection 0000000000002016 Aug.
157. NTH M, Phu NH, LNT N, et al. Central nervous system infection diagnosis by next-generation sequencing: a glimpse into the future? Open Forum Infect Dis. 2017;4(2):ofx046. https://doi.org/10.1093/ofid/ofx1046. eCollection 2017 Spring.
158. Yao M, Zhou J, Zhu Y, et al. Detection of Listeria monocytogenes in CSF from three patients with meningoencephalitis by next-generation sequencing. J Clin Neurol. 2016;12(4):446–51. https://doi.org/10.3988/jcn.2016.3912.3984.3446. Epub 2016 Jul 3926.
159. Greninger AL, Langelier C, Cunningham G, et al. Two rapidly growing mycobacterial species isolated from a brain abscess: first whole-genome sequences of mycobacterium immunogenum and mycobacterium llatzerense. J Clin Microbiol. 2015;53(7):2374–7. https://doi.org/10.1128/JCM.00402-00415. Epub 02015 Apr 00429.

Chapter 3
Neurological and Psychiatric Side Effects of Antimicrobials

Madison K. Bangert and Rodrigo Hasbun

Antimicrobial-associated neurotoxicity presents in a variety of ways, including headache, encephalopathy [1], psychosis, and seizure. When treating with antimicrobials it is important to be conscious of any changes in the natural history of disease or neurologic deterioration of the patient as it may signify a neurotoxic adverse effect of the chosen antimicrobial(s). Neurotoxicity from antimicrobial use is relatively rare, but being cognizant of it helps prevent misdiagnosis or delayed treatment. The goals of this section are to identify different neurotoxic side effects (SEs) of antimicrobials in adults, describe proposed mechanisms underlying those adverse reactions, and offer general management recommendations.

Drugs and Their Side Effects

β-Lactams

β-lactams have known neurologic adverse drug reactions (ADRs) and seizure-inducing properties. The epileptogenic capability of β-lactams was established by 1945 during early investigations of the direct effects of penicillin on the cerebral cortex of monkeys and intrathecally in humans with CNS infections [2–5]. Neurotoxicity of β-lactams is best approximated by brain tissue concentration rather than the amount in the CSF [7–10]. The most readily accepted hypothesis of

M. K. Bangert
Section of Infectious Diseases, UT Health McGovern Medical School, Houston, TX, USA
e-mail: madison.k.bangert@uth.tmc.edu

R. Hasbun (✉)
UT Health McGovern Medical School, Houston, TX, USA
e-mail: Rodrigo.Hasbun@uth.tmc.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_3

neurotoxicity is antagonism of gamma-amino butyric acid (GABA) through binding of the $GABA_A$ receptor. This action results in diminished inhibitory and heightened excitatory effects leading to a greater predisposition to seizures. Differing characteristics of $GABA_A$ receptor binding of the distinctive classes of β-lactams leads to varying levels of seizure activity [2]. The β-lactam ring structure directly correlates to $GABA_A$ receptor affinity. Prior studies revealed the elimination of the *in vivo* excitatory effects of penicillin on the cerebral cortex following removal of the β-lactam ring [3].

Penicillins

Bhattacharyya et al. found numerous reports of penicillin-induced encephalopathy over a 67-year span (1946–2013). Of the 72 reports, most were related to procaine penicillin use followed by classic penicillins then "other." Based on the data found, penicillins were categorized, along with cephalosporins, into type 1 antibiotic-associated encephalopathy (AAE). Within this class, symptom onset occurs within days and seizures, along with myoclonus, are common. Other characteristics include abnormal EEGs, normal MRIs, and symptom resolution within days of discontinuation [1]. Procaine penicillins were categorized as AAE type 2 based on their link to psychosis and less tendency toward seizures.

Even penicillins considered low risk of causing neurologic ADRs (i.e. ampicillin, amoxicillin) can lead to anxiety, encephalopathy, seizures, and abnormal behavior [2]. A study investigating mechanisms of antibiotic neurotoxicity discovered ampicillin does not induce cellular destruction of human primary neuron cells, which may posit an explanation as to why it is not commonly implicated in neurotoxicity [6].

Piperacillin (-tazobactam) is closely associated with disorientation [11]. Cognitive disturbance is most common in patients inappropriately dosed for their kidney function [12–14]. This drug's neurotoxic SEs are further impacted by age, nutrition status, albumin levels, and inflammation [11, 14].

Cephalosporins

Cephalosporins from each of the 5 generations are associated with neurotoxicity, with the exception of the 5th generation; which were well tolerated in phase III trials with minimal neurotoxic SEs. Headaches occurred in 5.8% of trial participants on ceftolozane and 3.4–5.2% on ceftaroline [15–18]. Insomnia occurred in ceftaroline and ceftolozane at 3.1% [16] and 3.5% respectively [18]. Ceftobiprole had very low rates of neurotoxicity in its early trials [19].

Cefazolin, cefoselis, ceftazidime, cefoperazone, and cefepime are considered high-risk cephalosporins for neurotoxicity based on prior literature. The same

article classified cephalexin, cefatoxime, and ceftriaxone as low-risk [20]. The French Pharmacovigilance Database (FPVDB) retrospectively identified 511 adverse reports linked to cephalosporin use. This study implicated 20 different cephalosporins in the causation of neurologic SEs; the most responsible were (in descending order) cefepime, ceftriaxone, ceftazidime, cefotaxime, and cefazolin [21]. Onset ranged 1–10 days [20] with a mean of 7.7 days [21]. After discontinuation of the responsible drug, resolution occurred between 2 and 7 days [20]. In the examination of antibiotic use in critically ill patients, a prospective study concluded that 1st-3rd generation cephalosporins increased the risk of delirium slightly more than twofold (OR 2.2) after controlling for confounders [22]. No relationship between delirium and cefepime, penicillins, carbapenems, fluoroquinolones, or macrolides was established [22–24]. It's proposed that in addition to having high affinity for $GABA_A$ receptors and competitively antagonizing GABA, cephalosporin-associated neurotoxicity may be related to a cytokine storm facilitated by endotoxin release [13, 20].

Cefepime causes a variety of neurologic SEs, from mild to severe. Its increased ability to cause neurotoxicity is attributed to its penetrance of the blood brain barrier (BBB) [13, 25]. Restlessness, hallucination, fluctuating mentation, myoclonus, tremor, coma, seizure, and nonconvulsive status epilepticus (NCSE) are common neurotoxic manifestations of cefepime [22, 25–28]. Looking specifically at 135 patient cases, the 4 most frequent neurologic SEs were altered mental status, reduced consciousness, confusion, and myoclonus [25]. Seizure is also commonly reported, particularly in the elderly or those with renal failure [25, 26]. In early trials, seizures were noted in 9/4445 (0.2%) cefepime-treated patients [26]. Encephalopathy is another frequent SE. A 60 y.o. patient with ESRD on HD developed confusion, agitation, and hallucinations following 5 days of cefepime. Despite continued HD, these symptoms persisted until cefepime was stopped [22]. NCSE presents as altered consciousness while its EEG is characterized by epileptiform discharges. NCSE also promptly responds to anticonvulsants [20, 29]. Although NCSE is most often correlated with cefepime use, a few cases followed treatment with ceftriaxone and cefixime [29–31]. Due to the clinically significant relationship between NCSE and cefepime, the US FDA made a formal statement in 2012 to healthcare professionals describing the link [32]. In a systematic review looking at EEG changes in cefepime-induced neurotoxicity, 100% of EEGs performed were abnormal (EEGs: 98, 73% of total cohort). Only 25% of the patterns were consistent with NCSE while triphasic waves (40%), focal sharp waves (39%), and myoclonic status epilepticus (7%) made up the remaining percentage [25]. Of the 511 patients with cephalosporin-induced neurotoxicity in the FPVDB, EEGs were performed in 195. Abnormal patterns were found in 158 or 81% [21]. The EEG findings were often indicative of nonspecific toxic-metabolic encephalopathy; demonstrating diffuse slowing with triphasic waves and the absence of epileptiform discharges [20].

Use of cefoxitin resulted in a unique case of catatonia in a 60 y.o. woman with end stage renal disease (ESRD). Despite appropriate dosing, she displayed waxing and waning cognition accompanied by mumbling, mutism, rigidity, and frightened appearance. Her symptoms resolved after the cessation of all antibiotics [27].

Ceftazidime, is closely associated with myoclonus as demonstrated in an article by Ong and Qin that highlighted 10 patients, of which 7 had myoclonus [32]. In additional literature on cephalosporins, myoclonus was also relatively common [20, 21, 28].

Carbapenems

Imipenem-cilastatin was the 1st carbapenem approved for clinical use; unfortunately, use is limited, especially for meningitic dosing, due to neurotoxic SEs [9]. Seizure frequency of imipenem-cilastatin was 0.2% in phase I-III trials [33]. After analysis of 26 phase III studies, seizures were noted in 0.7% of the sample population – only 0.4% were considered drug related [34]. Epileptogenic capabilities of imipenem-cilastatin are variable depending on the study. Higher rates range from 3% (Townsend et al.) to 6% (O'Donovan et al) [10]. A 50-month prospective study following 1951 patients documented seizures in only 4 patients (0.2%); all of which were excessively dosed [35, 36]. A meta-analysis of 37 papers written between 1984 and 1999, regarding seizure activity of imipenem-cilastatin, showed a seizure rate of 1.4% in a population >6000 patients [37]. Underlying CNS or renal dysfunction place individuals at greater risk of seizures.

In standardized mouse models, meropenem was shown to be less epileptogenic than imipenem (30% v 60% respectively) [38]. Contrary to that study, another trial found the incidence of seizures to be similar between the different carbapenems when all participants with potential risk factors were excluded (meropenem 0.38% v imipenem-cilastatin 0.43%) [39]. Seizure provoking properties of carbapenems, much like other β-lactams, comes from their ability to bind the $GABA_A$ receptor. An additional mechanism of seizure provocation is through interactions with the receptor complexes of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazolepropionate leading to excitatory activity [40]. The difference in epileptogenic power of carbapenems is directly linked to the basicity of a C2 side chain. The more basic the side chain, the greater the affinity it has for the $GABA_A$ receptor resulting in increased seizure activity [1]. In both human and animal models, doripenem demonstrated less epileptogenicity than all other carbapenems. This trait is attributed to its weaker affinity of $GABA_A$ receptors. On review of multiple clinical trials utilizing doripenem, 0/202 patients experienced convulsions. Postmarketing surveillance of doripenem in Japan further supports this conclusion [41].

In a study that compared the rate of seizures in meropenem to cefepime, meropenem was found to cause significantly less episodes of convulsions (0.54–2.73%) [32]. Meropenem showed a similar seizure rate as the third generation cephalosporins ceftriaxone or cefotaxime. Carbapenem-induced seizures are typically generalized tonic-clonic; however, simple and partial seizures are also documented [42].

Case reports of carbapenem-induced neurotoxicity have shown encephalopathy, delirium, hallucinations, myoclonus, and psychosis [42–45]. In one case study,

ertapenem caused profound neurologic changes in a dialysis-dependent 74 y.o. male being treated for ESBL *Klebsiella* bacteremia. Despite appropriate dosing for his HD schedule, patient presented with vocal tremor, weakness, confusion, and forgetfulness after a week of therapy. Ertapenem was discontinued and symptoms resolved shortly thereafter [43]. Similar findings occurred in a 42 y.o. female that developed hallucinations, myoclonus, and altered mental status on the 7th day of ertapenem. After discontinuation of ertapenem, her symptoms resolved and she returned to baseline within 2 days [44]. Four additional case reports demonstrated similar neurotoxic effects of ertapenem, although these cases were specific to those with preexisting spinal cord injuries. The authors suggested that due to ertapenem's high protein binding property, those with hypoalbuminemia, such as those with long-term spinal cord injuries, might be at greater risk of developing neurotoxic ADRs associated with ertapenem [46]. *In vivo* studies have shown binding at ~95% with a plasma level of <100 μg/mL or at ~85% for plasma concentrations of 300 μg/mL [47]. Albumin levels for the patients included in the case reports ranged from 2.3 to 3.1 g/dL. This particular article found that the onset of symptoms ranged from 2 to 14 days, with a median of 5 days – consistent with additional reports of ertapenem-associated neurotoxic SEs [46].

There are a few reported cases of carbapenem-induced exacerbations of myasthenia gravis (MG). One example involves a 45 y.o. male requiring mechanical ventilation after developing diplopia, weakness, and respiratory distress after being started on imipenem [48]. Although the exact mechanism with imipenem is unclear, other antibiotics are known to block presynaptic and postsynaptic cholinergic activity [49, 50]. A similar mechanism is suspected with carbapenems.

Meropenem and imipenem-induced delirium is seldom reported [51]. A 64 y.o. man in septic shock from a UTI received imipenem-cilastatin, within 24 hours of a dose increase he developed acute psychosis with violent visual and auditory hallucinations. Following speciation and sensitivities, the antibiotic was changed and the patient returned to his norm. Re-challenge 2 months later for an additional UTI resulted in similar symptoms [52]. Package inserts for imipenem, issued by the US FDA, warn against seizures, confusion, and myoclonus. The European Medicine Agency package inserts reveal that hallucinations due to imipenem-cilastatin range from 0.1% to 1.0%. There were 412 reports to the World Health Organization (WHO) Collaborating Center for International Drug Monitoring showing a causative relationship between imipenem use and various psychiatric disorders, delirium being the most common [52].

Macrolides

Macrolide use may lead to acute psychiatric syndromes or psychosis. Clarithromycin is most likely to cause psychosis, while azithromycin is the least. Clarithromycin also causes dizziness, agitation, confusion, depersonalization, and hallucinations [50, 53]. Abouesh et al. termed the concept of antibiotic-induced mania

"antibiomania" [54]. Their literature review revealed 6 cases of mania linked to clarithromycin and 1 to erythromycin. Of 82 cases of antibiotic-induced mania reported to the WHO, 23 involved clarithromycin. The US FDA similarly found clarithromycin to commonly precipitate mania [54]. Over 219 episodes of psychiatric syndromes are attributed to clarithromycin exposure [53]. Nightingale et al. reported two cases of mania – both characterized by hyperactivity, delusions, paranoia, and insomnia – secondary to 2 g daily of clarithromycin for disseminated *mycobacterium avium complex* (MAC) infections. Symptoms subsided quickly after discontinuation, but one patient developed psychosis within 24 h after rechallenge [55]. Five major diagnoses are linked to clarithromycin-induced psychiatric episodes based on 38 reports found in literature between 1994 and 2009: delirium (31.5%), acute psychosis (29%), mania (26%), hallucinations (3%), and major depressive episode (<1%). Symptom onset ranged 1–10 days, with a mean of 5. ADRs tended to resolve in <6 days following discontinuation [56]. Headache was actually the most common neurotoxic SE of clarithromycin in early trials. Of 3768 patients in the trials, 1.7% complained of headache [57, 58]. There are multiple hypotheses as to what the underlying mechanism is for CNS toxicity related to macrolides. Examples of possible etiologies include: drug interactions, metabolite accumulation, modification of cortisol and prostaglandin metabolism, and alterations of neurotransmitters (i.e. glutamate and GABA) [11]. The neurotoxicity of erythromycin and clarithromycin may occur in conjunction with concurrent use of medications metabolized by the cytochrome P450 isoenzymes of the CYP3A family, as both antibiotics (E > C) inhibit the pathway. Clarithromycin specifically has an active lipid-soluble metabolite with potential to cause neurotoxicity. Manev et al. found that macrolides demonstrate inhibitory effects on glutamatergic pathways, which may culminate in macrolide-associated psychiatric disorders [53, 59]. Risk factors for neuropsychiatric SEs include old age and preexisting neurologic dysfunction [50].

Macrolides – along with β-lactams, metronidazole, and fluoroquinolones – are amongst the most common antibiotics to cause encephalopathy [50]. Macrolides are classified as AAE type 2 due to their predilection to induce psychosis, rarely provoke seizures, and have normal imaging/EEG [1].

Macrolides are also implicated in the development of ototoxicity and, unlike the psychiatric ADRs of macrolides, are dose-dependent. In studies involving guinea pigs, the administration of erythromycin to the middle ear resulted in complete destruction of cochlear hair cells [2]. Two patients with liver dysfunction were given high dose erythromycin when they developed hearing loss. Of note, they both received additional ototoxic agents; however, hearing improved after decreasing the dose of erythromycin and resolved completely following discontinuation of the drug [60]. Long-term azithromycin use for prophylaxis of MAC in patients with AIDS has also caused transient deafness, albeit rarely. Phase II/III trials of azithromycin reported a low rate of hearing loss in patients at <0.2% [61]. A study looking at therapeutic azithromycin use for MAC treatment found that 8/46 (17%) patients experienced hearing loss after an average of 7.9 weeks of treatment. Hearing loss was accompanied by vertigo, tinnitus, and the sensation of "plugged ears."

Audiometry of the eight patients revealed mild-to-moderate sensorineural hearing loss and reflex decay. Symptoms took 4.9 weeks on average to return to baseline after stopping azithromycin [62]. An additional study showed ototoxicity in 3/21 (14%) patients while being treated for MAC. Onset occurred between 4–12 weeks and resolved 2–5 weeks after cessation of the drug. Symptoms recurred on rechallenge [63]. Risk factors for hearing loss include preexisting hearing impairment, use of additional ototoxic agents, and renal or liver dysfunction [60].

Macrolides are strongly associated with the induction of MG exacerbations [50]. Acute myasthenic crisis is more commonly precipitated by azithromycin and erythromycin than clarithromycin [64]. Severe exacerbation of MG may take place within an hour of taking azithromycin [65]. Telithromycin has been associated with several case reports of MG, often with onset within 2 h of administration [66]. The US FDA issued a boxed warning regarding the relationship in 2007 [67]. The proposed mechanism is that macrolides interrupt presynaptic processes leading to a crisis [65]. However, Perrot et al. concluded that telithromycin was unlikely acting presynaptically because reflexes and pupil diameter were unaffected. They hypothesized it was also not a matter of receptor interference because affected patients had varying MG antibodies; therefore, they purposed disruption of an unknown target on the neuromuscular (NM) junction [66].

Fluoroquinolones (FQs)

Like most antibiotics, FQs are well tolerated, but have a number of SEs, both minor and serious [68]. Safety profiles of FQs differ between the individual drugs. Headache, dizziness, somnolence, and insomnia are common neurologic SEs of the drug class. The more serious FQ-associated neurotoxic SEs are peripheral neuropathy, psychosis, delirium, seizures, and suicidal ideation and/or behavior. Neurotoxicity is the 2nd most common ADR category for FQs [69] based on incidence estimates of 1–2% [68] by one account and 1–3.3% in another [2].

The US FDA changed its label on FQs in 2013 to address the risk of developing peripheral neuropathy [70, 71]. As a response to the change, Etminan et al. completed a case control trial investigating the probability of developing FQ-induced peripheral neuropathy [70]. Over a 10-year period, 6000 cases were identified along with 24,000 control subjects from a cohort of men aged 45–80. The study concluded that “current users” of FQs were at high risk of developing peripheral neuropathy while “current new users” had the greatest risk with a rate ratio of 2.07 (compared to 1.83). Risk associated with individual FQs did not vary much; meaning there is not an inherently greater risk with any specific FQ. The big picture conclusion of this study was that any FQ use resulted in a 30% increased risk of peripheral neuropathy [70].

Episodes of psychosis may develop with FQ use [1, 68, 70]. Confusion, hallucination, agitation, and delusion were the most frequently described FQ-associated psychiatric SEs in 590 cases (51%, 27%, 13%, and 12% respectively) [72]. Due to

the relationship between FQ use and psychosis, they are grouped into type 2 AAE with sulfonamides and macrolides [1]. Abouesh et al. cited FQs as one of the classes of antibiotics to cause "antibiomania." Out of the 82 cases of psychosis associated with antibiotic use reported to the WHO, FQs accounted for 26 of them, with ciprofloxacin responsible for 12/26 [54]. US FDA reporting also supports ciprofloxacin as a leading drug in the precipitation of mania [54]. In some cases, causality was clearly demonstrated by re-administration of the suspected drug resulting in a resurgence of SEs [54, 73]. Insomnia is another commonly reported SE of FQs. The FPVDB reports insomnia in ~8% of those taking FQs [72]. About 4.7% of patients treated with ofloxacin report insomnia, while <1% demonstrate psychosis [68].

A potentially fatal neuropsychiatric ADR of FQ use is the development of suicidal thoughts and behaviors. Samyde et al. combed the WHO's adverse drug reaction database between 1970–2015 for reported suicidal thoughts and behaviors that correlated with FQ treatment [74]. There were 608 reports meeting the criteria amongst the 992,097 reports of adverse reactions overall with FQs. Unfortunately, 97/608 individuals completed suicide.

Although categorized as AAE type 2 due to the low rate of seizures with FQ use [1], they are still a concerning SE [50]. Incidence of FQ-induced seizure is between 0.1% and 0.5% [50]. Ciprofloxacin is more commonly associated with seizures than other FQs [2, 68]. Concurrent exposures to NSAIDs increases the likelihood of seizures. The degree of CNS penetration does not seem to correlate directly with epileptogenic activity [20, 68].

FQs can precipitate MG exacerbations [50]. Over 30 cases of a MG exacerbation following the administration of systemic FQ have been described. Average time to onset was 1 day after initial exposure [75]. In an *in vitro* study, FQs were found to progressively diminish miniature endplate potentials and currents in a dose-dependent manner. The pattern is suggestive of a direct influence on the acetylcholine receptor ion channel [76]. Additionally neostigmine did not reverse the NM blockage supporting a post-synaptic process.

There are several suggested mechanisms to explain the various neurotoxic SEs of FQs. Medications in this class cause encephalopathy that mimics psychosis related to illicit drug use, which develops via alterations in NMDA glutamate receptors and dopamine pathways. Due to the similarity, those pathways may play a role in developing FQ-induced neurotoxicity. An additional hypothesis is that FQs cause inhibition of GABA receptors [69] or at least a relative imbalance between the GABAergic and glutamatergic systems [74]. FQs do not directly bind NMDA receptors; rather they activate the receptor by removing the Mg^{2+} blockade from the ion channel [74]. Excessive activation leads to neurotoxic features of FQs, like seizures. This antibiotic class demonstrates weak GABA binding capabilities and interaction with $GABA_A$ receptors, leading to increased activity in the CNS [74]. A rat model showed that repeated dosing of ciprofloxacin created anxiety in the rats that correlated with decreased GABA concentrations in the brain [77]. There are reports that ofloxacin causes a Tourette-like syndrome suggesting some potential interaction with the D2 dopaminergic pathway [78]. Another neurotransmitter possibly affected by FQ use is serotonin. Rats in a forced swimming test displayed depressive symptoms

following ciprofloxacin administration. Cerebral levels of serotonin of these rats were noted to be lower than controls [77]. Decreased serotonin concentrations have been linked to depression and anxiety disorders [74]. Oxidative stress and altered microRNAs are additional hypotheses behind the neurotoxic ADRs of fluoroquinolones [74, 77].

Risk factors for FQ-induced neurotoxicity are numerous. Dosing and duration of therapy play a role in the development of SEs. Previous neurologic damage, known epilepsy, and alcohol use places patients at greater risk of seizures [2, 68] while comorbid psychiatric illnesses may increase the risk of psychosis or mood disorders. Concurrent conditions that independently cause peripheral neuropathy further increases the risk of developing potentially persistent or permanent neuropathies. Old age and renal dysfunction increase the risk of developing neurotoxicity overall.

A distinctive quality of FQs is their ability to cause delayed ADRs by inducing mitochondrial and cellular toxicity [79]. Slow onset of mitochondrial damage can lead to a progression of adverse outcomes despite discontinuation of the antibiotic. A number of cases highlight the postponed, persistent, and at times progressive, neurologic SEs of FQs. The 1st case is a 28 y.o. woman treated with a 7-day course of levofloxacin followed by an additional 10-day course several weeks later. She developed severe neurologic symptoms – peripheral, sensory, and autonomic nervous system disturbances – in addition to musculoskeletal and gastrointestinal complaints. Following discontinuation of the drug, her symptoms progressed to the point of complete disability from muscle spasms, fasciculations, and atrophy. An additional three cases in men and women demonstrated musculoskeletal pain and peripheral neuropathy, as well as CNS manifestations of mood disturbance, cognition impairment, and insomnia. Again, the symptoms worsened even after stopping the FQs. All patients had broad workups that were negative for other possible etiologies.

Aminoglycosides (AGs)

Neurotoxicity related to AG use most commonly manifests as ototoxicity, but may additionally present as peripheral neuropathy, encephalopathy, delirium, and inhibition of NM transmission. Individual AGs are structurally similar to one another resulting in a shared mechanism of action and comparable ADR profiles. There are slight variations in the gravity and regularity of SEs due to minor chemical differences [80].

AG-associated ototoxicity affects the vestibular or cochlear systems of the ear, and in some cases, both simultaneously. Hearing loss associated with AG use is often bilateral and permanent [81]. Permanence often occurs in patients with continued hearing loss after withdrawal of the AG, severe loss (>25 dB), or delayed presentation of symptoms [82]. Onset of symptoms may occur shortly after initiation of treatment; however, they most commonly develop during a protracted treatment course. Duration of therapy also plays a role in hearing loss. Between 1975

and 2006, 64 patients were treated with AGs for an average of 20 months for tuberculosis (TB), of which 19% developed irreversible hearing loss. Of those 12 people, 6.3% had hearing loss involving frequencies of normal speech [83].

Kanamycin, neomycin, and amikacin are AGs correlated with cochlear function disruption [84]. Cochlear toxicity is hallmarked by hearing loss, tinnitus, inner ear pressure, and occasionally ear pain. Some patients are asymptomatic and only have audiometric changes noted during screening. Clinically apparent hearing loss occurs in ~2–4% of patients with AG exposure, while pure tone audiometry hearing loss is ~26% [82]. High frequency hearing dysfunction often occurs long before clinically manifesting by preferentially affecting the basal turn of the cochlea [84]. Hearing impairment is the result of cochlear hair cell harm. Studies have found that individualized therapy based on peak and trough concentrations leads to less damage on the cochlear system [85]. Hair cell destruction it thought to be secondary to reactive oxygen species (ROS) created from overstimulation of NMDA receptors by the AG [81, 86]. Other studies report that the formation of iron-AG complexes potentiate damage of hair cells by the release of free oxygen radicals [2, 87]. This theory is supported by a reduction in damage in the presence of iron chelators and radical scavengers in *in vitro* studies. Hearing loss can ultimately progress to complete deafness as hair cell damage spreads from the cochlear base [81, 84, 87].

Vestibular ototoxicity is less common than cochlear, and is often overlooked [80]. It manifests as disequilibrium, dizziness, vertigo, ataxia, and nystagmus. Vestibular dysfunction occurs in ~1.4–3.7% of AG exposures. Gentamicin is the AG most often associated with vestibular toxicity. Unlike cochlear toxicity, vestibular disruption is often reversible, although it may take 1–6 months for symptoms to resolve [87]. Vestibular impairment is more closely related to therapy duration rather than serum concentration levels [78].

Risk factors for increased susceptibility to aminoglycoside ADRs include poor renal function, baseline hearing abnormalities, age, severity of illness, and dehydration. Ototoxicity is often seen in conjunction with nephrotoxicity as it results in elevated trough levels [78]. Patients with Ménière's disease have greater risk of developing hearing loss with AGs; seen in up to 30% of patients in one study. Significant drug related factors include dosing (daily and cumulative), duration, and prior exposure. In a guinea pig model, gentamicin was detected 11 months after the cessation of therapy in the outer hair cells. This may contribute to the toxicity seen on subsequent exposures [86]. Multiple ototoxic agents should not be used concomitantly if possible. Intermittent hearing exams should continue for at least 1 year after discontinuation of the AG as damage can continue to progress despite drug removal [81]. There is a population of genetically susceptible individuals that develop deafness acutely with AG exposure due to a specific mitochondrial DNA mutation [88].

AGs are considered one of the major classes of antibiotics to induce NM blockade. Gentamicin, streptomycin, and amikacin are the 3 main AGs associated with inhibition of NM transmission [11, 89]. The hypothesized mechanism of NM blockade is that it's mediated by AG antagonism of calcium in the presynaptic neuron preventing acetylcholine release. In support of this argument is the finding that the addition of calcium can reverse the blockade or protect against it [89].

There have been individual reports of AG-associated peripheral neuropathy and encephalopathy, specifically with gentamicin. Nerve biopsy revealed lysosomal abnormalities similar to those found in gentamicin-induced nephrotoxicity [90]. Additional lesions were found in brain tissue following intrathecal gentamicin. An experiment on rabbits found similar CNS lesions that were directly related to brain tissue and CSF concentrations [91].

Polymyxins

In the 1970s, polymyxins fell out of favor due to high rates of toxicity. This antibiotic class has made a recent reappearance due to the number of multidrug resistant organisms sensitive to polymyxins. ADRs are noted in up to 25% of exposures, with neurotoxicity in up to 7% of patients, even with normal renal function. Neurotoxicity is believed to be dose-dependent and attributed to the concentration of an active metabolite in the blood [92]. Most SEs are mild-to-moderate [93]. Weakness, headaches, and dizziness are regular neurotoxic manifestations while paresthesia, ataxia, seizures, and apnea are less frequent [93]. The incidence of paresthesia – generalized, facial/circumoral, or peripheral – varies depending on route of drug administration, with greater incidence associated with intravenous (IV) rather than intramuscular administration. Other infrequent ADRs include visual and auditory disturbance, vertigo, and hallucinations. A myasthenia-like syndrome, hallmarked by muscle weakness and NM blockade, may lead to respiratory muscle paresis or paralysis resulting in respiratory failure when severe [50, 94]. Meningeal irritation and CSF pleocytosis can occur after intrathecal administration of polymyxins. Severe CNS irritation may culminate in convulsions.

The chemical structures of polymyxins contain fatty acids that permit interaction with brain tissue and lipophilic portions of neurons resulting in disruption of activity [11]. Neuromuscular blockade may be secondary to the prevention of presynaptic release of acetylcholine due to polymyxin interference on receptor sites [11, 94]. Others hypothesize the precipitation of the myasthenia-like syndrome occurs because polymyxins competitively bind at acetylcholine receptor sites and cause calcium depletion within neurons, leading to prolonged depolarization [94]. Risk factors for neurotoxicity are impaired renal function, history of MG, hypoxia, concomitant CNS modifying drugs, and being female. Resolution of symptoms occurs after discontinuation and may be facilitated by dialysis if necessary [11].

Tetracyclines

Neurotoxicity is rarely associated with tetracyclines [2]. Early reports noted cranial nerve toxicity and in rare cases caused NM blockade. Action at the NM junction is responsible for the individual case reports of exacerbations of MG [20, 50, 95]. Seldomly, tetracyclines have been associated with benign intracranial hypertension

that self-resolves within 2–5 days after discontinuation of the responsible agent [2, 96]. In a trial looking at the effects of 18-months of minocycline on the progression of Parkinson's Disease, participants frequently experienced headaches and dizziness [97].

There are a variety of psychiatric symptoms associated with doxycycline use. A case series in 2013 showed a link between doxycycline and suicidality among three patients. Of the 3 patients, 2 completed suicide. The 3rd individual stopped therapy with doxycycline and returned to his baseline mood without the need for ongoing psychotropic medications. A few siblings of the individuals also experienced anxiety while on low doses of doxycycline. No definitive mechanism of action was found [98]. These case reports are further supported by 317 past reports of mood disturbance in patients on doxycycline sent to the US FDA. This includes 16 attempts at suicide.

A few animal models have actually shown that some tetracyclines, have dose-dependent neuroprotective qualities against partial seizures [99]. Other studies have shown beneficial effects, such as improved function, of minocycline when given over a 3-month period following acute ischemic strokes [100, 101].

Glycylcycline

In general, tigecycline has a favorable safety profile, with mild SEs. Its neurotoxic ADRs – headache, dizziness, and insomnia – are of no exception [102]. Since the drugs approval, there have been relatively few neuropsychiatric ADRs reported. Delirium was noted in a case report of an elderly Asian man with ESRD receiving tigecycline for a COPD exacerbation. The patient became altered and aggressive shortly after a loading dose infusion. Symptoms resolved after discontinuation, but when re-challenged, the patient once again became delirious [103].

Sulfonamides

Sulfonamides commonly cause headache and drowsiness. Trimethoprim-sulfamethoxazole (TMP-SMX), specifically, can cause tremor, aseptic meningitis, and delirium but seldomly does. TMP-SMX also causes abrupt behavioral changes, restlessness, and aggressiveness during acute episodes of psychosis [104]. Hallucinations, both visual and auditory, have been described [105]. Psychiatric symptoms often start to improve within 24 h of discontinuation. HD may help remove the drug if needed [104, 106–108]. Neurotoxicity risk factors include old age, preexisting psychopathology, malnutrition/folate deficiency, increased permeability of the BBB, additional agents capable of inducing psychosis, and renal or hepatic dysfunction [104, 106, 107]. IV formulations also put patients at greater risk of SEs than oral preparations. An immunocompromised state may additionally play a role as a study found that psychosis had an incidence of 11.9% with TMP-SMX

use in HIV patients [109]. To further support this notion, TMP-SMX ADRs are noted in ~8% of the general population, while ADRs are reported about 83% of the time in HIV positive patients [11]. Those with cytochrome P450 2C9 class mutations are at risk at developing SEs from TMP-SMX as its metabolized through this pathway. Mutant forms slow enzyme activity and the drug accumulates, including in the brain/CSF since TMP-SMX has good CNS penetratration [107]. Psychosis is likely dose-dependent, as Lee et al. found that for every 1 mg/kg increase in the dose of trimethoprim, the incidence of acute psychosis raised by 40% [109]. They also calculated that ~1/5 dosed at >15 mg/kg/day of trimethoprim develop psychosis [109]. In renal transplant patients receiving TMP-SMX, 25% of patients developed a psychiatric syndrome when dosed at ≤15 mg/kg. As the individual dose surpasses 15 mg/kg, the rate of acute psychiatric episodes increases to 100% [104, 110]. This is also corroborated by a case in which a patient was treated with TMP-SMX prior to stem cell transplantation for prophylaxis without issue. After the transplant, the patient was treated for PJP with higher dosed IV formulation TMP-SMX. After 5 days of therapy the patient had tremor, restlessness, and insomnia that progressed to hallucinations, disruptive behavior, and confusion [111]. Patient returned to baseline within 48 hours of medication withdrawal. Treatment 6 months later with an oral, reduced dose of TMP-SMX took place without complication.

Bhattacharyya et al. classified sulfonamides as type 2 AAE due to their predilection to cause psychiatric syndromes. They found encephalopathy to be associated with delusions, hallucinations, or psychosis with macrolides at 63%, FQs at 67%, and sulfonamides at 68%. Sulfonamide-induced encephalopathy was only linked to seizures 16% of the time. Range of SE onset was 1–16 days with a median of 3 days. Resolution of symptoms ranged from 1–5 days.

Glycopeptides

There are reports of vancomycin causing a dose-dependent, typically reversible ototoxicity; however, it remains controversial due to a lack of supporting animal models [112–114]. The hypothesized mechanism of vancomycin ototoxicity is direct damage to the auditory branch of the 8th cranial nerve by supratherapeutic serum concentration levels of 80–100 μg/mL [113, 115]. A 63 y.o. man treated with intrathecal vancomycin for meningitis developed bilateral, complete, and permanent sensorineural hearing loss following two doses [116]. Ototoxicity risk factors include prolonged dosing, renal dysfunction, older age, preexisting hearing loss, and concomitant use of additional ototoxic agents. A retrospective study analyzing audiograms taken before and after prolonged vancomycin use (~27 days), found that 12% had subclinical changes on audiometry posttreatment [117]. There is evidence to support that vancomycin augments aminoglycosides leading to increased risk of ototoxicity when used concomitantly. Vancomycin also rarely causes dizziness, vertigo, and tinnitus [113, 115, 118]. Tinnitus acts as a harbinger of impending hearing loss, therefore it should prompt cessation of vancomycin [113, 115].

During early safety trials of teicoplanin, 0.3% of patients developed hearing impairment [119]. Guinea pigs treated for 28 days with max doses of teicoplanin (75 mg/kg/day) failed to show any ototoxicity at any level – functionally or histologically [120]. Maher et al. discovered asymptomatic high frequency hearing loss in a 39 y.o. man with Down syndrome on routine audiogram on day 31 of teicoplanin use. Serum levels were within recommendations. Five months after discontinuation of the drug, a repeat audiogram showed only slight improvement of his high frequency hearing loss. The researchers tested 100 additional cases for teicoplanin ototoxicity, but did not find a single additional case. Maher et al. attributed the hearing loss in the man with Down syndrome to the premature aging associated with the disorder [121]. In 2004, a study following 12 patients treated with teicoplanin for severe staphylococcal infection showed a slight, but significant, increase in high frequency hearing thresholds on audiometry, specifically at 4 and 8 kHz [122]. These studies suggest that teicoplanin, like vancomycin, has ototoxic potential, but is relatively rare and often subclinical.

Lipoglycopeptides

Lipoglycopeptides are well tolerated and induce very few nervous system ADRs and those they do cause are mild and short-lived. Other than 25% of participants reporting headache, dalbavancin had a favorable SE profile during phase I-III trials [123]. In an additional article looking at data from seven randomized clinical trials between dalbavancin and comparators, headache and insomnia were among dalbavancin's top 10-reported SEs. Out of 1178 participants, 7% reported headaches while 2% developed insomnia [124]. There was no evidence of ototoxicity. Adverse effects lasted 7.7 days on average [125].

No neurotoxic SEs were noted with ortivancin in early studies while only one pharmacokinetic study reported headache. In one clinical trial, the ortivancin group did experience more tremor than the comparator group [125].

Telavancin has recurrently caused psychiatric disorders, headache, and paresthesia. In the FAST-2 trial it was found to alter taste, change sleeping patterns, and cause head discomfort [125].

Lipopeptide

In daptomycin phase III trials, the incidence of headaches was 5.4% [126, 127], dizziness 2.2% [126], while a few other neurotoxic effects – vertigo, mental status change, or paresthesia – occurred <1% experienced. In a separate arm of the phase III trials, difficulty sleeping developed in 9% [126].

Other neurological ADRs documented as "possibly or probably drug-related" during the early trials were dyskinesia, paresthesia, and hallucinations. Peripheral

neuropathy was not seen in early trials; rather it arose as a problem during postmarketing surveillance. Animal models using dogs have elicited peripheral neuropathy, but only when using supratherapeutic, nonclinical doses. The appearance of peripheral neuropathy was demonstrated at 40 mg/kg/day in the adult dogs, while clinically relevant doses are generally 4–6 mg/kg/day. The neuropathy was characterized as axonal degeneration accompanied by loss of reflexes and pain perception. Deficits were noted within 2 weeks of treatment and improved within 2 weeks of drug cessation [126]. In a randomized trial comparing 6 mg/kg/day of daptomycin to a comparator therapy, 11/120 patients in the daptomycin group developed peripheral nervous system SEs (i.e. paresthesia, dysesthesia). Only 2/116 of the comparator experimental group developed comparable symptoms [128]. All daptomycin symptoms fully resolved. Phase II trials also noted a few cases of neuropathy when patients were treated with 3 mg/kg twice daily [129].

Oxazolidinones

Based on early trials, linezolid and tedizolid are well tolerated. In a phase I trial of tedizolid, no SEs were severe enough to warrant dropping from the study [130]. In a direct comparison trial, linezolid and tedizolid had similar safety profiles and SEs. The main neurotoxic ADRs were insomnia (1.5% v 0.7%), dizziness (1.8% v 2.1%), and headache (6.2% v 5.9%) [131].

Linezolid-induced peripheral neuropathy is a treatment-limiting ADR. Due to an increased potential to develop painful paresthesia in the extremities following 4 weeks of linezolid, it's recommended that patients receive less than 28 days total [132–135]. In a study looking at 828 treatment courses of linezolid, only 32.9% extended beyond 28 days. Peripheral neuropathy was rare with only 3 (0.36%) of the patients developing neuropathic pain; all three patients were treated >28 days [136]. Linezolid-associated peripheral neuropathy is often symmetrical and can be a disruption of small nerve fibers, large nerve fibers, or a combination of both [132–134]. A mild motor component to the peripheral neuropathy is often present [133]. The neuropathy is most often irreversible, although reversibility has been noted in some cases following discontinuation of linezolid [135, 137]. Bressler et al. found that 9/12 cases reported irreversible changes [135]. Risk factors for the development of linezolid-induced neuropathy are long duration of therapy, preexisting neurological disease, diabetes, alcoholism, or concomitant use of chemotherapeutic or antiretroviral therapies [138]. Most reports of neuralgia develop following 4–6 months of treatment but there are exceptions. For example, a 35 y.o. female treated with linezolid 600 mg PO daily for multidrug resistant tuberculosis (MDR-TB) developed painful, bilateral paresthesia in her lower extremities after only 20 days. On exam she had impairment of pain and temperature sensation, mild disturbance of proprioception, diminished vibration at distal toes, and weakness of foot muscles. Reflexes were absent in the legs. Nerve conduction studies demonstrated decreased sensory and motor action potentials in the bilateral lower extremities [134]. Patient

was diagnosed with a small and large fiber neuropathy. Patient fully recovered within 2 months after stopping linezolid.

Linezolid largely induces a small fiber neuropathy by means of mitochondrial impairment in neurons and Schwann cells as demonstrated in *in vivo* and *in vitro* studies [139]. In the *in vivo* model, mice were given clinically relevant doses of linezolid over 4 weeks. At the end of the trial period, the mice exhibited increased reaction time to cold stimulus, prolonged latency time, and reduced amplitudes of sensory nerve action potentials [139]. *In vitro* studies showed increased sensory neuron death and shortening of axons with direct administration of linezolid [139]. In an additional study, linezolid lead to dose-dependent and time-dependent decreases in mitochondrial respiratory enzyme activity in tissues experiencing neuropathic dysfunction. The amount, structure, and sequence of mitochondrial DNA were not significantly altered [140].

Optic neuropathy is another feared side effect of linezolid; however, unlike the peripheral neuritis, it is generally reversible with discontinuation. Linezolid-induced optic neuropathy (LON) is characterized by bilateral, painless, and progressive visual changes; including alterations in visual acuity or color vision, optic disc swelling or pallor, and decreased central vision greater than peripheral vision loss [141, 142]. Optic changes induced by linezolid are consistent with a toxic metabolic neuropathy, which are presumed secondary to mitochondrial dysfunction [141]. The incidence of LON remains unknown, as the largest study to date did not report any vision loss or changes. In a study looking at patients receiving linezolid for MDR-TB, 24/86 reported a minimum of 1 ocular complaint during treatment; blurred vision representing the majority. Five (5.8%) had optic neuropathy based on ophthalmologic testing [142]. In one meta-analysis, optic neuropathy was diagnosed in 13.2% of 121 patients being treated for MDR-TB with linezolid [143]. In an additional meta-analysis, peripheral neuropathy was quite frequent at 31%, while optic neuritis was only noted in 8% patients (sample 246) [144]. Linezolid-induced peripheral neuropathy often precedes LON when occurring in the same patient and tends to persist despite discontinuation of linezolid and resolution of the vision irregularities [141, 142].

Tedizolid appears to have a lower risk of peripheral and optic neuropathy based on current data. In a phase I trial using healthy volunteers, no participants developed peripheral neuropathy; however, the trial was shorter than the average onset of linezolid-induced neuropathy [145]. In an animal model using rats, tedizolid was administered in varying doses over 1–9 months with no peripheral or optic neuropathy noted in the rats at any milestone [146]. In a case report, tedizolid was used for 18 months as suppressive therapy without the development of peripheral or optic neuropathy [147]. In a case series of 24 patients being treated for nontuberculous mycobacterium infections, 21% developed peripheral neuropathy while 0 developed optic neuritis. The median use of tedizolid during this case series was 101 days (range 15–369) [148].

Linezolid and tedizolid are weak reversible inhibitors of monoamine oxidase (MAO) activity *in vitro;* consequently decreasing the metabolism of serotonin. Linezolid is a nonselective inhibitor and therefore affects MAO-A and MAO-B, subsequently increasing serotonin and catecholamines [11]. In combination with

additional serotonin augmenting medications, serotonin syndrome (SS) may develop, albeit rarely. SS is a potentially fatal syndrome characterized by changes in mental status, autonomic hyperactivity, and neuromuscular abnormalities [149, 150]. Linezolid most often contributes to the development of serotonin toxicity when given concomitantly with selective serotonin reuptake inhibitors (SSRIs) [151]. Linezolid-associated SS has only rarely occurred without concurrent SSRIs or MAO inhibitors [152]. SS did not occur in phase III studies of linezolid or tedizolid. Additionally, when tedizolid was given at 30x the human equivalent dose, it was not found to increase head twitching in a murine animal model, suggesting no increase in serotonin [153]. To prevent linezolid-associated SS, recommended provisions include instituting a 14 day washout of any SSRIs/MAOIs prior to starting linezolid, reducing doses of other serotonin modifying drugs, and monitoring patients undergoing concomitant therapy. If SS develops, the medication should be held and supportive measures given [152].

Even more uncommonly, linezolid use may lead to the development of Bell's palsy [154], seizures [155–157], encephalopathy [138], and syndrome of inappropriate antidiuretic hormone (SIADH) [158, 159]. Bell's palsy was noted in a 49 y.o. female that developed facial hemi-paralysis 3 weeks into therapy. Linezolid was not immediately suspected but patient subsequently redeveloped facial paralysis on re-challenge [154]. Underlying mechanism was suspected to be mitochondrial dysfunction. Linezolid-induced seizures mostly occur in patients at increased risk due to history of epilepsy [155–157], In phase II/III trials with tedizolid, no seizures were reported [160]. A case report illustrates early onset encephalopathy following concomitant use of linezolid and hydroxyzine. Onset of encephalopathy was within 1.5 days of starting linezolid. The combination of an antihistamine with anticholinergic effects and linezolid's nonselective MAO inhibition may have potentiated toxicity through disruption of neurotransmitter concentrations [11, 138]. There are at least two reports of SIADH induced by linezolid use. In both cases the patients developed symptomatic hyponatremia shortly after starting linezolid. After its discontinuation, sodium levels normalized and remained stable [158, 159].

Lincosamide

Clindamycin's best-known SE is the detrimental effect it has on the gut microbiome resulting in overgrowth of *Clostridiodes difficile*. There are no well-defined neurologic ADRs linked to clindamycin use, but there have been cases of prolonged periods of NM blockade following inappropriate doses of clindamycin. One example involves a 58 y.o. woman that required ventilator assistance following an intraoperative clindamycin overdose [161]. Patient was unintentionally given 2400 mg instead of the requested 600 mg following the start of surgery. She remained ventilator-dependent for 11 h postoperatively, long after the effects of her anaesthesia/paralytics wore off. It's uncertain if this was a direct effect of clindamycin or a drug interaction with other medications used intraoperatively.

Nitroimidazole

In the short-term, metronidazole is generally well tolerated; however, when used for prolonged periods it can cause central and peripheral nervous system ADRs, including encephalopathy, cerebellar dysfunction, peripheral neuropathy, optic neuritis, seizures, and ototoxicity [162]. Overt psychosis, characterized by restlessness, disorientation, delusions, and/or hallucinations [163], has also been documented with metronidazole use, especially when taken in conjunction with disulfiram [164]. Metronidazole-induced encephalopathy (MIE) is a distinct, stereotypical pattern of encephalopathy specific to metronidazole use. Due to the unique pattern of MIE, metronidazole was classified into its own class of AAE, type 3 [1]. This class is characterized by an onset weeks after commencing the treatment regimen, frequent cerebellar dysfunction, rare seizures, nonspecific EEG findings, and an abnormal but patterned MRI [1]. MIE demonstrates a distinctive collection of abnormalities on MRI, potentially including changes in the cerebellar dentate nuclei, dorsal brainstem, or splenium of the corpus callosum [165]. MRI findings are suggestive of both vasogenic and cytotoxic effects. The exact mechanism of how neurotoxicity develops is not known, however, it is hypothesized that ROS and thiamine metabolism derangements play a role. In *in vitro* studies, metronidazole is transformed into a thiamine analog that impedes thiamine phosphorylation [166].The histopathology of brains from thiamine-deficient rats is similar to changes caused by toxic levels of metronidazole [167]. In humans the MRI findings resemble nonalcoholic Wernicke's encephalopathy. There are likely additional factors at play as the lesions are only similar and not identical, suggestive of underlying pathophysiology differences [1]. An experimental study by Xiao et al. revealed that metronidazole triggers apoptosis of human neuron cells but does so via an unclear ROS-independent pathway [6].

Neurologic SEs of metronidazole were once thought to be dose-dependent, however, there is no direct relationship between dose and symptom onset [162]. In a review of 64 cases of MIE, the average daily dose of metronidazole was 719 mg with ranges from 250 mg to 2000 mg. The average cumulative dosing amount prior to cessation was 93.4 g with a range from 0.25 g to 1095 g [162]. In a larger review (136 cases), cumulative exposure ranged from 5 g to 2000 g [168]. Looking at multiple reviews of MIE, the mean duration of therapy prior to the onset of symptoms ranges from 47.2 to 75 days [162, 168, 169]. Kuriyama et al. found that the majority of MIE cases occurred after at least 1 week of therapy (63%) while a small percentage developed in under 3 days (11%) [162]. One outlier case is of an 83 y.o. woman with dysarthria only 2 days after beginning metronidazole (and ciprofloxacin) for a recurrent liver abscess. Symptoms progressed over 2 weeks to include gait unsteadiness and bilateral lower extremity paresthesia culminating in the inability to stand. Her MRI was consistent with MIE and metronidazole was discontinued. Patient recovered completely within 6 days of cessation [162]. A more classical case of MIE can be seen in a 61 y.o. man with a history of a kidney transplant treated for an abdominal subcutaneous gas-containing fluid collection with metronidazole (plus meropenem later substituted by amikacin) for 11 weeks [169]. The patient developed cerebellar signs and gait instability with frequent falls towards the end of his

treatment. MRI demonstrated archetypal MIE changes. Metronidazole was discontinued and the patient began improving within 24 h.

Liver disease was found to be the leading preexisting comorbidity in patients with MIE in a systematic review by Sorensen et al. [168] Bhattacharyya et al. found a degree of hepatic dysfunction in 14% of MIE cases [1]. The liver partially metabolizes (30–60%) metronidazole; therefore, hepatic dysfunction leads to a prolonged half-life and elevations of serum and CSF concentrations [170]. In 2 review articles, men were predominantly affected with a disproportionate ratio of 2:1 in 1 article [162, 168].

With prompt intervention, patients with MIE have good outcomes with most fully recovering, including full resolution of MRI lesions [162, 168–172]. Degree of recovery is not associated with total dose received by the patients [168]. Contrary to the majority, the death of a 65 y.o. female with hepatitis B cirrhosis was attributed to metronidazole use. Patient was sent home on a 3-week course of ciprofloxacin and metronidazole for spontaneous bacterial peritonitis. Patient returned to the hospital on day 11 with slurred speech, confusion, and disorientation. Mental status further declined. On day 22 of metronidazole her MRI showed MIE and metronidazole was stopped. Despite discontinuation, the patient continued to deteriorate and MRI lesions progressed. Additional causes of encephalopathy were ruled out, and although not definite, it's believed she died from progression of MIE [171]. One additional death and 1 case of persistent vegetative state have been attributed to Metronidazole [168, 171].

Metronidazole can also cause a peripheral neuropathy that may present in conjunction with MIE or independently. When present together, the symptoms tend to develop consecutively, with peripheral neuropathy developing first followed by CNS dysfunction [173]. Patients may experience a variety of sensory symptoms ranging from numbness to pain. Diminished reflexes, weakness, and/or atrophy may accompany the sensory derangements [174]. The mechanisms behind the nerve damage are hypothesized to be the same as those seen in MIE: free radical production during the metabolism of metronidazole [175] and enzymatic conversion of metronidazole into a competing thiamine analog [166]. Additionally, metronidazole and products of degradation can bind directly to RNA resulting in the inhibition of protein synthesis and subsequent damage to axonal nerve fibers [176]. In review of 40 cases of metronidazole-induced peripheral neuropathy, most cases developed when use extended beyond 4 weeks and cumulative exposure was over 42 g [174]. Following discontinuation of metronidazole, outcomes were generally good with partial to complete resolution. Time to resolution was variable and did not correlate to severity of neuropathy or dosing regimen. In the same review, peripheral neuropathy rates varied from 0% to 50% [174] making it difficult to estimate a true incidence. In a study comparing peripheral to central toxicity effects, peripheral neuropathy endured longer and had more residual symptoms [173].

There have been a handful of cases of optic neuritis with metronidazole. Duration of use prior to onset has significant variability (range 7–365 days). A 67 y.o. female developed bilateral visual acuity loss after 8 months of treatment. As the inciting source was unknown at the time of presentation, she was continued on metronidazole for another 2 months resulting in progression of visual disease and worsening

peripheral neuropathy. After cessation of metronidazole, her vision improved significantly [177]. Not all cases of metronidazole-induced optic neuropathy are associated with neither peripheral neuropathy nor are all cases bilateral.

Nitrofurans

Nitrofurantoin's most common SE is headache, followed by dizziness and drowsiness [178]. In a study looking at the safety of long-term urinary tract infection prophylaxis with nitrofurantoin, neurologic SEs were found to be uncommon. Of the 219 participants only 2 felt faint, 3 complained of headache, and 3 were excessively fatigued. After 12 months, just one patient developed paresthesia of the fingertips and the sensation dissipated after discontinuation of nitrofurantoin.

Peripheral neuropathy is a known rare SE of nitrofurantoin. It was noted to occur in 0.0007% of those that used the medication long-term in a study that compared all those that had symptoms to the number of prescriptions written [179]. This particular neuropathy is categorized as a degenerative axonal sensorimotor neuropathy that is primarily sensory disturbance to start followed by motor-predominance [180]. The majority of cases develop after prolonged nitrofurantoin use but there have been reports after recurrent intermittent use [2, 181]. Development of neuropathy is hypothesized to be a result of dose-dependent depletion of glutathione [182]. Women and elderly are more often affected [183, 184]. Patients with predisposing conditions to neuropathy (i.e. diabetes mellitus) or renal failure are also more prone to nitrofurantoin-induced neuropathy [180]; however, there are reports in otherwise healthy individuals [182]. A unique case of nitrofurantoin-induced neuropathy in of a 38 y.o. woman that presented with thigh and chest pain rather than distal neuropathy after taking nitrofurantoin for over 7 years [180]. Her neuropathy progressed to involve her entire body culminating in numbness of her genitalia. Due to a delay in diagnosis and continued use of the nitrofurantoin, her symptoms did not improve until 21 months after cessation. She ultimately partially recovered but had permanent mild neuropathic pain, numbness, and temperature changes in her distal extremities [11, 180]. A case report analysis of over 100 cases of nitrofurantoin-induced polyneuropathy found that 34% fully recovered, 45% partially recovered, 13% failed to improve following discontinuation, and 8% died from unrelated events and could not comment on the status of their neuropathy [181]. Delayed diagnosis and continued use of nitrofurantoin after the onset of neuropathy often leads to poorer outcomes [180].

Antimycobacterials, First-Line Therapy

Medications in all lines of therapy used to treat TB have neurotoxic SEs. Of the classic, first line 4-drug regimen (rifampin, isoniazid, pyrazinamide, and ethambutol), three are associated with neurologic ADRs. Pyrazinamide is the only the only exception in the group.

Isoniazid (INH) and Pyridoxine (Vitamin B_6)

Isoniazid has well documented peripheral and central neurotoxic SEs. INH-induced peripheral neuropathy is one of INH's most common neurotoxic effects with an incidence of 0.2–2% [185]. INH's antagonism of pyridoxine can result in peripheral neuropathy [127, 186] characterized by damage of myelinated and unmyelinated nerve fibers [186]. This axonal injury results most commonly in lower extremity burning, pricking, tingling, and numbness but can develop in all appendages. It also potentially impairs perception of light touch, pain, temperature, and position or manifests as weakness or hyporeflexia. Symptoms of neuropathy tend to surface after at least 6 months of therapy [186–188], but the earliest documented onset is just 2 weeks after initiation [188]. Risk factors for toxicity include old age, malnourishment, pregnancy, "slow acetylation," and comorbid conditions at high risk for peripheral neuropathy (i.e. alcoholics, HIV, etc.) [185, 186, 189, 190]. "Slow acetylators" are individuals with an autosomal recessive state leading to slow acetylation of INH that increases the risk of neurotoxicity because it delays the inactivation of INH and results in increased drug levels [186, 189, 190]. Prophylactic pyridoxine supplementation is recommended in those with known risk factors of peripheral neuropathy [191, 192]; however; neuropathic changes have been noted in individuals without risk factors and require treatment with pyridoxine [185]. For example, an otherwise healthy 45 y.o. female developed sensorimotor polyneuropathy manifesting as muscle weakness and numbness following the initiation of RIPE therapy for a tubercular psoas abscess. Electromyography (EMG) showed severe axonal sensorimotor polyneuropathy with slowed conduction. Patient was started on pyridoxine resulting in slow improvement, but unfortunately, had mild long-lasting sensory peripheral neuropathy extending beyond her course of RIPE [185]. Prophylactic dosages of pyridoxine vary between 10-100 mg daily based on assumed risk [192].

Isoniazid use also has the potential to cause other neuropsychiatric SEs, including insomnia, agitation, headaches, optic neuropathy, and psychosis [2, 186, 189]. Overt psychosis – manifested as disorganized thought, hallucinations, delusions, peculiar behavior – may be precipitated by isoniazid, and is estimated in 1.9% of patients [2, 186]. The timing of psychosis varies but the onset of florid psychosis may be preceded days to weeks in advance by a collection of milder symptoms – anxiety, restlessness, irritability, and/or headache [193, 194]. The mechanism behind INH-induced psychiatric episodes is not well defined, but there are several hypotheses. One suggested pathogenesis is that INH interferes with MAO activity leading to the accumulation of serotonin and catecholamines [2, 195]. Conflicting opinions exist regarding the usefulness of pyridoxine at the onset of psychosis, as psychiatric syndromes have occurred in regimens with [196] and without the use of pyridoxine [195]. Psychosis generally dissipates with the removal of INH alone as seen in a case report of an 84 y.o. man that developed psychosis after initiation of RIPE therapy. After the substitution of INH for another agent, he was successfully continued on anti-tubercular treatment without further cognitive disturbance [197]. According to Bhattacharyya et al., INH does not fit clearly into the categories of AAE; therefore, placed in a category of its own. General characteristics of this

group are: weeks to months to onset, common psychosis, rare seizures, and frequently abnormal EEGs with nonspecific patterns [1].

Cognitive decline without clear psychosis is another SE of INH as demonstrated in a prospective study looking at cognitive patterns of patients receiving 9 months of INH monotherapy. Mild and temporary impairment was documented in 7% of the sample population. Advanced age was a key risk factor [198]. INH-induced pellagra can cause additional cognitive effects, such as dementia and encephalopathy [186], as result of INH's antagonism of pyridoxine and inadequate creation of niacin. The administration of pyridoxine does not guarantee the avoidance of pellagra [199]. Unlike traditional pellagra, niacin deficiency may lead to dementia and/or confusion alone, without the other components of the classic triad – diarrhea or dermatitis. Malnourished or those with strict dietary restrictions are considered high risk [199, 200].

Incorrect dosing of INH, in the acute or chronic setting, may lead to excessive accumulation of the drug [201]. INH overdose generally presents in a typical sequence of events starting with vomiting, dysarthria, and incoordination followed by confusion and mental deterioration, including coma and repetitive grand mal seizures [186, 189]. Sizeable doses of pyridoxine are used to treat INH-induced seizures. Pyridoxine is generally given in comparable doses to the amount of INH consumed [202, 203]; however, if the amount ingested is unknown, then the initial dose of pyridoxine is 5 g given over 5–10 min with repeat dosing as necessary. Diazepam is often given in conjunction with pyridoxine as it has the best results in regards to attenuating seizure activity. HD is an effective treatment of refractory seizures [186]. The epileptogenicity of INH is credited to diminished GABA concentrations and amassing of glutamic acid [204]. Animal models support a disruption of neurotransmitters as a possible nidus for seizures; however, animal studies find a resulting increase in GABA and decrease of glutamate following INH overdose [205–207]. On the surface this appears contrary to the suggested notion that diminished GABA leads to seizures; however, in one particular study, the rats were sacrificed several days after the manifestation of seizures and hind limb paralysis and therefore glutamate may have already been consumed [205]. In additional studies, inhibition and activation of particular enzymes, glutamic acid decarboxylase (GAD) and GABA aminotransferase (GABA-T), appear to play major roles. GAD is responsible for converting glutamic acid into GABA while GABA-T flows in the opposite direction creating glutamate from GABA. In an experiment on chicks by Woods and Peesker, they noted initial inhibition of GAD and GABA-T with the inhibitory effects on GAD more significant early on leading to decreased GABA [206]. The inhibition of GABA-T was prolonged compared to GAD ultimately resulting in decreased glutamate and increased GABA levels. Wood and Peesker found that seizures were not clearly associated with either stage, rather a function of the combined disruptions [206]. A study performed in 1981 found that hydrazine, a metabolite of INH, caused a significant increase in inhibition of GABA-T without affecting GAD [207]. According to the authors, this suggests that the metabolite plays a greater role later in the development of neurotoxicity while INH's effects on pyridoxine make an impact earlier in the process. They also concluded that INH

disturbs cellular energy metabolism leading to disruptive disorders of neurotransmission and cell death culminating in neurotoxicity [207].

Of note, pyridoxine does have the potential to be neurotoxic and create a generally reversible, painful pure sensory neuropathy [182, 186]. When used in small doses along with isoniazid it is protective; however, if taken inappropriately it becomes harmful. In a rare case, pyridoxine use was attributed to a concomitant loss of all deep tendon reflexes [208].

Rifampin/Rifampicin

Rifampin is rarely associated with neurologic SEs, and when it is, they are more commonly due to drug-drug interactions. This is due to rifampin's effect on the metabolism of many drugs through its strong induction of cytochrome P450. The neurotoxic SEs rifampin may cause on its own are mild and include: headache, dizziness, drowsiness, or ataxia [186].

Ethambutol

Neurotoxicity associated with ethambutol can be life altering as it can cause permanent bilateral visual impairment. Ethambutol optic neuropathy (EON) manifests as a painless and progressive loss of central vision. Blurred vision, color changes, or frequent alterations in prescriptions of corrective lenses are all possible patient complaints. Most patients with EON notice symptoms within the first 9 months of therapy, but rarely within the first month. Overall, the incidence of EON is ~1% with some slight variation between countries. Based on findings of multiple studies, this particular SE is likely dose-dependent [186, 209, 210]. Over a 10 year period, a Taiwanese study looked at 4803 patients treated an average dose of 16 mg/kg of ethambutol and found the incidence to be 1.29% [209, 211]. In India a cumulative incidence of EON by all taking ethambutol was 2.25%, with permanent vision loss of 0.43%. Exclusion of patients on doses >27.5 mg/kg/day, decreases the incidence to 1.92% with only 0.23% developing permanent loss [212]. After discontinuation of ethambutol, recovery took an average 3 months. A study of 415 patients on an average ethambutol dose of 14.5 mg/kg/day for treatment of pulmonary MAC found an EON incidence of 0.7%. Analysis including only those patients on <15 mg/kg/day, reduced incidence further to 0.3% [210].

EON risk factors include duration of therapy, age over 65, hypertension, and renal dysfunction [213]. Age and optic atrophy are prognostic indicators. Prior studies showed greater recovery in patients <60 years old. Of 10 patients with severe EON, only 5 improved to some degree and of those 5 patients, only 1 (20%) was >60 [214]. The presence of optic atrophy is another prognostic indicator, with its development suggestive of a poor outcome, especially when early on [209].

Routine vision screening is important before, during, and after ethambutol use. A baseline eye exam that checks visual fields, visual acuity, color vision, and the fundus should always be done before or immediately after initiation of ethambutol [209]. Clinical and subclinical visual changes should prompt immediate discontinuation of ethambutol to prevent progression of visual impairment.

The disease process of EON is still not entirely clear; although Chung et al. may have found a possible explanation related to ethambutol's ability to act as a zinc chelator [215, 216]. They found that ethambutol stimulated vacuole production in cultured retinal cells. Vacuole number is dependent on the concentration of intracellular zinc – absence of free zinc leads to fewer vacuoles, while the presence of zinc increases their production [215]. The vacuoles were actually revealed to be lysosomes full of zinc. The researchers conjectured that the lysosomes are essential for confining and eradicating the mycobacterium. In general the process is beneficial; however, lysosomal excess within the retina likely causes disruption of normal function and results in toxicity [216].

Other Anti-infectives

Antimicrobials other than antibacterials, including antifungals, antiparasitics, antivirals, antimalarials, and antiretrovirals, all have neurologic SEs of their own.

Antifungals

A variety of the different types of antifungals may cause neurotoxic ADRs. Azoles and polyenes are specific classes known to cause neurologic SEs. On the other end of the spectrum, echinocandins cause no known neurotoxic SEs [217].

A meta-analysis of antifungals found that voriconazole use substantially increases the probability of neurotoxicity [218]. Plasma drug levels of voriconazole relate closely to its efficacy and toxicity. Neuropsychiatric SEs, such as confusion, agitation, or hallucination, are more likely to occur at a serum concentration level >5.0–5.5 mg/L. [219, 220] In a study by Dolton et al., CNS toxicity developed in ~10%. Average onset of symptoms was 4 days [219] after initiation while resolution occurred between 2 and 5 days following cessation [220].

In phase II/III trials of posaconazole, dizziness and headache were the only documented neurotoxic SEs. In the <6 month treatment group, 2% reported dizziness while 3% reported headache. For those treated >6 months, 1% reported dizziness and 3% reported headaches. Only 5/428 trial participants dropped from the studies due to CNS-related SEs [221].

Itraconazole may cause headaches and rarely dizziness. Delirium was described in an individual case report involving a 74 y.o. man treated for disseminated histoplasmosis [222]. The patient rapidly recovered to baseline after the itraconazole was

stopped. Delirium resurfaced when the patient was re-challenged with the drug. The delirium is hypothesized to be a result of prostaglandin and cytokine stimulation, ultimately affecting the release of neurotransmitters. An indirect mechanism is suspected because itraconazole does not cross the BBB to cause direct effects of its own [222].

In one study investigating the treatment of severe fungal infections, 2–5% of 232 patients developed headache, dizziness, and seizures following treatment with fluconazole. Delirium and dysesthesia were reported in only 3/232 participants [223]. Generally, the most severe CNS-related SEs tend to occur when doses are >1200 mg/day; at such levels, the SEs may become treatment limiting [224]. Renal dysfunction is a known risk factor for ADRs. In two patients with renal failure, prolonged use resulted in convulsions. Once the dosages were appropriately reduced, the seizures stopped [225].

Polyenes, specifically amphotericin, are known to cause significant ADRs, including neurotoxicity. Amphotericin most commonly results in headaches, but may additionally cause seizures, tremor, weakness, or neuropathy [127]. In an individual case, amphotericin was linked to the sudden onset of dysphoria, suicidal ideation, and altered sensorium [226].

Terbinafine, an allylamine, can lead to several neurologic SEs. Headache was frequently reported and noted in up to 12.9% of 465 participants in clinical trials [227]. Alterations in 4 out of the 5 major taste sensations via an olfactory-independent mechanism was found in 0.6–2.8% based on self-reporting; however, chemosensory disruption is often poorly reported and therefore may be an underestimation [228]. Following the discontinuation of terbinafine, taste recovery may be prolonged; often taking weeks to months to possibly over a year [227]. Risk factors of taste disruption include age > 65 and low body mass [228].

Antiparasitics

Albendazole use may lead to a wide range of neurotoxic ADRs; however, most of the SEs are secondary to the death of the targeted parasite rather than the drug itself. For example, a CNS syndrome, consisting of fever, headaches, nuchal rigidity, and photophobia, may be seen following the treatment of neurocysticercosis [127]. Additional treatment consequences may include hydrocephalus, cerebral edema, and/or intracranial hypertension [229, 230]. Steroids are recommended to help prevent or treat ADRs. Albendazole, on occasion, has also worsened extrapyramidal disorders and increased seizure frequency in those with epilepsy [231]. Another drug in the same class, mebendazole, has mild SEs including headache and dizziness. Although the symptoms occur frequently, they are generally tolerable [127].

Praziquantel is used to treat a number of different types of infections [232] and is usually well tolerated. It generally causes very few severe SEs, but may cause life-threatening complications when treating the acute form of neurocysticercosis or other forms of parasitic parenchymal brain cysts [233]. Praziquantel, similar to

albendazole, results in an inflammatory response secondary to parasite destruction leading to headache, fever, nuchal rigidity, vasculitic stroke, and/or the exacerbation of preexisting neurological deficits [234, 235]. Steroids are again recommended for prevention and treatment of serious intracranial sequelae. Death may occur, but is extremely rare [234]. Other neurologic ADRs include seizures, headache, drowsiness, and dizziness [236–238]. Those with epilepsy or history of seizure are at greater risk of developing seizures during treatment [238]. Dizziness occurs in ~14% of patients when treated with high doses [237]. Headache and drowsiness are generally temporary and improve with eradication of the lesions [127]. In general, symptom severity is usually correlated with degree of parasitic burden [232].

Ivermectin has demonstrated effectiveness with only mild CNS-related ADRs over the course of its many years in use; however, the drug may be implicated in more serious neurological SEs than previously described, specifically when used for indications other than Onchocerciasis. With general use for all indications, there were a total of 16,668 adverse event reports with the most common neurologic SEs being headache and dizziness [239]. When stratified by ADR type, neurological SEs made up 426 reports, of which 156 were considered serious. After excluding cases involving the treatment of *Onchocerca volvulus*, a wide range of neurological SEs was documented, including incoordination, seizure, syncope, confusion, and coma. Improvement followed discontinuation of ivermectin [239]. Drug-drug interactions were believed to be the underlying mechanism for the ADRs. One fatal case revealed elevated doses of ivermectin in brain tissue despite the last dose being given 14 days prior to death [240]. No genetic or iatrogenic factors were found to explain the prolonged elevation of ivermectin concentrations. The authors suggested that a hyperinfection with *Strongyloides* might have been at fault. Chandler goes on to suggest that infectious weakening of the BBB may result in increased drug penetration and therefore greater neurological SEs than reported in the package insert of ivermectin [239]. In a trial involving 109 patients given ivermectin for strongylodiasis, nervous system SEs reported were dizziness (2.8%), vertigo (0.9%), tremor (0.9%), and somnolence (0.9%) [241]. In an additional study looking at healthy volunteers given fixed dosing regimens of ivermectin, headache was the main SE reported, at 6.02% [242]. There are known serious complications when treating *Onchocerca* with a concomitant infection of *Loa loa* with ivermectin. *Loa loa* encephalopathy is a progressive syndrome that starts within 3–5 days of receiving ivermectin with the onset of new neurological deficits that may ultimately progress to coma that lasts for several days. Due to this complication, *Loa loa* should be pretreated prior to starting ivermectin for *Onchocerca* [243]. *Loa loa* encephalopathy appears to be particularly prominent in those with high infectious burden or older in age.

Pyrantel and nitazoxanide are additional antiparasitic medications; both of which have good tolerance and generally cause minor, temporary SEs that do not lead to discontinuation of the drugs. Common SEs of pyrantel include headache, drowsiness, and dizziness [244, 245]. Ototoxicity, optic neuritis, and hallucinations have been reported in individual cases, but no definitive causal link to pyrantel has been established [244]. Pyrantel use is connected to a report of an exacerbation of MG [246]. In an Egyptian study of nitazoxanide, 137 patients were given 500 mg for

6 days with only 3 reported ADRs, none of which were neurologic [247]. In an additional study, 16 volunteers were given 500 mg nitazoxanide for 7 days with no significant difference found between the experimental and placebo groups in terms of SEs. When the dose was increased to 1000 mg, four reported headache [248]. Analysis of >2000 clinical trial participants revealed that >1% experienced temporary dizziness that did not affect compliance to the drug [249].

Antimalarials

A majority of the different types of antimalarials cause significant neuropsychiatric side effects. Mefloquine use is associated with forgetfulness, mood disorders, hallucinations, attention difficulties, and paranoia [13]. In 2013, the US FDA modified its package inset to warn against the potential development of severe, and potentially permanent, neurologic or psychiatric SEs with general use [250]. The previous label only advised caution when prescribing mefloquine in those with preexisting mental health disorders [251]. Vertigo is an extremely common SE, experienced by up to 96% of those taking mefloquine; with ~70% of cases severe enough to require bed rest and additional medications to help mitigate symptoms. Vertigo often takes up to 3 weeks to resolve and may even be permanent [250, 252]. Additional frequent SEs include headache, tinnitus, imbalance, and dizziness [252]. Women tend to have more pronounced ADRs [253]. In multiple head-to-head studies, mefloquine caused significantly more neuropsychiatric SEs when compared to atovaquone plus proguanil [254, 255]; with one study reporting neuropsychiatric SEs in 29% of the mefloquine group compared to 14% in the atovaquone plus proguanil group [254]. Mefloquine caused considerably more CNS-related SEs and sleep disruptions than a quinine-based antimalarial regimen despite both groups reporting similar rates of SEs overall [256]. For those with severe malaria treated with mefloquine, ~4–5% develop postmalaria syndrome; a condition marked by tremor, encephalopathy, and seizures [257]. There are at least two published cases of mefloquine-induced peripheral neuropathy [258]. The vast array of mefloquine-associated CNS SEs are hypothesized to be secondary to a direct effect on the limbic system. Due to mefloquine's lipophilic structure, it is able to directly affect CNS tissue and neurons and may therefore preferentially accumulate in the limbic system and disrupt intercellular interaction [259].

Atovoquone and proguanil may lead to sleep disturbances and abnormal dreams but are often not a harbinger of worse symptoms to come and therefore the medication can often be continued [260].

Malaria-dosed chloroquine is better tolerated than when used for autoimmune disorders; despite this finding, there are still a number of neuropsychiatric SEs linked to the drug at antimalarial dosing. Sleep disturbance and insomnia are commonly reported. Chloroquine may lead to symptoms that resemble a temporary psychotic episode with delusions, derealization, agitation, hallucinations, and even suicidality. Rare reports of catatonia and transient amnesia are also documented

[260]. CNS drug levels influence the development of neuropsychiatric ADRs [127]. Those with epilepsy are at risk of seizures and elderly are at greater risk of developing general neurotoxicity. Chronic use or inappropriately dosed chloroquine in the short term may lead to neuromyopathy [261].

Quinine can provoke a variety of psychiatric SEs, including depression, anxiety, mania, and irritability [260], in addition to causing headache, vertigo, and tinnitus [127]. Acute overdose may result in seizures and coma. A 24 y.o. woman that acutely overdosed, presented with a number of the know ADRs of quinine, including headache, blurry vision, vertigo, tinnitus, hearing loss, disorientation, and incoherent thought, she ultimately progressed to convulsions and coma. Her symptoms resolved with withdrawal of the medication. In severe acute toxicity, dialysis can be beneficial [262]. Serotonin dysregulation is hypothesized as the main underlying mechanism for CNS-related SEs via disruption of tryptophan uptake and metabolism [263].

Despite a track record of being tolerated well, antimalarial medications derived from artemisinin showed mixed results in animal models [264–266]. Tremors, gait abnormalities, ataxia, incoordination, and imbalance – symptoms of brainstem toxicity – were evidenced in numerous such studies. There are also cases of hearing disturbance associated with this class of drugs [266]. Over 30% of patients experience headache and dizziness, common SEs of artemether. Rarely, ataxia, clonus, or sensory impairment results from artemether use [264]. Artesunate's most frequent CNS ADRs are dizziness, headaches, and ringing in the ears. Tinnitus may occur with and without hearing loss. Artesunate, on rare occasion, may lead to peripheral neuropathy or isolated paresthesia [265].

Antivirals

Use of acyclovir, valacyclovir, and ganciclovir may lead to myoclonus, waxing and waning consciousness, tremor, speech difficulties, fatigue, hallucinations, and imbalance [13, 267]. Neuropsychiatric symptoms are most commonly associated with acyclovir, while headaches are associated with all three drugs. Oral acyclovir use leads to headache in 0.6–5.9% of those taking the drug [267]. Acyclovir-induced neurotoxicity of 24 patients helped describe and quantify the frequency of CNS effects. The collection of symptoms, in descending order of percentage of presentation, included: tremor/myoclonus, confusion, agitation, lethargy, hallucinations, extrapyramidal symptoms, clouding of consciousness, dysarthria, and unilateral focal symptoms [268]. Intravenous acyclovir results in more neurotoxicity than oral administration. A major risk factor for acyclovir-induced neurotoxicity is renal dysfunction. Studies have shown that >2/3 of acyclovir-associated neurotoxicity are marked by new or preexisting renal impairment [267]. The half-life of acyclovir drastically lengthens from 3 to 20 h in ESRD, potentially precipitating neurotoxicity if not dosed for [267]. Elderly patients are also at increased risk of developing toxicity [269]. Manifestations of acyclovir-associated neurotoxicity may arise

1–3 days after initiation, correlating with peak serum concentrations [13, 267]; however, it has been seen within hours following a single supratherapeutic dose [13]. Acyclovir alone may precipitate its own neurotoxicity by provoking renal injury. Additionally, valacyclovir is the prodrug to acyclovir, so when converted to acyclovir it may lead to the same problems of nephro- and neurotoxicity [13, 270]. Changes on EEG may be noted from these medications [270]. Removal of acyclovir, valacyclovir, or ganciclovir promotes symptom resolution within 2–7 days [268]. HD expedites clearance and improvement. The accumulation of active metabolites is hypothesized to be the cause of resultant CNS toxicity [269].

Foscarnet is rarely associated with neurotoxic SEs, but may induce headache, seizure, hand cramping, and paresthesia [271, 272]. In early drug trials, muscle twitching was experienced by 14–30% of participants [273]. Foscarnet-associated peripheral neuropathy has been reported in individual cases. For example, a 41 y.o. female developed polyneuritis several months into foscarnet therapy (in addition to renal failure requiring HD); symptom exacerbations corresponded with drug infusions. Clinical exam exhibited reduced sensory perception and absent reflexes. EMG revealed symmetrical neuropathy of all limbs, while biopsy showed axonal and myelin deterioration [271]. Suggested rationale for the development of the patient's polyneuritis was foscarnet interrupted peripheral nerve metabolism leading to myelin destruction, axon degeneration, and vacuole formation in Schwann cells and peripheral nerve histiocytes. Risk factors for neurologic ADRs with foscarnet are renal dysfunction, serum electrolyte abnormalities, or preexisting CNS impairment [272]. Foscarnet should be discontinued at the onset of ADRs if feasible; despite withdrawal, symptoms may persist.

Anti-retrovirals

Memory and attention impairment, executive function disruption, and cognitive processing delay are all known cognitive adverse effects of HIV. Furthermore, opportunistic infections may affect the CNS and result in diminished function or neurologic deficits. Fortunately, consistent use of antiretroviral drugs may delay/prevent neurologic decline associated with HIV as well as diminish the risk of contracting secondary infections; however, some antiretroviral medications cause neuropsychiatric effects of their own.

Nucleoside reverse transcriptase inhibitors (NRTIs) can lead to a symmetrical, distal peripheral neuropathy via mitochondrial toxicity [274]. Motor symptoms are often absent. Risk factors include old age and poorly controlled HIV with CD4 counts below 150 cells/mm^3. When stavudine and didanosine are used together, a mild-to-moderate peripheral neuropathy is experienced in up to 12% within 4 months of starting therapy [275]. Symptoms resolve with removal of the offending agents.

Non-nucleoside reverse transcriptase inhibitors are associated with many psychiatric SEs. Nightmares, hallucinations, irritability, depression, and psychosis are

associated with efavirenz use [275, 276]. Use can reveal undiagnosed mood disorders or other mental health conditions. Efavirenz is also linked to suicidal ideation and behavior; therefore, use is contraindicated in HIV positive patients with comorbid psychiatric disorders. Risk of SEs is increased with elevated serum concentrations [277]. Taking efavirenz with food also increases the risk of toxicity as it boosts plasma levels of the drug. If patients don't have a severe reaction to the drug and can keep with it, ADRs tend to improve after several weeks of therapy [275]. Rilpivirine causes neuropsychiatric SEs such as insomnia, headache, dizziness, and depression [275]. In direct comparison studies, rilpivirine precipitated neuropsychiatric effects less often than efavirenz [278].

The most frequent neurotoxic ADRs of integrase strand transfer inhibitors (INSTI) include headache and insomnia; both of which are not severe enough to discontinue therapy [274]. In early trials of bictegravir, headaches occurred in 2–5% of patients, while insomnia and dizziness occurred in 2% each [279]. Dolutegravir causes insomnia in 3–15% of those taking it [280]. Similar to other INSTIs, raltegravir causes insomnia, headaches, and dizziness ≥2% [281].

The protease inhibitor (PI), tipranavir is no longer used due to its association with serious, potentially fatal complications of intracranial hemorrhage for which a boxed warning is issued [282]. Other PIs may lead to headache or taste disturbance [283]. The entry inhibitor, ibalizumab, most commonly causes dizziness [274]. As like many other antiretrovirals, maraviroc, another entry inhibitor, can cause headache and dizziness [283].

Management

Discontinuation of the responsible medication is the primary remedy for antimicrobial-induced neurotoxicity. Upon cessation of the offending medication, patients typically return to baseline after reversal of the neurotoxic ADR, though some SEs persist, even permanently. The protracted neurotoxic SEs can considerably reduce quality of life and spur further complications. For instance, patients with peripheral neuropathy are subjected to pain and distress, as well as heightened susceptibility to injury or even death.

Attentiveness and thoroughness are compulsory to uncovering the root cause of any changes in cognition, mental status, or neurologic condition. Symptoms should be evaluated in the context of the known SEs of the administered drug to determine whether the drug itself is the culprit. Recall of a medication's common risks or propensities for certain SEs can facilitate determination of the neurotoxic instigator from among the array of possible sources. Medication plasma level tracking can be an additional resource when available.

Use of supportive efforts, such as supplemental symptom-mitigating medications or dialysis may be required. Hemodialysis can actively purge the inciting drug to more rapidly resolve symptoms. Antipsychotics, benzodiazepines, or mood stabilizers may counterbalance the severity of mood disorders or psychiatric syndromes

precipitated by antimicrobials. Antiepileptics may assuage seizures while the provoking drug is still present within the system, though they are rarely needed over prolonged durations.

Prevention is a key component of management. Neurotoxicity may be avoided or lessened by correct dosing, circumventing adverse drug interactions, and using alternate drugs, when possible, if the patient has known risk factors for developing ADRs.

Conclusion

Antimicrobials have great potential to save lives and reduce morbidity, but as with any medication, they have known SEs. The severity of SEs differs between the various drugs and individual patients, but antimicrobials do have the ability to cause pronounced harm. In a physician's best attempt to "do no harm," it is important that physicians are aware of the neurotoxic SEs of antimicrobials and have a level of suspicion of their conceivable role in the development of new neurologic signs and syndromes. By being cognizant of the potential ADRs, physicians can better detect SEs and change treatment accordingly.

References

1. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez LN, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology. 2016;86:963–71.
2. Esposito S, Canevini MP, Principi N. Complications associated with antibiotic administration: neurological adverse events and interference with antiepileptic drugs. Int J Antimicrob Agents. 2017;50(1):1–8. https://doi.org/10.1016/j.ijantimicag.2017.01.027.
3. Gutnick MJ, Prince DA. Penicillinase and the convulsant action of penicillin. Neurology. 1971;21:759–64.
4. Walker AE, Johnson HC, Kollros II. Penicillin convulsions; the convulsive effects of penicillin applied to the cerebral cortex of monkey and man. Surg Gynecol Obstet. 1945;81:692–701.
5. Walker AE, Johnson HC. Principles and practice of penicillin therapy in disease of the nervous system. Ann Surg. 1945;122:1125–35.
6. Xiao Y, Xiong T, Meng X, Yu D, Xiao Z, Song L. Different influences on mitochondrial function, oxidative stress and cytotoxicity of antibiotics on primary human neuron and cell lines. J Mol Toxicol. 2018:e22277. https://doi.org/10.1002/jbt.22277.
7. Schliamser S, Bolander H, Kourtopoulos H, et al. Neurotoxicity of benzylpenicillin: correlation to concentrations in serum, cerebrospinal fluid, and brain tissue fluid in rabbits. J Antimicrob Chemother. 1988;21:365–72.
8. Schliamser S, Bolander H, Broholm KA, et al. Neurotoxicity of benzylpenicillin in experimental renal failure and *Enterobacter cloacae* meningitis. J Antimicrob Chemother. 1989;24:215–25.
9. Schliamser S, Broholm KA, Norrby SR. Comparative neurotoxicity of benzylpenicillin, imipenem/ciliastatin and FCE 22101, a new injectable penem. J Antimicrob Chemother. 1988;22:687–96.
10. Norrby SR. Neurotoxicity of carbapenem antibacterials. Drug Saf. 1996;2:87–90.

11. Mattappalil A, Mergenhagen KA. Neurotoxicity with antimicrobials in the elderly: a review. Clin Ther. 2014;36(11):1489–511. https://doi.org/10.1016/j.clinthera.2014.09.020.
12. Ye RH, Lin MY, Sung CC, Lin SH. Standard dose of piperacillin induced neurotoxicity in advanced renal failure. Acta Nephrologica. 2011;25(2):89–92.
13. Warstler A, Bean J. Antimicrobial-induced cognitive side effects. Mental Health Clin (online). 2016;6(4):207–14. https://doi.org/10.9740/mhc.2016.07.207.
14. Huang WT, Hsu YJ, Chu PL, Lin SH. Neurotoxicity associated with standard doses of piperacillin in an elderly patient with renal failure. Infection. 2009;37(4):374–6. https://doi.org/10.1007/s15010-009-8373-3.
15. File TM, Wilcox MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. Clin Infect Dis. 2012;55(33):173–S180. https://doi.org/10.1093/cid/cis559.
16. Rank DR, Friedland HD, Laudano JB. Integrated safety summary of FOCUS 1 and FOCUS 2 trials: Phase III randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with community-acquired pneumonia. J Antimicrob Chemother. 2011;66(3):iii53–9. https://doi.org/10.1093/jac/dkr099.
17. Corrado ML. Integrated safety summary of CANVAS 1 and 2 trials: Phase III, randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother. 2010;65(4):iv67–71. https://doi.org/10.1093/jac/dkq256.
18. Sorbera M, Chung E, Ho CW, Marzella N. Ceftolozane/Tazobactam: a new option in the treatment of complicated gram-negative infections. Pharm Ther. 2014;39(12):825–32.
19. Noel GJ. Clinical profile of ceftobiprole, a novel beta lactam antibiotic. Clin Microbiol Infect. 2007;13(2):25–9. https://doi.org/10.1111/j.1469-0691.2007.01725.x.
20. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol. 2011;72(3):381–93. https://doi.org/10.1111/j.1365-2125.2011.03991.x.
21. Lacroix C, Kheloufi F, Montastruc F, Bennis Y, Pizzoglio V, Micallef J. Serious central nervous system side effects of cephalosporins: A national analysis of serious reports registered in the French Pharmacovigilance Database. J Neurol Sci. 2019; in press. https://doi.org/10.1016/j.jns.2019.01.018.
22. Grahl JJ, Stollings JL, Rakhit S, Person AK, Wang L, Thompson JL, Pandharipande PP, Ely EW, Patel MB. Antimicrobial exposure and the risk of delirium in critically ill patients. Crit Care. 2018;22:337. https://doi.org/10.1186/s13054-018-2262-z.
23. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306–16.
24. Salluh JL, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systemic review and meta-analysis. BMJ. 2015;350:h2538.
25. Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21:276. https://doi.org/10.1186/s13054-017-1856-1.
26. Neu HC. Safety of cefepime: a new extended-spectrum parenteral cephalosporin. Am J Med. 1996;100:S68–75.
27. Debysenko L, Nicolson SE. Cefoxitin and ciprofloxacin neurotoxicity and catatonia in a patient on HD. Psychosomatics. 2011;52(4):379–83.
28. Dakdouki GK, Al-Awar GN. Letter to the Editor: cefepime-induced encephalopathy. Int J Infect Dis. 2004;8:59–61. https://doi.org/10.1016/j.ijid.2003.09.003.
29. Abanades S, Nolla J, Rodriguez-Campello A, Pedro C, Valls A, Farré M. Reversible coma secondary to cefepime neurotoxicity. Ann Pharmacother. 2004;38:606–8. https://doi.org/10.1345/aph.1D322.
30. Hsuan H, Yun-Chung C, Yi-Hsin L. Ceftriaxone-induced non-convulsive status epilepticus in an elderly patient with renal insufficiency. Int J Gerontol. 2018; in press. https://doi.org/10.1016/j.ijge.2018.03.016.

31. Anzelloti F, Ricciardi L, Monaco D, Ciccocioppo F, Borelli I, Zhuzhuni H, Onofrj M. Cefixime-induced nonconvulsive status epilepticus. Neurol Sci. 2012;33:325–9.
32. Tanaka A, Takechi K, Watanabe S, Tanaka M, Suemaru K, Araki H. Comparison of the prevalence of convulsions associated with the use of cefepime and meropenem. Int J Clin Pharm. 2013;35:683–7. https://doi.org/10.1007/s11096-013-9799-3.
33. Calandra GB, Wang C, Aziz M, et al. The safety profile of imipenem/ciliastatin: worldwide clinical experience based on 3470 patients. J Antimicrob Chemother. 1986;18 Suppl E:193–203.
34. Cunha BA. Meropenem in eldery and renally impaired patients. Int J Antimicrob Agents. 1999;11:167–77.
35. Pestotnik SL, Classen DC, Evans RS, et al. Prospective surveillance of imipenem/cilastatin use and associated seizures using a hospital information system. Ann Pharmacother. 1993;27:497–501.
36. Hoffman J, Trimble J, Brophy GM. Safety of imipenem/cilastatin in neurocritical care patients. Neurocrit Care. 2009;10:403–7. https://doi.org/10.1007/s12028-008-9170-z.
37. Rodloff AC, Goldstein EJ, Torres A. Two decades of imipenem therapy. J Antimicrob Chemother. 2006;58(5):916–29.
38. Sunbagawa M, Matsumura H, Sumita Y, et al. Structural features resulting in convulsive activity of carbapenem compounds: effect of C-2 side chain. J Antimicrob Chemother. 1995;45:408–16.
39. Norrby SW, Newell PA, Faulkner KL, et al. Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. J Antimicrob Chemother. 1995;36 suppl A:207–23.
40. Snavely SR, Hodges GR. The neurotoxicity of antibacterial agents. Ann Intern Med. 1984;101:92–104.
41. Zhanel GG, Ketter N, Rubinstein E, Friedland I, Redman R. Overview of seizure-inducing potential of doripenem. Drug Saf. 2009;32(9):709–16.
42. Seto AH, Song JC, Guest SS. Ertapenem-associated seziures in a peritoneal dialysis patient. Ann Pharmacother. 2005;39:352–6.
43. Hanna RM, Sun S, Gaynor P. A case of Ertapenem neurotoxicity resulting in vocal tremor and altered mentation in a dialysis dependent liver transplant patient. Antibiotics. 2019;8:1. https://doi.org/10.3390/antibiotics8010001.
44. Apodaca K, Baker BA, Bin-Bilal H, Raskin Y, Quinn D. Ertapenem-induced delirium: a case report and literature review. Psychosomatics. 2015;56:561–6.
45. Duquaine S, Kitchell E, Tate T, Rannen RC, Wickremasinghe IM. Central nervous system toxicity associated with ertapenem use. Ann Pharmacother. 2011;45:e6. https://doi.org/10.1354/aph.1P528.
46. Patel UC, Fowler MA. Ertapenem-associated neurotoxicity in the spinal cord injury (SCI) population: a case series. J Spinal Cord Med. 2018;41:1. https://doi.org/10.1080/10790268.2017.1368960.
47. Oo Y, Packham D, Yau W, Munckhof WJ. Ertapenem-associated psychosis and encephalopathy. Intern Med J. 2014. https://doi.org/10.1111/imj.12504.
48. O'Riordan J, Javed M, Doherty C, Hutchinson M. Worsening of myasthenia gravis on treatment with imipenem/cilastatin. J Neurol Neurosurg Psychiatry. 1994;57:383.
49. Alván G, Nord CE. Adverse effects of monobactams and carbapenems. Drug Saf. 1995;12(5):305–13.
50. Bhattacharyya S, Darby R, Berkowitz AL. Antibiotic-induced neurotoxicity. Curr Infect Dis Rep. 2014;16:448.
51. Munoz-Gomez S, Gran A, Cunha BA. Meropenem delirium: a previously unrecognized neurologic side effect. J Chemother. 2015;27(2):120–1. https://doi.org/10.1179/1973947814Y.0000000179.
52. Ninan J, George GM. Imipenem-cilastatin-induced psychosis: a case report. J Med Case Rep. 2016;10:107. https://doi.org/10.1186/s13256-016-0883-x.

53. Prime K, French P. Neuropsychiatric reaction induced by clarithromycin in a patient on highly active antiretroviral therapy (HAART). Sex Transm Infect. 2001;77(4):297. https://doi.org/10.1136/sti.77.4.297.
54. Abouesh A, Stone C, Hobbs W. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. J Clin Psychopharmacol. 2002;22(1):71–81.
55. Nightingale SD, Koster FT, Mertz GJ, Loss SD. Clarithromycin-induced mania in two patients with AIDS. Clin Infect Dis. 1995;20(6):1563–4.
56. Bandettini di Poggio M, Anfosso S, Audenino D, Primavera A. Clarithromycin-induced neurotoxicity in adults. J Clin Neurosci. 2011;18:313–8. https://doi.org/10.1016/j.jocn.2010.08.014.
57. Rubinstein E. Comparative safety of the different macrolides. Int J Antimicrob Agents. 2001;18(suppl 1):71–6. https://doi.org/10.1016/S0924-8579(01)00397-1.
58. Guay DR, Patterson DR, Seipman N, Craft JC. Overview of the tolerability profile of clarithromycin in preclinical trials. Drug Saf. 1993;8(5):350–64.
59. Manev H, Favaron M, Candeo P, Fadda E, et al. Macrolide antibiotics protect neurons in culture against the N-methyl-D-aspartate (NMDA) receptor-mediated toxicity of glutamate. Brain Res. 1993;624(1–2):331–5. https://doi.org/10.1016/006-8993(93)90098-8.
60. Umstead GS, Neumann KH. Erythromycin ototoxicity and acute psychotic reaction in cancer patients with hepatic dysfunction. Arch Intern Med. 1986;146:897–9.
61. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med. 1991;91:405–55.
62. Tseng AL, Dolovich L, Salit IE. Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. Clin Infect Dis. 1997;24:76–7. https://doi.org/10.1093/clinids/24.1.76.
63. Wallace MR, Miller LK, Nguyen MT, Shields AR. Ototoxicity with azithromycin. Lancet. 1994;343:241.
64. Juel VC. Myasthenia gravis: management of myasthenic crisis and perioperative care. Semin Neurol. 2004;24(1):75–81. https://doi.org/10.1055/s-2004-829595.
65. Pascuzzi RM. Medications and myasthenia gravis. Indianapolis: Myasthenia Gravis Foundation; 2007.
66. Perrot X, Bernard N, Vial C, Antoine JC, et al. Myasthenia gravis exacerbation or unmasking associated with telithromycin treatment. Neurologija. 2006;67(12):2256–8. https://doi.org/10.1212/01.wnl.0000247741.72466.8c.
67. FDA. Telithromycin FDA safety alert: contraindication in myasthenia gravis. Clin-Alert. 2007;45(4):1–8.
68. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):466–88.
69. Stahlmann R, Lode H. Toxicity of quinolones. Drugs. 1999;58(suppl 2):37–42. https://doi.org/10.2165/00003495-199958002-00007.
70. FDA. Drug safety communication. Food and Drug Administration. 2013. Online: www.fda.gov.
71. Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: a pharmacoepidemiologic study. Neurology. 2014;83:1261–3.
72. Doussau de Bazignan A, Thiessard F, Miremont-Salamé G, Conri C, Haramburu F. Psychiatric adverse effects of fluoroquinolones: review of cases from the French pharmacologic surveillance database. Rev Med Interne. 2006;27(6):448–52.
73. Lambrichts S, Van Oudenhove L, Sienaert P. Antibiotics and mania: a systematic review. J Affect Disord. 2017;219:149–56. https://doi.org/10.1016/j.jad.2017.05.029.
74. Samyde J, Petit P, Hillaire-Buys D, Faillie JL. Quinolone antibiotics and suicidal behavior: analysis of the World Health Organization's adverse drug reactions database and discussion of potential mechanisms. Psychopharmacology. 2016;233:2503–11. https://doi.org/10.1007/s00213-016-4300-3.
75. Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation. Drug Saf. 2011;34(10):839–47. https://doi.org/10.2165/11593110-000000000-00000.

76. Sieb JP. Fluoroquinolone antibiotics block NM transmission. Neurologija. 1998;50(3):804–7. https://doi.org/10.1212/WNL.50.2.804.
77. Ilgin S, Can OD, Atil O, Ucel UI, Sener E, Guven I. Ciprofloxacin-induced neurotoxicity: evaluation of possible underlying mechanisms. Toxicol Mech Methods. 2015;25(5):374–81.
78. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. Ann Pharmacother. 1996;30(2):138–41. https://doi.org/10.1177/106002809603000205.
79. Golomb BA, Koslik HJ, Redd AJ. Fluoroquinolone-induced serious, persistent, multisystem adverse effects. BMJ Case Rep. 2015. https://doi.org/10.1136/bcr-2015-209821.
80. Lerner SA, Schmitt BA, Seligsohn R, Matz GJ. Comparative study of ototoxicity and nephrotoxicity in patients randomly assigned to treatment with amikacin or gentamicin. Am J Med. 1986;80(6):98–104. https://doi.org/10.1016/0002-9343(86)90486-9.
81. Lanvers-Kaminsky C, Ciarimboli G. Pharmacogenetics of drug-induced ototoxicity caused by aminoglycosides and cisplatin. Pharmacogenomics. 2017;18(18):1683–95. https://doi.org/10.2217/pgs-2017-0125.
82. Fee WE. Aminoglycoside ototoxicity in the human. Laryngoscope. 1980;90(S24):1–19. https://doi.org/10.1288/00005537-198010001-00001.
83. Duggal P, Sarkar M. Audiologic monitoring of multidrug resistant tuberculosis patients on aminoglycoside treatment with long term follow up. BMC Ear Nose Throat Disord. 2007;7:5. https://doi.org/10.1186/1472-6815-7-5.
84. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989;33(6):797–800.
85. Watling SM, Dasta JF. Aminoglycoside dosing considerations in intensive care unit patients. Ann Pharmacother. 1993;27(3):351–6. https://doi.org/10.1177/106002809302700319.
86. Rybak L. Ototoxicity. Curr Opin Otolaryngol Head Neck Surg. 1996;4:302–7.
87. Guthrie OW. Aminoglycoside induced ototoxicity. Toxicology. 2008;249:91–6. https://doi.org/10.1016/j.tox.2008.04.015.
88. Gao Z, Chen Y, Guan M. Mitochondrial DNA mutations associated with aminoglycoside induced ototoxicity. J Otolaryngol. 2017;12(1):1–8. https://doi.org/10.1016/j-joto.2017.02.001.
89. Paradelis AG, Triantaphyllidis C, Giala MM. NM blocking activity of aminoglycoside antibiotics. Meth Find Exp Clin Pharmacol. 1980;2(1):45–51. https://doi.org/10.1007/978-1-4684-3123-0_51.
90. Bischoff A, Meier C, Roth F. Gentamicin neurotoxicity (polyneuropathy-encephalopathy). Schweiz Med Wochenschr. 1977;107:3–8.
91. Watanabe I, Hodges GR, Dworzack DL, Kepes JJ, Duencsing GF. Neurotoxicity of intrathecal gentamicin: a case report and experiemental study. Ann Neurol. 1978;4:564–72.
92. Hoeprich PD. The polymyxins. Med Clin North Am. 1970;54:1257–65.
93. John JF, Falci DR, Rigatto MH, Oliveira RD, Kremer TG, Zavascki AP. Severe infusion-related adverse events and renal failure in patients receiving high-dose IV polymyxin B. Antimicrob Agents Chemother. 2018;62(1). https://doi.org/10.1128/AAC.01617-17.
94. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care. 2006;10(1):R27. https://doi.org/10.1186/cc3995.
95. Thomas RJ. Neurotoxicity of antibacterial therapy. South Med J. 2001;87:869–74.
96. Kesler A, Goldhammer Y, Hadayer A, Pianka P. The outcome of pseudo tumor cerebri induced by tetracycline therapy. Acta Neurol Scand. 2004;110:408–11.
97. NINDS investigators. A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. Clin Neuropharmacol. 2008;31:141–50.
98. Atigari OV, Hogan C, Healy D. Doxycycline and suicidality. BMJ Case Rep. 2014. https://doi.org/10.1136/bcr-2013200723.
99. Wang DD, Englot DJ, Garcia PA, Lawton MT, Young WL. Minocycline and tetracycline-class antibiotics are protective against partial seizures in vivo. Epilepsy Behav. 2012;24(3):314–8. https://doi.org/10.1016/j.yebeh.2012.03.035.

100. Liu Z, Fan Y, Won SJ, Neumann M, Hu D, Zhou L, Weinstein PR, Liu J. Chronic treatment with minocycline preserves adult new neurons and reduces functional impairment after focal cerebral ischemia. Stroke. 2007;38:146–52.
101. Padma SMV, Bhasin A, Bhatia R, Garg A, Gaikwad S, Prasad K, Singh MB, Tripathi M. Efficacy of minocycline in acute ischemic stroke: A single-blinded, placebo-controlled trial. Neurol India. 2012;60:23–8.
102. Greer ND. Tigecycline (Tygacil): the first in the glycylcycline class of antibiotics. Proc (Baylor Univ Med Cent). 2006;19(2):155–61.
103. Zheng X, Jiang H, Xue L, Qiu F, Zhu S, Li X. Delirium induced by tigecycline treatment for Acinetobacter baumannii infection. Medicine (Baltimore). 2019;98(19):e15399. https://doi.org/10.1097/MD.0000000000015399.
104. Walker LE, Thomas S, McBride C, Howse M, Turtle LCW, et al. 'Septrin psychosis' among renal transplant patients with *Pneumocystis jirovecii* pneumonia. J Antimicrob Chemother. 2011;66:1117–9. https://doi.org/10.1093/jac/dkr050.
105. Parashar S, Roy N, Osuagwa FC, Khalid Z, Tinklepaugh M, Mehr S, Dillon JE. Trimethoprim-sulfamethoxazole-induced psychosis culminating in catastrophic self-injury: a case report. Prim Care Companion CNS Disord. 2016;18(1). https://doi.org/10.4088/PCC.15I01828.
106. Saidinejad M, Burns Ewald M, Shannon MW. Transient psychosis in an immune-competent patient after oral trimethoprim-sulfamethoxazole administration. Pediatrics. 2005;115(6):e239–741. https://doi.org/10.1542/peds.2004-1352.
107. Weis S, Karagülle D, Kornhuber J, Bayerlein K. Cotrimoxazole-induced psychosis: a case report and review of literature. Pharmacopsychiatry. 2006;39:236–7. https://doi.org/10.1055/s-2006-950393.
108. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. Am J Med. 1991;90:528–9.
109. Lee KY, Huang CH, Tang HJ, Yang CJ, et al. Acute psychosis related to use of trimethoprim/sulfamethoxazole in the treatment of HIV-infected patients with *Pneumocystis jirovecii* pneumonia: a multicenter, retrospective study. J Antimicrob Chemother. 2012;67:2749–54. https://doi.org/10.1093/jac/dks283.
110. Lu YM, Lee YT, Chang HC, Yang HS, et al. Combination of Echinocandins and trimethoprim/sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia after heart transplantation. Transplant Proc. 2017;49:1893–8. https://doi.org/10.1016/j.transproceed.2017.04.020.
111. Hsiao HH, Chu NS, Tsai YF, Chang CS, Lin SF, Liu TC. Trimethoprim/sulfamethoxazole-related acute pscyosis in the second course of treatment after a stem cell transplant: case report and literature review. Exp Clin Transplant. 2013;5:467–8. https://doi.org/10.6002/ect.2013.0119.
112. Brummett RE. Ototoxicity of vancomycin and analouges. Otolaryngol Clin N Am. 1993;26:821–8.
113. Bruniera FR, Ferreira FM, Saviolli LRM, Bacci MR, Feder D, et al. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci. 2015;19:694–700.
114. Gupta A, Biyani M, Khaira A. Vancomycin nephrotoxicity: myths and facts. Neth J Med. 2011;69(9):379–83.
115. TOXNET. United States National Library of Medicine. American Society of Health System Pharmacists; AHFS Drug Information; 2009. http://toxnet.nlm.nih.gov.
116. Klibanov OM, Filicko JE, DeSimone JA, Tice DS. Sensorineural hearing loss associated with intrathecal vancomycin. Ann Pharmacother. 2003;37:61–5.
117. Forouzesh A, Moise PA, Sakoulas G. Vancomycin ototoxicity: a reevaluation in an era of increasing doses. Antimicrob Agents Chemother. 2009;53(2):483–6. https://doi.org/10.1128/AAC.01088-08.
118. Mellor JA, Kingdom J, Cafferkey M, Keane CT. Vancomycin toxicity: a prospective study. J Antimicrob Chemother. 1985;15:773–80.
119. Davey PG, Williams AH. A review of the safety profile of teicoplanin. J Antimicrob Chemother. 1991;27:69–73.

120. Brummett RE, Fox KE, Warchol M, Himes D. Absence of ototoxicity of teichomycin A2 in guinea pigs. Antimicrob Agents Chemother. 1987;31:612–3.
121. Maher ER, Hollman A, Grüneberg RN. Teicoplanin-induced ototoxicity in Down's syndrome. Lancet. 1986;327(8481):613.
122. Bonnet RM, Mattie H, Laat JA, Schoemaker HC, Frijns JH. Clinical ototoxicity of teicoplanin. Ann Otol Rhinol Laryngol. 2004;113:310–2.
123. Chen AY, Zervos MJ. Vazquez. Dalbavancin: a novel antimicrobial. Int J Clin Pract. 2007;61(5):853–63.
124. Dunne MW, Talbot GH, Boucher HW, Wilcox M, Puttagunta S. Safety of dalbavancin in the treatment of skin and skin structure infections: a pooled analysis of randomized, comparative studies. Drug Saf. 2016;39:147–57. https://doi.org/10.1007/s40264-015-0374-9.
125. Zhanel GG, Calic D, Schweizer F, Zelenitsky S, Adam H, Lagacé-Wiens PRS, Rubinstein E, Gin AS, Hoban DJ, Karlowsky JA. New lipoglycopeptides. Drugs. 2010;70(7):859–86.
126. Cubist Pharmaceuticals. Cubicin (daptomycin for injection) for IV use [package insert]. 2014.
127. Aronson JK. Meylers side effects of drugs. Philadelphia; Elsevier Science. 2016. p. e16.
128. Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006;355:653–65.
129. Stein GE. Safety of newer parenteral antibiotics. Clin Infect Dis. 2005;41:S293–302.
130. Chen R, Shen K, Chang X, Tanaka T, Li L, Hu P. Pharmacokinetics and safety of tedizolid after single and multiple IV/oral sequential administrations in healthy Chinese subjects. Clin Ther. 2016;38(8):1869–79. https://doi.org/10.1016/j.clinthera.2016.06.014.
131. Shorr AF, Lodise TP, Corey GR, De Anda C, et al. Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. Antimicrob Agents Chemother. 2015;59:864–71. https://doi.org/10.1128/AAC03688-14.
132. Chao CC, Sun HY, Chang YC, Hsieh ST. Painful neuropathy with skin denervation after prolonged use of linezolid. J Neurol Neurosurg Psychiatry. 2008;79:97–9. https://doi.org/10.1136/jnnp.2007.127910.
133. Zivkovic SA, Lacomis D. Severe sensory neuropathy associated with long-term linezolid use. Neurologija. 2005;64(5):926–7. https://doi.org/10.1212/01.WNL.0000152883.53691.5B.
134. Vishnu VY, Modi M, Goyal MK, Lal V. Linezolid induced reversible peripheral neuropathy. Am J Ther. 2016;23:e1839–41.
135. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. Lancet. 2004;4:528–31.
136. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, et al. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin Infect Dis. 2003;36(2):159–68.
137. Vasquez JA, Arnold AC, Swanson RN, Biswas P, Bassetti M. Safety of long-term use of linezolid: results of an open-label study. Ther Clin Risk Manag. 2016;12:1347–54. https://doi.org/10.2147/TCRM.S109444.
138. Fletcher J, Aykroyd LE, Feucht EC, Curtis JM. Early onset probable linezolid-induced encephalopathy. J Neurol. 2010;257:433–5. https://doi.org/10.1007/s00415-009-5340-y.
139. Bobylev I, Maru H, Joshi AR, Lehmann HC. Toxicity to sensory neurons and Schwann cells in experimental linezolid-induced peripheral neuropathy. J Antimicrob Chemother. 2016;71:685–91. https://doi.org/10.1093/jac/dkv386.
140. De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. CID. 2006;42:1111–7.
141. Rucker JC, Hamilton SR, Bardenstein D, Isada CM, Lee MS. Linezolid-associated toxic optic neuropathy. Neurologija. 2006;66:595–8.
142. Mehta S, Das M, Laxmeshwar C, Jonckheere S, Thi SS, Isaakidis P. Linezolid-associated optic neuropathy in drug-resistant tuberculosis patients in Mumbai, India. PLoS One. 2016;11(9):e0162138. https://doi.org/10.1371/journal.pone.0162138.
143. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar JW, Anger HA, Caminero JA, et al. Efficacy, safety, and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB:

systematic review and meta-analysis. Eur Respir J. 2012;40(6):1430–42. https://doi.org/10.1183/09031936.00022912.
144. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, Liu Y. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015;7(4):603–15. https://doi.org/10.3978/j.issn.2072-1439.2015.03.10.
145. Zhanel GG, Love R, Adam H, Golden A, Zelenitsky S, et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. Drugs. 2015;75(3):253–70. https://doi.org/10.1007/s40265-015-0352-7.
146. Schlosser MJ, Hosako H, Radovsky A, Butt MT, et al. Lack of neuropathological changes in rats administered tedizolid phosphate for nine months. Antimicrob Agents Chemother. 2015;59(1):475–81. https://doi.org/10.1128/AAC.03950-14.
147. Nigo M, Luce AM, Aria CA. Long-term use of Tedizolid as suppressive therapy for recurrent methicillin-resistant *Staphylococcus aureus* graft infection. Clin Infect Dis. 2018;66(12):1975–6. https://doi.org/10.1093/cid/ciy041.
148. Kim T, Wills A, Makus A, Prevots DR, Olivier KN. Safety and tolerability of long term use of tedizolid for treatment of nontuberculous mycobacterial infections. Open Forum Infect Dis. 2016;3:577
149. Bergeron L, Boulé M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. Ann Pharmacother. 2005;39:956–61. https://doi.org/10.1345/aph.1E523.
150. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. CID. 2006;43:180–7.
151. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. CID. 2006;42:1578–83.
152. Sutton J, Stroup J, Som M. Linezolid-induced serotonin toxicity in a patient not taking monoamine oxidase inhibitors or serotonin receptor antagonists. Proc (Baylor Univ Med Cent). 2016;29(2):214–5.
153. Flanagan S, Bartizal K, Minassian SL, Fang E, Prokocimer P. In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. Antimicrob Agents Chemother. 2013;57(7):3060–6. https://doi.org/10.1128/AAC.00431-13.
154. Thai XC, Bruno-Murtha LA. Bell's palsy associated with linezolid therapy: case report and review of neuropathic adverse events. Pharmacotherapy. 2006;26(8):1183–9.
155. Cholongitas E, Karatzi C, Spyrou S, Georgousaki C, Dasenaki M. Linezolid-induced complex partial seizures in a patient with epilepsy. Scand J Infect Dis. 2009;41:540–1. https://doi.org/10.1080/00365540902896087.
156. Balkan II, Delil S, Karabacak ER, Yemisen M, Ozaras R, Yeni N. Linezolid-induced complex partial seizure in a patient without epilepsy. Int J Infect Dis. 2015;35:120. https://doi.org/10.1016/j.ijid.2015.05.007.
157. Shneker BF, Baylin PD, Nakhla ME. Linezolid inducing complex partial status epilepticus in a patient with epilepsy. Neurologija. 2009;72:378–9.
158. Loannou P, Stavroulaki M, Mavrikaki V, Papakitsou I, Panagiotakis S. A case of severe hyponatremia due to linezolid-induced SIADH. J Clin Pharm Ther. 2018;43:434–6. https://doi.org/10.1111/jcpt.12681.
159. Baik SH, Choi YK, Kim HS, Yoon YK, Sohn JW, Kim MJ. A probable case of syndrome of inappropriate antidiuretic hormone secretion associated with linezolid. Am J Health Syst Pharm. 2015;72:1865–9. https://doi.org/10.2146/ajhp150208.
160. Mishra S. Tedizolid. FDA: Center for drug evaluation and research. 2014.
161. Al Ahdal O, Bevan DR. Clindamycin-induced NM blockade. Can J Anaesth. 1995;42(7):614–7.
162. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. Clin Neuropharmacol. 2011;34(6):241–7.
163. Mahl TC, Ummadi S. Metronidazole and mental confusion. J Clin Gastroenterol. 2003;36:373–4.

164. Luykx JJ, Vis R, Tijdink JK, Dirckx M, Van Hecke J, Vinkers C. Psychotic symptoms after combined metronidazole-disulfiram use. J Clin Psychopharmacol. 2013;33:136–7.
165. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. MR imaging of metronidazole-induced encephalopathy: lesion distribution and diffusion-weighted imaging findings. AJNR Am J Neuroradiol. 2007;28:1652–8.
166. Alston TA, Abeles RH. Enzymatic conversion of the antibiotic metronidazole to an analog of thiamine. Arch Biochem Biophys. 1987;257:357–62.
167. Von Rogulia P, Kovac W, Schmid H. Metronidazole encephalopathy in rats. Acta Neuropathol. 1973;25:36–45.
168. Sørensen CG, Karlsson WK, Amin FM, Lindelof M. Metronidazole-induced encephalopathy: a systematic review. J Neurol. 2018. https://doi.org/10.1007/s00415-018-9147-6.
169. Graves TD, Condon M, Loucaidou M, Perry R. Reversible metronidazole-induced cerebellar toxicity in a multiple transplant patient. J Neurol Sci. 2009:238–240. https://doi.org/10.1016/j.jns.2009.06.011.
170. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet. 1999;36:353–73.
171. Hobbs K, Stern-Nezer S, Buckwalter MS, Fischbein N, Caulfield AF. Metronidazole-induced encephalopathy: not always a reversible situation. Neurocrit Care. 2015;22:429–36. https://doi.org/10.1007/s12028-014-0102-9.
172. Mizuta K, Sohohata M, Nozaki O, Kobatake T, Nakayama D, Morimoto T, Mawatari M. Metronidazole-induced encephalopathy in a patient with pyogenic spondylitis: a case report. BMC Musculoskelet Disord. 2018;19(336). https://doi.org/10.1186/s12891-018-2255-8.
173. Cação G, Fontes S, Salgado M, Rodrigues T, Damásio J. Metronidazole-induced central and peripheral nervous system toxicity. Neurol Sci. 2015;36:1737–9. https://doi.org/10.1007/s10072-015-2260-8.
174. Goolsby TA, Jakeman B, Gaynes R. Clinical relevance of metronidazole and peripheral neuropathy: a systematic review of the literature. Int J Antimicrob Agents. 2018;51:319–25. https://doi.org/10.1016/j.ijantimicag.2017.08.033.
175. Rao DN, Mason RP. Generation of nitro radical anions of some 5-nitrofurans, 2- and 5-nitroimidazoles by norepinephrine, dopamine, and serotonin. A possible mechanism for neurotoxicity caused by nitroheterocyclic drugs. J Biol Chem. 1987;262:11731–6.
176. Bradley WG, Karlsson IJ, Jassol CG. Metronidazole neuropathy. BMJ. 1977;2:610–1.
177. McGrath NM, Kent-Smith B, Sharp DM. Reversible optic neuropathy due to metronidazole. Clin Exp Ophthalmol. 2007;35:585–6.
178. Brumfitt W, Hamilton-Miller JMT. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. J Antimicrob Chemother. 1998;24:363–71.
179. D'Arcy PF. Nitrofurantoin. Drug Intell Clin Pharm. 1985;19:540–7.
180. Rajabally YA. Neuropathies in the older patient. Rev Clin Gerontol. 2006;16:113–24.
181. Toole JF, Parrish ML. Nitrofurantoin polyneuropathy. Neurology. 1973;23:554–9.
182. London Z, Albers JW. Toxic Neuropathies associated with pharmaceutic and industrial agents. Neurol Clin. 2007;25:257–76. https://doi.org/10.1016/j.ncl.2006.10.001.
183. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. BMP. 1982;284:1440–2.
184. Kammire LD, Donofrio PD. Nitrofurantoin neuropathy: a forgotten adverse effect. Obstet Gynecol. 2007;110:510–2.
185. Arsalan R, Sabzwari S. Isoniazid induced motor-dominant neuropathy. J Pak Med Assoc. 2015;65(10):1131.
186. Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. CNS Drugs. 2010;24:655–67.
187. Thompson JE. How safe is isoniazid? Med J Aust. 1978;1(3):165–9.
188. Zaoui A, Abdelghani A, Salem HB, Ouanes W, Hayouni A, et al. Early-onset severe isoniazid-induced motor-dominant neuropathy: a case report. EMHJ. 2012;18(3):298–9.

189. Holdiness MR. Neurological manifestations and toxicities of the antituberculosis drugs: a review. Med Toxicol. 1987;2(1):33–51.
190. Eichelbaum M, Kroemer HK, Mikus G. Genetically determined differences in drug metabolism as a risk factor in drug toxicity. Toxicol Lett. 1992;64:115–22. https://doi.org/10.1016/0378-427(92)90180-R.
191. Eakarnath A, Koomanachai P, Thamlikitkul V. Pyridoxine (Vitamin B6) usage in tuberculosis patients at Siriraj Hospital. Siriraj Med J. 2007;59:348–9.
192. CDC: Division of Tuberculosis. Latent tuberculosis infection: a guide for primary health care providers. Centers for Disease Control and Prevention (online). www.cdc.gov/tb/publications/ltbi/treatment.htm.
193. Wasik A. Mental disorders caused by isonicotinic acid hydrazine (INH) in the course of treatment of pulmonary tuberculosis. Pol Med J. 1970;9:1498–503.
194. Duncan H, Kerr D. Toxic psychosis due to isoniazid. Br J Dis Chest. 1962;56:131–8.
195. Alao AO, Yolles JC. Isoniazid-induced psychosis. Ann Pharmacother. 1998;32:889–91.
196. Duggal HS, Nizamine SH. Novel antipsychotic drugs and INH-related psychosis. Aust N Z J Psychiatry. 2000;34:343–4.
197. Masood I, Bhat S, Beigh A, Gupta V. Isoniazid-induced psychosis in a patient on DOTS therapy. Ann Trop Med Public Health. 2011;4:126–7.
198. Denholm J, McBryde E, Eisen D, Chen C, Penington J, Street A. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. Drug Healthc Patient Saf. 2014;6:145–9. https://doi.org/10.2147/DHPS.S68837.
199. Bender DA, Russell Jones R. Isoniazid-induced pellagra despite vitamin-B6 supplementation. Lancet. 1979;2:1125–6.
200. Thomas RHM, Payne CMER, Black MM. Isoniazid-induced pellagra. BMJ. 1981;283:287–8.
201. Temmerman W, Dhondt A, Vandewoude K. Acute isoniazid intoxication: seizures, acidosis, and coma. Acta Clin Belg. 1999;54(4):211–6.
202. Wason S, Lacouture PG, Lovejoy FH. Single high-dose pyridoxine treatment for isoniazid overdose. JAMA. 1981;246(10):1102–4. https://doi.org/10.1001/jama.1981.03320100038026.
203. Yarbrough BE, Wood JP. Isoniazid overdose treated with high-dose pyridoxine. Ann Emerg Med. 1983;12:303–5. https://doi.org/10.1016/S0196-0644(83)80514-9.
204. Lockman P, Shum S, Allen D. Case report: visual toxicity in acute isoniazid overdose. Internet J Med Toxicol. 2001;4(3):21.
205. Ruan LY, Fan JT, Hong W, Zhao H, et al. Isoniazid-induced hepatotoxicity and neurotoxicity in rats investigated by ^{1}H NMR based metabolomics approach. Toxicol Lett. 2018;295:256–69. https://doi.org/10.1016/j.toxlet.2018.05.032.
206. Wood JD, Peesker SJ. A correlation between changes in GABA metabolism and isonicotinic acid hydrazine-induced seizures. Brain Res. 1972;45(2):489–98. https://doi.org/10.1016/0006-8993(72)90477-5.
207. Perry TL, Kish SJ, Hansen S, Wright JM, Wall RA, Dunn WL, Bellward GD. Elevation of brain GABA content by chronic low-dosage administration of hydrazine, a metabolite of isoniazid. J Neurochem. 1981;37(1):32–29.
208. Moudgal R, Hosseini S, Colapietro P, Awosika O. Vitamin B6 toxicity revisited: a case of reversible pyridoxine-associated neuropathy and disequilibrium. Neurology. 2018;90:4021
209. Chamberlain PD, Sadaka A, Shauna B, Lee A. Ethambutol optic neuropathy. Curr Opin Ophthal. 2017;28(6):545–51. https://doi.org/10.1097/ICU.0000000000000416.
210. Yang HK, Park MJ, Lee JH, et al. Incidence of toxic optic neuropathy with low-dose ethambutol. Int J Tuberc Lung Dis. 2016;20:261–4.
211. Chen SC, Lin MC, Sheu SJ. Incidence and prognostic factor of ethambutol-related optic neuropathy: 10-year experience in southern Taiwan. Kaohsiung J Med Sci. 2015;31:358–62.
212. Ezer N, Benedetti A, Darvish-Zargar M, Menzies D. Incidence of ethambutol-related visual impairment during treatment of active tuberculosis. Int J Tuberc Lung Dis. 2013;17:447–55.
213. Chen HY, Lai SW, Muo CH, et al. Ethambutol-induced optic neuropathy: a nationwide population-based study from Taiwan. Br J Ophthalmol. 2012;96:1368–71.

214. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997;13(5):473–7. https://doi.org/10.1089/jop.1997.13.473.
215. Yoon YH, Jung KH, Sadun AA, Shin HC, Koh JY. Ethambutol-induced vacuolar changes and neuronal loss in rat retinal cell culture: mediation by endogenous zinc. Toxicol Appl Pharmacol. 2000;162:107–14.
216. Chung H, Yoon YH, Hwang JJ, Cho KS, Koh JY, Kim JG. Ethambutol-induced toxicity is mediated by zinc and lysosomal membrane permeabilization in cultured retinal cells. Toxicol Appl Pharmacol. 2009;23:163–70. https://doi.org/10.1016/j.taap.2008.11.006.
217. Chandrasekar PH. Micafungin: a new echinocandin. Clin Infect Dis. 2006;42(8):1171–8. https://doi.org/10.1086/501020.
218. Xiang Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. BMC Infect Dis. 2017;17:798. https://doi.org/10.1186/s12879-017-2913-8.
219. Dolton MJ, Ray JE, Chen SCA, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56(9):4793–9.
220. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 2008;46(2):201–11. https://doi.org/10.1086/524669.
221. Raad II, Graybill JR, Bustamante AB, Cornely OA, et al. Safety of long-term oral posaconazole use in treatment of refractory invasive fungal infections. Clin Infect Dis. 2006;42(12):1726–34. https://doi.org/10.1086/504328.
222. Mittal D, Wikaitis J. Itraconazole-induced delirium. Psychosomatics. 2003;44(3):260–1.
223. Robinson PA, Knirsch AK, Joseph JA. Fluconazole for life-threatening fungal infections in patients who cannot be treated with conventional antifungal agents. Rev Infect Dis. 1990;12:S349–63.
224. Anaisse EJ, Kontoyiannis DP, Huls C, Vartivarian SE, Karl C, Prince RA, Bosso J, Bodey GP. Safety, plasma concentrations, and efficacy of high-dose fluconazole in invasive mold infections. J Infect Dis. 1994;172:599–602.
225. Matsumoto K, Ueno K, Yoshimura H, Morii M, Takada M, Sawai T, Mitsutake K, Shibakawa M. Fluconazole-induced convulsions at serum trough concentrations of approximately 80microg/mL. Ther Drug Monit. 2000;22:635–6.
226. Weddington WW. Delirium and depression associated with amphotericin B. Psychosomatics. 1982;23(10):1076–8.
227. Novartis Pharmaceuticals Corporation. Lamasil (terbinafine hydrochloride) Tablets [package insert]. 2017.
228. Doty RL, Haxel BR. Objective assessment of terbinafine-induced taste loss. Laryngoscope. 2005;115(11):2035–7. https://doi.org/10.1097/01mlg.0000181462.08683.0c.
229. Garcia HH, Gilman RH, Horton J, Martinez M, Herrera G, Altamirano J, Cuba JM, Rios-Saavedra N, Verastegui M, Boero J, Gonzalez AE. Albendazole therapy for neurocysticercosis: a prospective double-blind trial comparing 7 versus 14 days of treatment. Neurology. 1997;48:1421–7.
230. Noboa C. Albendazole therapy for giant subarachnoid cysticerci. Arch Neurol. 1993;50:347–8.
231. Del Brutto OH. Clues to prevent cerebrovascular hazards of cysticidal drug therapy. Stroke. 1997;28:1088.
232. Bayer HealthCare Pharmaceuticals. Biltricide tablets (praziquantel) [package inset]. 2010.
233. Garg RK. Medical management of neurocysticercosis. Neurol India. 2001;49:329–37.
234. Chang GY, Ko DY. Isolated Echinococcus granulosus hydatid cyst in the CNS with severe reaction to treatment. Neurology. 2000;54:778–9. https://doi.org/10.1212/WNL.54.3.778.
235. Woo E, Yu YL, Huang CY. Cerebral infarct precipitated by praziquantel in neurocysticercosis – a cautionary note. Trop Geogr Med. 1988;40:143–6.
236. Chai JY. Praziquantel treatment in trematode and cestode infections: an update. Infect Chemother. 2013;45:32–43.

237. Guisse F, Polman K, Stelma FF, Mbaye A, et al. Therapeutic evaluation of two different dose regimens of praziquantel in a recent *Schistosoma mansoni* focus in northern Senegal. Am J Trop Med Hyg. 1997;56:511–4. https://doi.org/10.4269/ajtmh.1997.56.511.
238. Bada JL, Trevino B, Cabezos J. Convulsive seizures after treatment with praziquantel. BMJ. 1988;296:646. https://doi.org/10.1136/bmj.296.6622.646-a.
239. Chandler RE. Serious neurological adverse effects after Ivermectin – do they occur beyond the indication of Onchocerciasis? Am J Trop Med Hyg. 2018;98(2):382–8. https://doi.org/10.4269/ajtmh.17-0042.
240. Van Westerloo DJ, Landman GW, Prichard R, Lespine A, Visser LG. Persistent coma in *Strongyloides* hyperinfection syndrome associated with persistently increased ivermectin levels. Clin Infect Dis. 2014;58:143–4.
241. Merck & Co, Inc. Stromeectol tablets (Ivermectin) [package insert]. 2009.
242. Muñoz J, Ballester MR, Antonijoan RM, Gich I, et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Negl Trop Dis. 2018;12(1):e0006020. https://doi.org/10.1371/journal.pntd.0006020.
243. Gardon J, Gardon-Wendel N, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet. 1997;350:18–22.
244. McEnvoy GK. American Hospital Formulary service, drug information. Bethesda: American Society of Health-System Pharmacists; 1999.
245. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman AG. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1996. p. 1022.
246. Bescansa E, Nicolas M, Aguado C, Toledano M, Vinals M. Myasthenia gravis aggravated by pyrantel pamoate. J Neurol Neurosurg Psychiatry. 1991;54:563.
247. Rossignol JF, Abaza H, Friedman H. Successful treatment of human fascioliasis with nitazoxanide. Trans R Soc Trop Med Hyg. 1998;92:103–4. https://doi.org/10.1016/S0035-9203(98)90974-9.
248. Duombo O, Rossignol JF, Pichard E, Traore HA, Dembele TM, et al. Nitazoxanide in the treatment of cyrptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. Am J Trop Med Hyg. 1997;56:637–9. https://doi.org/10.4269/ajtmh.1997.56.637.
249. Hemphill A, Mueller J, Esposito M. Nitazoxanide, a broad-spectrum thiazolide anti-infective agent for the treatment of gastrointestinal infections. Expert Opin Pharmacother. 2006;7(7):953–64. https://doi.org/10.1517/14656566.7.7.
250. FDA. Drug safety communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. Food and Drug Administration. 2013. Online: www.fda.gov.
251. Aschenbrenner DS. Drug Watch: antimalarial drug can produce neurologic or psychiatric symptoms. AJN. 2013;113(11):22.
252. Harinasuta T, Lasserre R, Bunnag D, Leimer R, Vinijanont S. Trials of mefloquine in vivax and of mefloquine plus 'fansidar' in falciparum malaria. Lancet. 1985;325(8434):885–8. https://doi.org/10.1016/S0140-6736(85)91670-8.
253. Rendi-Wagner P, Noedl H, Wernsdorfer WH, Wiedermann G, et al. Unexpected frequency, duration, and spectrum of adverse events after therapeutic dose of mefloquine in health adults. Acta Trop. 2002;81:167–73. https://doi.org/10.1016/S0001-706X(01)00210-8.
254. Overbosch D, Schilthuis H, Bienzle U, Behrens RH, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis. 2001;33:1015–21. https://doi.org/10.1086/322694.
255. Nwokolo C, Wambebe C, Akinyanju O, Raji AA, et al. Mefloquine versus proguanil in short-term malaria chemoprophylaxis in sicle cell anaemia. Clin Drug Invest. 2001;21(8):537–44.
256. Matteelli A, Saleri N, Bisoffi Z, Gregis G, et al. Mefloquine versus quinine plus sulphalene-pyrimethamine (Metakelfin) for treatment of uncomplicated imported falciparum malaria

acquired in Africa. Antimicrob Agents Chemother. 2005;49:663–7. https://doi.org/10.1128/AAC.49.2.663-667.2005.
257. Nguyen TH, Day NP, Ly VC, Waller D, Mai NT, et al. Post-malaria neurological syndrome. Lancet. 1996;1996:917–21. https://doi.org/10.1016/S0140-6736(96)01409-2.
258. Jha S, Kumar R, Kumar R. Mefloquine toxicity presenting with polyneuropathy – a report of two cases in India. Trans R Soc Trop Med Hyg. 2006;100(6):594–6. https://doi.org/10.1016/j.trstmh.2006.08.006.
259. Ritchie EC, Block J, Nevin RL. Psychiatric side effects of mefloquine: applications to forensic psychiatry. J Am Acad Psychiatry Law Online. 2013;41(2):224–35.
260. Nevin RL, Croft AM. Psychiatric effects of malaria and anti-malarial drugs: historical and modern perspectives. Malar J. 2016;15:332. https://doi.org/10.1186/s12936-016-1391-6.
261. Wasay M, Wolfe GI, Herrold JM, Burns DK, Barohn RJ. Chloroquine myopathy and neuropathy with elevated CSF protein. Neurologija. 1998;51(4):1226–7. https://doi.org/10.1212/WNL.51.4.1226.
262. Browne GF, Coppel DL. Management of quinine overdose. Hum Toxicol. 1984;3(5):399–402. https://doi.org/10.1177/096032718400300 50.
263. Islahudin F, Tindall S, Mellor I, Swift K, et al. The antimalarial drug quinine interferes with serotonin biosynthesis and action. Sci Rep. 2015;4:3618. https://doi.org/10.1038/srep03618.
264. Novartis Pharmaceuticals Corporation. Coartem (artemether/lumefantrine) tablets [package insert]. 2018.
265. Guilin Pharmaceuticals. Artesun (Artesunate for injection) [package insert]. 2012.
266. Genovese RF, Newman DB. Understanding artemisinin-induced brainstem neurotoxicity. Arch Toxicol. 2008;82(6):379–85. https://doi.org/10.1007/s00204-007-0252-z.
267. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. Ann Pharmacother. 1998;32(1):111–3. https://doi.org/10.1345/aph.17135.
268. Haefeli W, Schoenenberger RAZ, Weiss P, Ritz RF. Acyclovir-induced neurotoxicity: concentration-side effect relationship in acyclovir overdose. Am J Med. 1993;94:212–5.
269. Chowdry MA, Derar N, Hasan S, Hinch B, Ratnam S, Assaly R. Acyclovir-induced neurotoxicity: a case report and review of literature. Am J Ther. 2016;23(3):e941–3. https://doi.org/10.1097/MJT.0000000000000093.
270. Watson WA, Rhodes NJ, Echenique IA, Angarone MP, Scheetz MH. Resolution of acyclovir-associated neurotoxicity with the aid of improved clearance estimates using a Bayesian approach: a case report and review of literature. J Clin Pharm Ther. 2018;42(3):350–5. https://doi.org/10.1111/jcpt.12520.
271. Chatelain E, Deminière C, Lacut JY, Potaux L. Severe renal failure and polyneuritis induced by foscarnet. Nephrol Dial Transplant. 1998;13:2368–9.
272. Lor E, Liu YQ. Neurologic sequelae associated with foscarnet therapy. Ann Pharmacother. 1994;28(9):1035–7. https://doi.org/10.1177/106002809402800908.
273. MacGregor RR, Graziani AL, Weiss R, Grunwald JE, Gambertoglio JG. Successful foscarnet therapy for cytomegalovirus retinitis in an AIDS patient undergoing HD: rationale for empiric dosing and plasma level monitoring. J Infect Dis. 1991;164:785–7.
274. Kinney RG, Spach DH. Antiretroviral therapy: adverse effects of antiretroviral medications. National HIV Curriculum. 2018. Online: www.hiv.uw.edu/go/antiretroviral-therapy/adverse-effects/core-concept/all/.
275. Reliquet V, Mussini JM, Chennebault JM, Lafeuillade A, Raffi F. Peripheral neuropathy during stavudine-didanosine antiretroviral therapy. HIV Med. 2001;2(2):92–6. https://doi.org/10.1046/j.1468-1293.2001.00066.x.
276. Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf. 2007;6:147–54.
277. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15:71–5.

278. Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomized, non-inferiority trial. Lancet. 2011;378:229–37. https://doi.org/10.1016/S0140-6736(11)60983-5.
279. Gilead Sciences, Inc. Biktarvy (bictegravir sodium, emtricitabine and tenofovir aladenamide fumarate) tablet [package insert]. 2019.
280. Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. Clin Infect Dis. 2014;59(2):265–71. https://doi.org/10.1093/cid/ciu22.
281. Merck Sharp & Dohme Corporation. Isentress (Raltegravir) film-coated tablets/chewable tablets, for oral use [package insert]. 2007.
282. Chan-Tack KM, Struble KA, Birnkrant DB. Intracranial hemorrhage and liver-associated deaths associated with tipranavir/ritonavir: a review of cases from the FDA's adverse event reporting system. AIDS Patient Care STDs. 2008;22:843–50. https://doi.org/10.1089/apc.2008.0043.
283. McNicholl I, Coffey S. Adverse effects of antiretroviral drugs. HIV InSite. http://hivinsite.ucsf.edu/InSite?page=ar-05-01#S2.4X. Accessed 2 Dec 2019.

Part II
Bacterial Infections

Chapter 4
Neurological Complications of Infective Endocarditis

Marie Cantier, Mikael Mazighi, and Romain Sonneville

Infective endocarditis (IE) is a severe disease associated with high mortality rates. Neurologic complications are the most frequent extra-cardiac complications of left-sided IE, occurring in 20–55% of patients [1, 2]. They contribute to a poor prognosis, including an increased mortality and morbidity from disabling sequelae [1, 3]. Neurologic complications may impact diagnosis and therapeutic plans, particularly in patients requiring emergent cardiac surgery.

Many questions on the pathophysiology and natural history of neurologic events during left-sided IE are still unanswered. Cerebral embolism from vegetations may not be the only mechanism involved in cerebrovascular complications.

The initial management of patients with IE includes early identification of patients at risk for developing new or recurrent neurologic events, an accurate evaluation of those complications with appropriate neuroimaging tools, and the identification of optimal timing of cardiac surgery, when indicated [4]. Additionnal

M. Cantier (✉)
Department of Neurology, Saint-Antoine University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France

INSERM U1148, Université Paris Diderot, Paris, France
e-mail: marie.cantier@aphp.fr

M. Mazighi
INSERM U1148, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Department of Neurology, Lariboisière University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France
e-mail: mikael.mazighi@aphp.fr

R. Sonneville
INSERM U1148, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France
e-mail: romain.sonneville@aphp.fr

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_4

important points include the management of antiinfectious agents, antithrombotic agents (anticoagulants, anti-platelet therapy) and endovascular therapy in acute brain infarction, and specific therapy for mycotic aneurysms. A multidiscpilinary management by an expert team is of paramount importance to improve outcomes in such patients [4, 5].

The aim of this chapter is to provide recent insights and perspectives in management of neurologic complications of endocarditis.

Epidemiology and Outcomes of Neurologic Events in IE

The reported prevalence of neurologic complications in IE patients is variable, depending on the severity of illness, and considering non-symptomatic events detected only by systematic brain imaging. Recent studies conducted in patients admitted to the ICU with severe IE reported a prevalence of 55% of neurologic complications at admission [2, 6]. Studies conducted with use of systematic brain MRI at hospital admission reported an incidence of neurologic complications in up to 80% of patients [7]. The main risk factors for neurologic events in severe IE patients include infection with *Staphylococcus aureus*, large vegetations measured on echocardiograpy (>10 mm), mitral valve involvement and non-neurologic embolic events [1, 2, 8].

Cerebrovascular events represent more than 65% of neurologic complications, and include brain infarction, transient ischemic attack, intracranial hemorrhage, cerebral microbleeds (CMB), and subarachnoid hemorrhage [2, 8]. Brain infarction is the most frequently observed complication, occurring in 60–80% of cases. Although embolic complications can be the presenting symptom of IE, these often occurs during the first week of antibiotic therapy. In contrast, infectious complications (i.e. abscesses, meningitis) seem to be less common, occurring in 1–20% of cases [9, 10] (Fig. 4.1d). Compared to primary bacterial meningitis, meningitis secondary to IE is associated to higher rates of brain ischemic and hemorrhagic events, and less favourable outcomes, with increased disability and mortality rates [9].

More than two-thirds of patients admitted to the ICU with neurologic manifestations of IE either die or have residual neurologic sequelae [2]. Altered mentation at IE onset represents a major predictor of mortality in IE, irrespective of its underlying mechanism [11]. Symptomatic brain infarction and hemorrhage are determinants of poor outcome and mortality, unlike silent neurologic events [8, 12]. Non-neurological predictors of poor prognosis include septic shock and multiorgan failure, vegetation size ≥15 mm, and prosthetic mechanical valve IE [11, 13]. Early cardiac surgery is independently associated with improved outcome, irrespective of severity at ICU admission. Performed within 48 h in patients with acute left-sided IE and severe valve regurgitation, surgery is associated with a significant reduction in the composite endpoint of embolic events or death at 6 weeks [14].

The onset of neurologic complications in IE patients remains a serious issue, whose management and diagnosis are challenging.

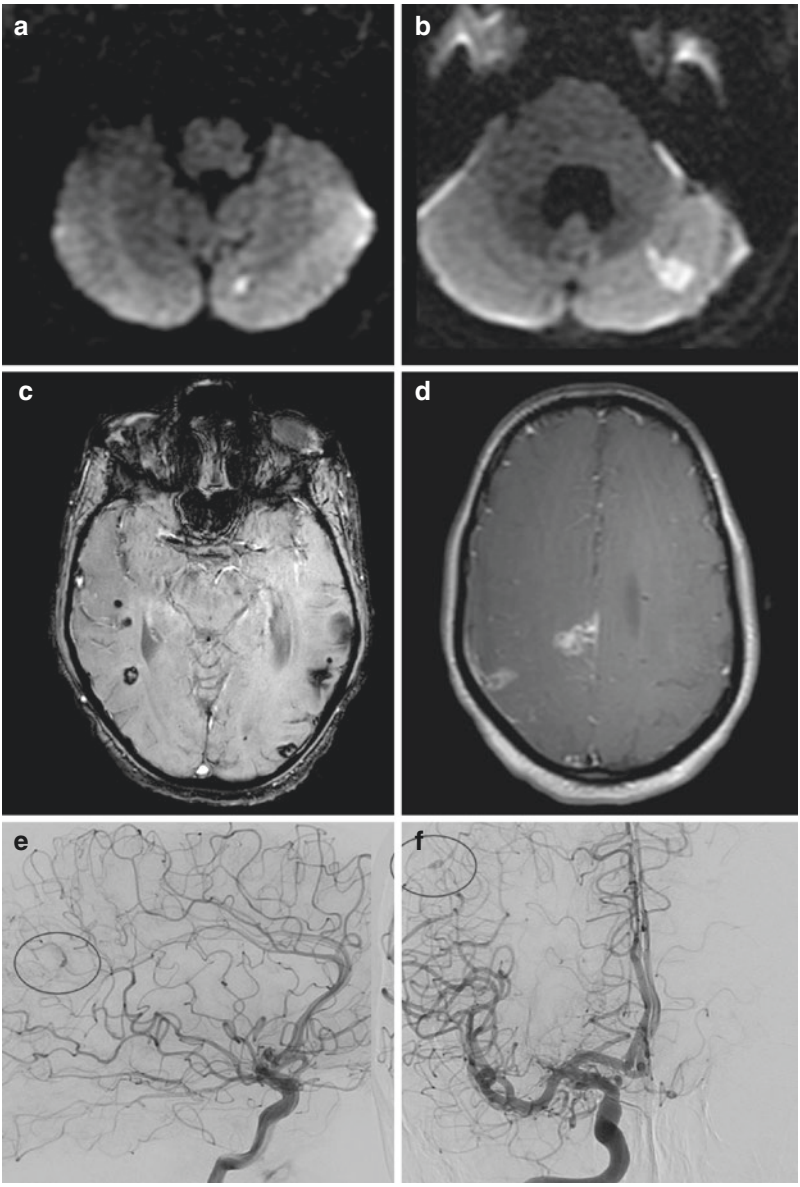


Fig. 4.1 Ischemic, hemorrhagic and infectious cerebral complications in a 40-years old patient with mitral valve endocarditis due to *Streptococcus salivarus*. (**a**, **b**) diffusion-weighted MRI showing multiple hyperintensities corresponding to recent cerebellar infarctions. (**c**) susceptibility-weighted imaging showing hypointensities corresponding to deep and superficial micro-hemorrhages (or cerebral microbleeds), associated with subarachnoid hemorrhages due to a ruptured mycotic aneurysm (non-visible on MR angiography), and hemorrhagic tranformation of an ischemic lesion. (**d**) gadolinium-enhancing T1 lesions corresponding to cerebral abscesses. (**e**) mycotic micro-aneurysm located in a distal segment of the left middle cerebral artery. (**f**) mycotic micro-aneurysm located in a distal segment of the right middle cerebral artery

Pathophysiology of Neurologic Complications in IE

Septic embolism from vegetations is commonly accepted as the main mechanism responsible for the observed brain lesions in IE. In fact, the nature of IE-related cerebral events at the acute and subacute phases is still debated: many hypotheses are discussed, including cerebral small-vessel vasculitis, mediated by autoimmune or *vasa vasorum* embolic processes occurring after the embolic phase [15–17]. The radiological brain lesion pattern in IE patients is similar to those observed in cerebral vasculitis, e.g. central nervous system primary vasculitis [18–21]. The latter is described as the coexistence of cortical cerebral CMB, microabscesses and small ischemic lesions, located in multiple vascular territories and of different ages. However, this nonspecific pattern is observed in other small-vessel diseases. The histological brain lesion pattern in primary cerebral vasculitis has been described to be limited exclusively to small and medium arteries. Interestingly, central nervous system primary vasculitis is thought to be triggered by infections, and secondary CNS vasculitis is most commonly associated with infections. Moreover, it has been reported that, in *S. aureus*-related IE, uncontrolled sepsis is risk for developing diffuse vasculitis [22]. Systemic inflammation related to bacteremia in IE may act as the trigger of small-vessel cerebral vasculitis and subsequent neurologic complications. *Post-mortem* histopathological cerebral studies in IE patients and experimental studies on brain lesions in pigs and rats with IE support this hypothesis, reporting the same lesion pattern with septic emboli associated with extensive pyogenic arteritis (small vessels transmural infiltrates composed of inflammatory cells), disseminated brain infarctions, CMB, abscesses, and meningitis [23–27]. Interestingly, in experimental models of IE, cerebral lesion load is larger on histopathological studies than the one observed on MRI, and bacteremia appears to amplify the observed brain injury, supporting the hypothesis of synergistic conditions leading to neurologic complications of IE.

Hemorrhagic lesions may involve other complex mechanisms. One third of brain hemorrhages are actually hemorrhagic transformation of ischemic lesions. Regarding CMB, recent clinical data from MRI studies report their presence in more than 50% of IE cases [7, 15]. Physiopathology hypotheses for CMB include endothelial injury and blood brain barrier leakage after septic embolism leading to small vessels rupture, coagulatopathy and erythrocytes stasis, and vasculitis with segmental arterial wall disorganizations of small cerebral arteries [28, 29]. Interestingly, CMB are also described in patients with mechanical valves (without IE), supporting a possible link between CMB and thromboembolism from valvular lesions, withour any associated infection [30].

Few data are available on the pathophysiology of meningitis occurring in the setting of IE. As above-mentioned, meningitis in IE patients may increase the risk of cerebral ischemic and hemorrhagic events. Brain infarction is a well described complication of bacterial meningitis, whereas hemorrhages are rarely observed [9, 10]. However some studies suggest a higher risk of cerebral bleeding in patients on anticoagulant therapy presenting with IE and secondary meningitis [31]. Interestingly, cerebral vasculitis, responsible for ischemic and hemorrhagic lesions,

is associated with infectious diseases including meningitis and IE. Bacteremia, valvular infection and meningeal reaction in IE patients, may all trigger cerebral vasculitis.

All these findings support the hypothesis of a synergistic combination of thromboembolism from valvular damage, meningitis and small-vessel cerebral vasculitis triggered by additional sepsis, to generate a distinctive pattern of neurological lesions in IE.

Brain MRI in Management of IE Patients

The prevalence of neurologic complications is difficult to estimate because of asymptomatic events. Symptomatic neurologic events are observed in 10–40% of patients with IE [1, 7]. Conversely, asymptomatic events detected on brain MRI are present in 60 to 80% of patients. Consequently, about one third of embolic events would be clinically silent [17, 32–34].

The most frequent observed patterns on brain imaging include acute ischemic lesions and CMB [2, 15] (Fig. 4.1a–c). To identify such complications, brain CT scan is often the initial imaging because it is easily available and highly sensitive for the detection of brain hemorrhages and large ischemic stroke [35]. However, ischemic lesions in IE are characterized by small, multiple, and disseminated infarctions. The superiority of MRI is now established, as this is more sensitive than CT in IE patients with neurologic symptoms. This holds true for both the detection of clinically symptomatic events (100 versus 81% of patients, respectively), and of additional asymptomatic events (50 versus 23% of patients, respectively). A recent study found that each millimeter increase in vegetation length was associated with a 10% increase in the rate of ischemic lesions detected on brain MRI [36]. MRI results can impact diagnosis or therapeutic plans in up to 28% of patients [7, 32]. In fact, the use of systematic brain MRI in IE may improve prognostic assessment and aid in decision-making, especially for cardiac surgery indication and timing [33]. Embolic events are significantly associated with worsened long-term mortality [11]. A few studies suggest that patients with symptomatic and asymptomatic embolism had similar long-term mortality [34, 37]. Conversely, others found higher survival rates in patients with asymptomatic embolism than in patients with symptomatic events or without neurologic complications. These results are thought to be related to a higher rate of surgery in patients with asymptomatic embolism, suggesting a protective role of valve replacement, guided by systematic MRI [33]. Taking into account recent literature, the detection of asymptomatic events may induce substantial changes in prognosis assessment and therapeutic decisions.

The current guidelines of the European Society of Cardiology recommend routine brain imaging and valve replacement in all patients presenting with embolic event (symptomatic or silent) with large vegetations persistence [4]. Systematic brain MRI in IE patients represents a necessary approach to assess the determinants of neurologic complications.

Right Timing of Cardiac Surgery in IE Patients with Neurologic Complications

Valve replacement surgery is required in about 50% cases during the acute phase of IE and is associated with a reduction of embolic envents and mortality rates [14]. Current indications for cardiac surgery include heart failure (severe acute regurgitation or obstruction with refractory pulmonary edema or signs of poor hemodynamic tolerance), uncontrolled infection (locally uncontrolled infection, persistant fever or positive blood cultures >7 days, or difficult-to-treat pathogens) and prevention of embolism (in patients with large vegetations, after one or more embolic events despite appropriate antibiotic therapy or other predictors of complicated course).

In patients with neurologic complications, the optimal timing of surgery remains controversial. On the one hand, cardiopulmonary bypass and anticoagulation required during valve replacement can be responsible for neurologic deterioration, as a consequence of infarct or hemtoma growth, hemorrhagic transformation, or new ischemic and/or hemorrhagic lesions [38]. On the other hand, IE patients with a delayed surgery strategy are exposed to heart failure and recurrent cerebral embolism, that are associated with increased morbidity and mortality. Some authors found early surgery (i.e. performed within 2–4 weeks following IE diagnosis) performed in patients with moderate to severe brain infarction, or brain hemorrhage, was associated with perioperative neurologic deterioration and higher mortality [8].

Other recent cohort studies suggest that early surgery (i.e. performed within 1 week following diagnosis) in IE patients with ischemic stroke is not associated with increased perioperative complications or mortality [14, 39–41]. Studies conducted with systematic brain MRI before surgery suggest that brain infarction is present in 55 to 72% of patients [16, 38, 42]. Preoperative acute ischemic lesions detected on MRI did not predict postoperative complications. In sicker patients requiring ICU admission, no association between timing of surgery and mortality could be determined [11, 38, 43, 44].

In the same way, the risk of postoperative neurological deterioration resulting from the exacerbation of hemorrhagic lesions seems relatively low, even in IE patients who underwent valve surgery within 2 weeks of hemorrhage onset [45, 46].

Although statistically insignificant, a recent retrospective study found that early surgery (i.e. performed within 2 weeks following neurologic event) was associated with lower mortality rates in patients with brain infarction, unlike those with brain hemorrhage, who had higher mortality rates [41].

Above-mentioned conclusions need to be carefuly analyzed, considering the variability in early surgery timing definitions, and the retrospective nature and small samples of some studies [38, 43]. For these reasons, experienced multidisciplinary team (intensivists, cardiac surgeons, cardiologists, infectious diseases specialists, neurologists, neurosurgeons) should assess individual benefit-risk to determine the right timing of cardiac surgery in IE patients with neurologic complications, through the help of the current guidelines. The latter include the 2015 recommendations from the European Society of Cardiology (ESC), the American Heart Association

(AHA) and the Society of Thoracic Clinical Practical Guidelines [4, 47, 48]. Except for patients with imminent risk of death, delay of 4 weeks is recommended for major neurological injury due to ischemic stroke, or hemorrhagic strokes. No delay for surgery can be considered if neurologic events are minor or asymptomatic, to manage heart failure, uncontrolled infection or abscess, high risk of embolism, or recurrent systemic embolism or stroke.

Specific Management of Mycotic Aneurysms

Hemorrhages account for 12–30% of neurological complications observed in IE patients [1, 2, 8]. They may be the consequence of ruptured infectious intracranial aneurysms (mycotic aneurysms) (MA). MA correspond to arterial dilatations caused by septic emboli. Bacterial invasion of the arterial wall, local inflammatory responses and pulsatile pressure on the vessel wall lead to aneurysmal dilatation. MA are observed in 2–4% of IE patients, and detected in 5–15% of those with neurologic symptoms [34, 49]. In a recent meta-analysis, 72% of patients with MA had hemorrhages (subarachnoid (22%), intraparenchymal (28%), and intraventricular (5%) hemorrhage) [50]. In fact, their overall prevalence remains difficult to quantify because the diagnosis, of asymptomatic unruptured MA located in small distal vessels, is sometimes challenging.

Brain vascular imaging is indicated in every patient with IE presenting with intracranial hemorrhage, to rule out a ruptured MA. Conventional cerebral angiography is though to be much more sensitive than noninvasive neuroimaging (CT or MRI), particularly for detection of small MA (<3 mm) [49] (Fig. 4.1e, f). Nevertheless, the absence of hemorrhage on noninvasive imaging provides a strong negative predictive value for the presence of MA [51]. The sensitivity of multislice CT angiography has been reported to be 100% for large MA (>13 mm) and 90.6% for medium-size MA (5–12 mm) [52]. However, as small aneurysms may not be identified with non-invasive imaging, conventional angiography remains the gold standard for the detection of MA. Considering these data and risks of the procedure, conventional angiography might be reserved for patients with evidence of hemorrhage on noninvasive imaging.

Given the lack of evidence-based data due to the rarity of MA, there are no current recommendations to guide clinicians in management. Ruptured MA should be immediately secured by surgical or endovascular approach. In such cases, cardiac surgery is often delayed. For unruptured MA, the literature supports a medical approach. In fact, MA may resolve with antibiotic therapy. Surgical or endovascular treatment should be considered in case of persistent MA despite directed antibiotics, or if cardiac surgery is indicated [1, 53]. Some authors suggest an endovascular approach prior to cardiac surgery, which should not be delayed. The decision-making process should take into account the risk of rupture, based on symptoms, size, location, growth rate and anatomic characteristics of MA. Smaller MA may be monitored by clinical and imaging follow-up, wherever possible since MA are

dynamic lesions [49]. Assessing medical practices is difficult, due to the heterogeneity of the studies. In a meta-analysis, surgical management was performed in 45% versus an endovascular approach in only 17% of patients. Overall, 5% of patients died prior to surgical or endovascular intervention, 12% died following intervention, 20% had neurological decline, and 62% had favorable outcome after intervention [50]. Progress is needed in MA detection and management to improve outcome.

Antibiotic Therapy and Neurologic Complications

Early appropriate antibiotic therapy is the cornerstone of IE management. Of note, the incidence of neurologic events appears to be dramatically reduced 2 weeks after antibiotic initiation [8, 54]. However, significant neurotoxicity may occur in patients treated with high-dose beta-lactams, especially in older patients with renal failure [55]. A recent study monitored therapeutic drug concentrations in patients treated with oxacillin 12 g/day for severe staphylococcal infections, and revealed overdosed plasma concentrations in more than 80% of cases. Oxacillin overdose contributed to significant neurological deterioration during antibiotic therapy, in the form of delirium or coma [56]. In this regard, therapeutic drug monitoring of beta-lactams levels during IE treatment may be necessary in case of unexplained neurologic symptoms (i.e. deterioration of mental status or non-convulsive seizures). The presence of neurologic complications does not modify the recommended antibiotic regimens except in patients who develop *S. aureus* brain abscess requiring the use of molecule with high cerebral diffusion (rifampin, fluoroquinolones).

Uncertainties About Antithrombotic Therapies

There is scant data regarding the management of anticoagulation in IE patients with mechanical valve and neurologic complications. Decisions must consider the need for embolism prevention, versus the risk of brain hemorrhage progressing or hemorrhagic transformation of ischemic lesions. European guidelines suggest that unfractionated or low molecular weight heparin should replace oral anticoagulation for 1–2 weeks in patients with ischemic stroke, or with high risk of neurologic lesion. Interruption of anticoagulation is recommended in case of brain hemorrhage, and should be reinitiated as soon as possible [4]. In case of indicated cardiac surgery in patients with brain lesions, some authors prefer bioprosthetic to mechanic valves to not extend the duration of anticoagulation [57].

Thrombolysis is not recommended in IE patients presenting with acute ischemic stroke, because data on efficacy and safety are few, contradictory, and based on case-reports [58]. Thrombectomy could be an alternative in selected patients [59], but no data are currently available in IE patients.

Decisions on antithrombotic therapies may be discussed on a case-by-case basis with a multidisciplinary experienced team for IE patients presenting with brain lesions.

Conclusions

Neurologic complications of left-sided IE, mainly consisting of ischemic or hemorrhagic events, are frequent and associated with poor outcomes. Pathophysiology may involve synergistic mechanisms leading to neurologic events, including thromboembolism form vegetations, sepsis, meningitis and cerebral vasculitis. Asymptomatic neurologic lesions may be identified in the majority of patients through radiographic screening, and may impact prognosis and therapeutic plans. Systematic brain MRI on all patients with IE should be considered, especially before cardiac surgery. Recent studies suggest that early cardiac surgery, when indicated, could be performed safely in patients with cerebral ischemic events. Many other important points remain debated in IE patients presenting with neurologic complications, including optimal anti-infectious therapy, use of antithrombotic therapy, and the management of intracranial mycotic aneurysms. Management of such patients requires a multidisciplinary experienced team for decisions made on a case-by-case basis.

References

1. Pigretti S, Zurru MC, Arias A, Parcerisa F, Luzzi A, Belziti C. Neurologic complications of infective endocarditis: do they have an impact on prognosis? Medicina. 2017;77(2):89–94.
2. Sonneville R, Mirabel M, Hajage D, Tubach F, Vignon P, Perez P, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. Crit Care Med. 2011;39(6):1474–81.
3. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463–73.
4. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128.
5. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: challenges and perspectives. Lancet. 2012;379(9819):965–75.
6. Leroy O, Georges H, Devos P, Bitton S, De Sa N, Dedrie C, et al. Infective endocarditis requiring ICU admission: epidemiology and prognosis. Ann Intensive Care. 2015;5(1):45.
7. Duval X, Iung B, Klein I, Brochet E, Thabut G, Arnoult F, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med. 2010;152(8):497–504, W175.

8. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013;127(23):2272–84.
9. Lucas MJ, Brouwer MC, van der Ende A, van de Beek D. Endocarditis in adults with bacterial meningitis. Circulation. 2013;127(20):2056–62.
10. Heiro M, Helenius H, Hurme S, Savunen T, Engblom E, Nikoskelainen J, et al. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. BMC Infect Dis. 2007;7:78.
11. Mirabel M, Sonneville R, Hajage D, Novy E, Tubach F, Vignon P, et al. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. Eur Heart J. 2014;35(18):1195–204.
12. Lee SJ, Oh SS, Lim DS, Na CY, Kim JH. Clinical significance of cerebrovascular complications in patients with acute infective endocarditis: a retrospective analysis of a 12-year single-center experience. BMC Neurol. 2014;14:30.
13. Patrat-Delon S, Rouxel A, Gacouin A, Revest M, Flecher E, Fouquet O, et al. EuroSCORE II underestimates mortality after cardiac surgery for infective endocarditis. Eur J Cardiothorac Surg. 2016;49(3):944–51.
14. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366(26):2466–73.
15. Klein I, Iung B, Labreuche J, Hess A, Wolff M, Messika-Zeitoun D, et al. Cerebral microbleeds are frequent in infective endocarditis: a case-control study. Stroke. 2009;40(11):3461–5.
16. Okazaki S, Yoshioka D, Sakaguchi M, Sawa Y, Mochizuki H, Kitagawa K. Acute ischemic brain lesions in infective endocarditis: incidence, related factors, and postoperative outcome. Cerebrovasc Dis. 2013;35(2):155–62.
17. Hess A, Klein I, Iung B, Lavallee P, Ilic-Habensus E, Dornic Q, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR Am J Neuroradiol. 2013;34(8):1579–84.
18. Ay H, Sahin G, Saatci I, Soylemezoglu F, Saribas O. Primary angiitis of the central nervous system and silent cortical hemorrhages. AJNR Am J Neuroradiol. 2002;23(9):1561–3.
19. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, et al. Primary central nervous system vasculitis presenting with intracranial hemorrhage. Arthritis Rheum. 2011;63(11):3598–606.
20. Terruso V, Bonanni I, Dinia L, Canepa C, Gandolfo C, Del Sette M. Neurological complication of infective endocarditis mimicking temporal arteritis. Eur Neurol. 2008;59(3–4):198–9.
21. Alvarez Soria MJ, Carrasco Garcia de Leon S, Hernandez Gonzalez A. Isolated Sylvian vasculitis as presentation of a subacute bacterial endocarditis. Neurologia. 2009;24(4):280.
22. Hart RG, Foster JW, Luther MF, Kanter MC. Stroke in infective endocarditis. Stroke. 1990;21(5):695–700.
23. Wang KY, Shimajiri S, Yoshida T, Yamada S, Sasaguri Y. An autopsy case of microscopic polyangiitis associated with bacterial endocarditis. J UOEH. 2010;32(3):273–9.
24. Weeks SG, Silva C, Auer RN, Doig CJ, Gill MJ, Power C. Encephalopathy with staphylococcal endocarditis: multiple neuropathological findings. Can J Neurol Sci. 2001;28(3):260–4.
25. Christiansen JG, Oscarson M, Jensen HE, Jensen LK, Koch J, Aalbaek B, et al. Embolic encephalitis in a porcine model of endocarditis. In Vivo. 2013;27(5):591–7.
26. Karstrup CC, Jensen HE, Aalbaek B, Leifsson PS, Boye M, Agerholm JS. Endocarditis-associated brain lesions in slaughter pigs. J Comp Pathol. 2011;144(4):289–95.
27. Cantier M, Mazighi M, Klein I, Desilles JP, Wolff M, Timsit JF, et al. Neurologic complications of infective endocarditis: recent findings. Curr Infect Dis Rep. 2017;19(11):41.
28. Yates PA, Villemagne VL, Ellis KA, Desmond PM, Masters CL, Rowe CC. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. Front Neurol. 2014;4:205.

29. Schreiber S, Bueche CZ, Garz C, Braun H. Blood brain barrier breakdown as the starting point of cerebral small vessel disease? - new insights from a rat model. Exp Transl Stroke Med. 2013;5(1):4.
30. Jeon SB, Lee JW, Kim SJ, Chung CH, Kwon SU, Choi CG, et al. New cerebral lesions on T2*-weighted gradient-echo imaging after cardiac valve surgery. Cerebrovasc Dis. 2010;30(2):194–9.
31. Mook-Kanamori BB, Fritz D, Brouwer MC, van der Ende A, van de Beek D. Intracerebral hemorrhages in adults with community associated bacterial meningitis in adults: should we reconsider anticoagulant therapy? PLoS One. 2012;7(9):e45271.
32. Goulenok T, Klein I, Mazighi M, Messika-Zeitoun D, Alexandra JF, Mourvillier B, et al. Infective endocarditis with symptomatic cerebral complications: contribution of cerebral magnetic resonance imaging. Cerebrovasc Dis. 2013;35(4):327–36.
33. Selton-Suty C, Delahaye F, Tattevin P, Federspiel C, Le Moing V, Chirouze C, et al. Symptomatic and asymptomatic neurological complications of infective endocarditis: impact on surgical management and prognosis. PLoS One. 2016;11(7):e0158522.
34. Misfeld M, Girrbach F, Etz CD, Binner C, Aspern KV, Dohmen PM, et al. Surgery for infective endocarditis complicated by cerebral embolism: a consecutive series of 375 patients. J Thorac Cardiovasc Surg. 2014;147(6):1837–44.
35. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, et al. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. Stroke. 2009;40(11):3646–78.
36. Iung B, Tubiana S, Klein I, Messika-Zeitoun D, Brochet E, Lepage L, et al. Determinants of cerebral lesions in endocarditis on systematic cerebral magnetic resonance imaging: a prospective study. Stroke. 2013;44(11):3056–62.
37. Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Lin M, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. Circulation. 2009;120(7):585–91.
38. Yoshioka D, Sakaguchi T, Yamauchi T, Okazaki S, Miyagawa S, Nishi H, et al. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. Ann Thorac Surg. 2012;94(2):489–95; discussion 96.
39. Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J. 2007;28(9):1155–61.
40. Barsic B, Dickerman S, Krajinovic V, Pappas P, Altclas J, Carosi G, et al. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis. 2013;56(2):209–17.
41. Okita Y, Minakata K, Yasuno S, Uozumi R, Sato T, Ueshima K, et al. Optimal timing of surgery for active infective endocarditis with cerebral complications: a Japanese multicentre study. Eur J Cardiothorac Surg. 2016;50(2):374–82.
42. Chakraborty T, Scharf E, DeSimone D, El Rafei A, Brinjikji W, Baddour LM, et al. Variable significance of brain MRI findings in infective endocarditis and its effect on surgical decisions. Mayo Clin Proc. 2019;94(6):1024–32.
43. Oh TH, Wang TK, Pemberton JA, Raudkivi PJ. Early or late surgery for endocarditis with neurological complications. Asian Cardiovasc Thorac Ann. 2016;24(5):435–40.
44. Lee HA, Lin CY, Chen YC, Chen SW, Nan YY, Liu KS, et al. Surgical interventions of isolated active mitral valve endocarditis: predisposing factors and impact of neurological insults on final outcome. Medicine (Baltimore). 2018;97(11):e0054.
45. Yoshioka D, Toda K, Sakaguchi T, Okazaki S, Yamauchi T, Miyagawa S, et al. Valve surgery in active endocarditis patients complicated by intracranial haemorrhage: the influence of the timing of surgery on neurological outcomes. Eur J Cardiothorac Surg. 2014;45(6):1082–8.

46. Diab M, Guenther A, Scheffel P, Sponholz C, Lehmann T, Hedderich J, et al. Can radiological characteristics of preoperative cerebral lesions predict postoperative intracranial haemorrhage in endocarditis patients? Eur J Cardiothorac Surg. 2016;49(5):e119–26.
47. Byrne JG, Rezai K, Sanchez JA, Bernstein RA, Okum E, Leacche M, et al. Surgical management of endocarditis: the society of thoracic surgeons clinical practice guideline. Ann Thorac Surg. 2011;91(6):2012–9.
48. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132(15):1435–86.
49. Hui FK, Bain M, Obuchowski NA, Gordon S, Spiotta AM, Moskowitz S, et al. Mycotic aneurysm detection rates with cerebral angiography in patients with infective endocarditis. J Neurointerv Surg. 2015;7(6):449–52.
50. Ducruet AF, Hickman ZL, Zacharia BE, Narula R, Grobelny BT, Gorski J, et al. Intracranial infectious aneurysms: a comprehensive review. Neurosurg Rev. 2010;33(1):37–46.
51. Monteleone PP, Shrestha NK, Jacob J, Gordon SM, Fraser TG, Rehm SJ, et al. Clinical utility of cerebral angiography in the preoperative assessment of endocarditis. Vasc Med. 2014;19(6):500–6.
52. Dammert S, Krings T, Moller-Hartmann W, Ueffing E, Hans FJ, Willmes K, et al. Detection of intracranial aneurysms with multislice CT: comparison with conventional angiography. Neuroradiology. 2004;46(6):427–34.
53. Ohtake M, Tateishi K, Ikegaya N, Iwata J, Yamanaka S, Murata H. Initial treatment strategy for intracranial Mycotic aneurysms: 2 case reports and literature review. World Neurosurg. 2017;106:1051.e9–e16.
54. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J. 2007;154(6):1086–94.
55. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology. 2016;86(10):963–71.
56. Neuville M, El-Helali N, Magalhaes E, Radjou A, Smonig R, Soubirou JF, et al. Systematic overdosing of oxa- and cloxacillin in severe infections treated in ICU: risk factors and side effects. Ann Intensive Care. 2017;7(1):34.
57. Yanagawa B, Pettersson GB, Habib G, Ruel M, Saposnik G, Latter DA, et al. Surgical management of infective endocarditis complicated by embolic stroke: practical recommendations for clinicians. Circulation. 2016;134(17):1280–92.
58. Ong E, Mechtouff L, Bernard E, Cho TH, Diallo LL, Nighoghossian N, et al. Thrombolysis for stroke caused by infective endocarditis: an illustrative case and review of the literature. J Neurol. 2013;260(5):1339–42.
59. Haider AS, Garg P, Watson IT, Leonard D, Khan U, Haque A, et al. Mechanical thrombectomy for acute ischemic stroke after cardiac surgery. Cureus. 2017;9(4):e1150.

Chapter 5
Neurobrucellosis

Murat Kutlu and Önder Ergönül

Brucellosis is one of the most common zoonotic infections in many parts of the world including the Mediterranean countries and Middle East, Central Asia, India, Central and South America [1, 2]. Brucellosis is caused by the bacterial genus *Brucella*. *Brucella* is a small gram- negative, non motile and facultative intracellular bacterium. Among the *Brucella* species (spp.), *B. melitensis, B. abortus, B. suis,* and *B. canis* are the most common causative agents of brucellosis in humans [3]. In neurobrucellosis (NB), the most commonly *B. melitensis* and *B. abortus* and less commonly *B. suis* are the causative species [4, 5]. *B. ceti* and *B. pinnipedialis* which were isolated from marine mammals, were reported as the responsible agents of intracranial granuloma formation [6]. *B. neotomae* was reported to be isolated from cerebrospinal fluid samples from two patients with NB [7]. Although there are few studies about the effect of different species in the pathogenesis of the human brucellosis [8, 9] virulence and neurotropisim of *B. melitensis* are considered to be higher than the other species [10, 11].

Brucella infection usually presents with an acute febrile illness, but could cause to subacute or chronic diseases in human. The bacterium can affect various systems or organs and may present with a broad spectrum of clinical manifestations [12]. The clinical features of brucellosis changes according to the stage of infection and affected organ or system. In some occasions brucellosis can be insidious or present atypical features which can mimic various disorders [3, 13].

M. Kutlu
Infectious Diseases and Clinical Microbiology Department, Pamukkale University, Denizli, Turkey

Ö. Ergönül (✉)
Infectious Diseases and Clinical Microbiology Department, Koç University, Şişli, Istanbul, Turkey
e-mail: oergonul@ku.edu.tr

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_5

Any neurological involvement caused by brucellosis is defined as neurobrucellosis. Neurobrucellosis may develop at any stage of the disease and this serious complication is affected by several factors, such as affected area in the nervous system and duration of neurological involvement. Thus, NB may lead to widespread involvement of nervous system, including meningitis, meningoencephalitis, encephalitis, myelitis, peripheral and cranial neuropathies, subarachnoid haemorrhage and psychiatric manifestations [1, 2, 14].

Epidemiology

Brucellosis has been eliminated in several developed countries, but it is still endemic in some parts of the world [15]. Globally half a million new human cases are estimated to have the disease annually [16]. The vast majority of these cases are occurring in developing or undeveloped coutries and the main sources of human diseases are the contact with infected animals and consumption of infected animal products in these countries. *Brucella spp.* can infect various animals, such as *B. melitensis* in goats and sheep, *B. abortus* in cattle, and *B. suis* in pigs [17]. *Brucella* spp. can be transmitted to humans by direct contact with infected animals, through cuts and abrasions, or inhalation of aerosols, or ingestion of unpasteurized milk or milk products [1, 18]. Occupational exposure is more important in developed countries and brucellosis is usually seen in the farm workers, veterinarians, and hunters [19]. Other risk groups are immigrants from endemic countries, people traveling to endemic countries, and laboratory workers [19–21]. In developing countries, the consumption of raw or unpasteurized milk and dairy products have more prominent role in transmission of brucellosis. Besides, the presence of widespread infection among animals increases the occupational risks in endemic countries, too [22–25].

The frequency of NB was reported as 4% in brucellosis in a systematic review [26]. In two series of brucellosis from China and Kosovo NB was reported as 11.8% and 12.6%, respectively [27, 28]. On the other hand the prevelance of NB was reported as 37.5% in a prospective study from a tertiary center in Turkey [29].

Pathogenesis

Brucella spp. do not have toxins that cause direct damage to host cells and structural determinants that are important for virulence, such as capsule and fimbria, but they have some other virulence factors [30]. Pathogenic *Brucella spp.* can evade host immunity and multiply in phagocytic cells. This property of the bacteria is recognized as the major factor in the pathogenesis of disease [31]. The inhibition of apoptosis of the infected macrophage and dendtritic cell maturation are the other factors influencing the development of disease and could explain the chronicity in animals and humans [32–34].

The mechanism of central nervous system (CNS) invasion by the *Brucella* spp. is still obscure. Central nervous system ivolvement usually occurs by hematogenous dissemination but CNS involvement may be secondary to septic embolism in endocarditis or with the spread of parameningeal infection [35]. One of the mechanisms for CNS invasion is infection of endothelial cells [36]. In a *B. abortus* in vitro model demonstrated that *B. abortus* to adhere, invade and replicate in human brain microvascular endothelial cells [35]. Mononuclear phagocytic cells that the bacteria infect and multiply, play an important role in the spread of the bacteria. It is considered that infected macrophages and other phagocytes mediate the CNS invasion. It was reported that, in an vitro model, *B. Abortus* could pass the endothelial barrier if the monocytes were [35].

Brucella spp. can live both in the astrocytes and microglial cells following CNS invasion and lead to cytokine release like, TNFα, IL-6, IL-12 and IL-1β [37–39]. The innate immunity is responsible for the primary response. In vitro studies demonstrated that *B. abortus* could not directly infect and damage the neural cells. The damage was demonstrated to be related to the activation of TLR 2 and release of NO [40]. Among the macaques those were infected with *B.melitensis* via aerosols, growth in astrocytes, branching and increased TLR2 activity in white substance were detected in histopathologic examinations [41]. The inflammatory response caused by *Brucella* spp., which is relatively less severe but more chronic, result in tissue damage [42]. Inflammatory cell infiltration, astrogliosis, apoptosis of the astrocytes and reactive microgliosis are the main pathological findings in tissue materials from patients and experimental models [6, 37, 38, 40, 41, 43]. Occasionally CNS invasion can result from a neighbouring abscess or granuloma [10]. In some cases, vasculitis secondary to inflammation may develop and may cause to spasm, thrombus amd infarction [14, 44, 45].

Brucella spp. can cause an indirect effect of triggering an immunological mechanism leading to neural pathology. The demyelinating lesions that can accompany neurobrucellosis may be due to a vasculitic process or "molecular mimicry" mechanisms [46, 47]. Guillain-Barré syndrome (GBS) can also accompany to NB and similar molecular mimicry is considered as the possible pathogenetic mechanism. Additionally, *B. melitensis* infection can induce anti-GM1 ganglioside production and lead to flaccid limb paresis in mouse models [48]. However, the lack of antiganglioside antibody in a NB patient with Miller-Fischer syndrome is disproving this hypothesis [49]. Still, there is not enough evidence to prove that antiganglioside antibodies are present in patients with brucellosis and neurobrucellosis.

Clinical Characteristics

Both brucellosis and NB can present in a broad spectrum and various signs and symptoms (Table 5.1). Many authors have tried to classify the clinical presentations according to several aspects, like involvement site, course of the disease, and complications. However, these classifications have many limitations in terms of

Table 5.1 The signs and symptoms of brucellosis and neurobrucellosis

Brucellosis	Neurobrucellosis
Fever	Severe and persistent headache
Headache	Nausea
Fatigue	Vomiting
Chill	Lethargy
Sweating	Hearing loss
Anorexia	Blurred vision
Myalgia	Loss of vision
Arthralgia	Motor weakness
Low back pain	Sensory loss
Weight loss	Walking difficulty
Arthritis	Incontinance
Splenomegali	Neck stiffness
Hepatomegali	

accuracy [46, 49, 50]. Clinical syndromes are ultimately diverse, and the clinical picture may be confused by the coexistence of two or more syndromes in the same patient. Neurobrucellosis can present during the acute stage of brucellosis or other complications of brucellosis and several months later with a wide variety of symptoms. Clinical characteristics are discussed under three sub-headings; clinical features of brucellosis, common neurologic clinical presentations, and rare neurologic clinical presentations.

Clinical Features of Brucellosis

Patients with brucellosis have various signs and symptoms (Table 5.1) [29, 51, 52]. However, these signs and symptoms are non-specific for brucellosis and clinical presentations may resemble other diseases. It might be difficult to recognize brucellosis in non-endemic areas even sometimes in endemic areas.

Common Neurologic Clinical Features

In spite of many non-specific signs and symptoms patient with brucellosis may only have neurological signs and symptoms (Table 5.1). The nervous system involvement in brucellosis is variable and the signs and symptoms of neurobrucellosis depend, in part, on the site of infection and different pathogenetic processes play important role in the variability of the clinical features (Table 5.2) [29, 53].

The most common presentations of neurobrucellosis are acute or chronic meningitis or meningoencephalitis [29, 49]. The most frequent symptom in NB is severe

Table 5.2 Clinical presentations of neurobrucellosis

Frequent
Meningitis/meningoencephalitis
Encephalitis/myelitis/myeloencephalitis
Cranial nerve involvement
Peripheral neuropathy/Radiculopathy
Cerebellar syndromes
Vascular syndromes
Psychiatric manifestations
Rare
Brain/intramedullary abscess or granuloma
Demyelinization syndromes
Pseudotumor syndromes
Isolated papilledema
Isolated hearing loss
Isolated seizures
Diabetes insipidus

Data from Pappas et al. [53]

and persistent headache [14, 29, 49, 54]. Patients may present with nausea, vomiting, lethargy, hearing loss, blurred vision and loss of vision. Disease may result in motor weakness and sensory loss, walking difficulty and incontinance. In a case series, less than half of the patients with acute or chronic meningitis had neck neck stiffness [14, 49, 55]. Alterations in mental status is found in a minority of patients with brucellar meningitis. Besides, different than menengitis due to other infectious agents, the concomitance of the classic triad of meningitis (fever, neck stiffness and altered mental status) is rare.

Brucella infection can involve any parenchymal site in CNS, but cerebral white matter, cerebellum and medulla spinalis are more frequently affected in NB. Encephalitis is usually accompanied by meningeal and/or spinal involvement and rarely alone [10, 14]. Various signs and symptoms such as headache, nausea, vomiting, mental blunting, mild to moderate reduction in alertness, epileptic seizure, motor deficite, tremor, and ataxia can be seen depending on the affected area [10, 14, 56].

Spinal involvement is usually accompanied by other CNS involvements [57]. Myelitis often develops in months or years following systemic brucellosis, but sometimes occurs with acute meningoencephalitis [10, 58]. Myelitis may occur by compression of the abscess or irritation of the spondylodiscitis. Difficulty in walking, sphincter problems, paresis, spasticity, hyperreflexia and extensor plantar response are seen in NB patients. Additionally, myelitis can be associated with sensory loss and ataxia without cerebellar involvement [49, 58–60].

The cranial nerves (CNs) are at particular risk in NB and a pooled analysis from Turkey reported that CN involvement is present in one-fifth of the cases [54]. The eighth cranial nerve isparticularly at risk, therefore sensorineural hearing loss can occur. The isolated deafness or hearing loss may be the only clinical finding in some

NB cases [61]. The sixth and seventh cranial nerves may also be involved more frequently than other CNs [14, 29, 46, 54, 55]. Blurred vision, painful eye movements and relative afferent pupillary defect may occur due to optic nerve involvement. Damage of optic nerve can also lead to optic atrophy and permanent loss of vision [62–64]. Rarely, occulomotor nerve involvement was reported [64, 65].

Peripheral nerve involvement may occur as radiculopathy or polyradiculopathy in NB patients [14, 46, 66–68]. In a study from China, peripheral nerve involvement was reported in 47% of the patients with NB [27]. The usual clinical picture in peripheral nerve involvement is proximal polyradiculopathy without sensory loss, however in some cases sensory changes were reported [68, 69]. On the other hand Zhao et al., reported that the disease mainly involves axonal damage, and the sensory nerve involvement is higher than the motor nerve involvement [27]. Generally, lower extremities are affected and the clinical presentation is characterized by back pain, leg weakness and flaccid paraparesis.

Some psychiatric disturbances, including sleep disorders, nightmares, depression, agitation, behavioural disorders, irritability, psychosis and mutism can occur in NB [14, 46, 59, 70, 71]. During the course of brucellosis, depression may be seen without neurological involvement, however its frequency was 5% in NB [54]. Eren et al., have shown that significant improvemet can be achieved in Hamilton Depression Scale and Mini-Mental State Examination with anti-infective treatment in NB patients with psychiatric findings [70].

During the course of the diseases, some vascular complications such as subarachnoid hemorrhage, mycotic cerebral aneurysms, subdural hematoma, intracerebral hemorrhage, venous thrombosis, and ischemia may occur [14, 55, 60, 66, 72]. Gul et al., reported that cerebrovascular complications of NB were as frequent as 3.2% [54]. Vasospasm, vasculitis, and reccurent septic emboli that originate from the endocardium can play a role in the pathogenesis of meningovascular complications [44, 73].

Rare Neurologic Clinical Features

Guillain–Barre´ syndrome rarely develops following *Brucella* infections. There are reports that emphasize the misdiagnosis of GBS because of poyradiculopathy [74]. On the other hand GBS can be found concomittantly during *Brucella* infections [49, 75–79]. Axonal and the demyelinating forms of GBS were reported with NB [80].

Mass lesions in the brain are uncommon in *Brucella* infection. However, parenchymal abscess or granuloma in the brain, cerebellum and spinal cord and epidural absces can be seen in NB [6, 81–86]. Additionally, NB may cause a space-occupying intracranial mass lesions mimicking cerebral tumor [87–89]. Radiologic findings of these lesions also interfere with other diseases such as other infectious disease, autoimmune disease, neurosarcoidosis, and lymphoma [86, 89].

Demyelinating disorders can be seen in cases with NB. Some of these cases are mimicking multiple sclerosis [47, 90]. Neurobrucellosis may only present with

pseudotumor cerebri and increased intracranial pressure [91–95]. Rarely, epileptic seizures were reported [96]. The pituitary region involvement of brucellosis may cause diabetes insipidus or other hormonal disorders [97, 98].

Diagnosis

The first step for diagnosis of NB is having suspicion about it. Brucellosis could be at the top of the preliminary diagnosis list in endemic countries, however it is difficult to diagnose brucellosis in non-endemic coutries. It is important to suggest brucellosis in patients who are among the risk groups for brucellosis and have signs and symptoms that can not be explained with any other reasons. The broad spectrum of neurological signs and symptoms can make the diagnosis more difficult. A detailed history to identify the risk factors for *Brucella* infection and neurological evaluation is required. According to some authors, the diagnosis of neurobrucellosis might be based on clinical neurological symptoms, whereas according to some other authors the diagnosis is based on microbiological and/or biochemical evidences from cerebrospinal fluid [10, 29, 55, 99]. The presence of any one of the criteria listed in Table 5.3 is required for the diagnosis of NB.

Besides neurological signs and symptoms headache, nausea and vomiting were predictive for neurologic involvement in brucellosis [29, 55]. Increased age and a prolonged duration of disease were risk factors for NB in patients with brucellosis in another study [27].

Cerebrospinal fluid (CSF) analysis is required in NB diagnosis [55]. Lymphocytosis, increased protein and decreased glucose levels in the CSF indicate NB. The rates of isolation of *Brucella* spp. are low, therefore usually the NB cases were diagnosed by using serological methods. Tube agglutination test of CSF is widely used worldwide and it is a gold standart test for diagnosis of NB, as well. However, low antibody titres and the presence of incomplete antibody in the CSF may lead to false negative results. Also, tube agglutination test may be negative in the early stages of *Brucella* infection. Occasionally, it is possible to obtain positive results from tube agglutination with Coombs test and / or isolate the *Brucella* spp.

Table 5.3 Diagnostic criteria for neurobrucellosis among laboratory confirmed brucellosis patients

Symptoms and signs for suspect of neurobrucellosis (neurological signs, headache, nausea and vomiting)
The presence of lymphocytosis, increased protein and decreased glucose levels in the cerebrospinal fluid (CSF)
Isolation of *Brucella* spp. from CSF and/or presence of anti-*Brucella* antibodies in CSF and/or PCR positivity in CSF for *Brucella* spp
Findings in cranial MRI or CT

CSF cerebrospinal fluid, *CT* computed tomography, *MRI* magnetic resonance imaging, *PCR* polimerase chain reaction

in CSF, in case of negative tube agglutination test [29, 63, 100, 101]. The diagnostic cut-off value for antibody titre in CSF is controversial, but according to many authors it is acceptable to diagnose neurobrucellosis even with low antibody titers in CSF [98, 102–104]. Guven et al., showed that tube agglutination with Coombs test in CSF is highly sensitive and specific when the cut-off value is above or 1/8 [29]. Slide agglutination test (Rose Bengal) which is an easy and cheap test can also be used to detect the antibodies in CSF [105, 106]. This test could be false negative if the titer of antibodies was low. Another serological test, the enzyme-linked immunosorbent assay (ELISA) has a high sensitivity and specifity for diagnosis for NB and it is particularly recommended for chronic disease instead of tube agglutination test [107–110].

Polymerase chain reaction (PCR) test has a high sensitivity and specificity in isolating *Brucella* spp. from CSF samples. This diagnostic test is more rapid and safe for laboratory workers than classic isolation methods [111]. Recently, the next-generation metagenomic sequencing of CSF was used in diagnosis of NB [112, 113].

The findings of computed tomography (CT) or magnetic resonance imaging (MRI) are usually nonspecific and about half of patients affected with NB presents with radiological abnormalities. The MRI is the preffered imaging modality (Fig. 5.1). The cranial neuroimaging can reveal findings of inflammation such as menigeal, perivascular and nevre root enhancement, granuloma and abscess, white matter changes, and vascular changes [61].

On the other hand, there are supportive diagnostic methods to reveal CNS involvement, such as pathological and electrophysiological investigations. Pathological evaluation of the biopsy materials revealed that modarete mononuclear cell infiltration, reactive astrogliosis and microgliosis and astrosit apopitosis were

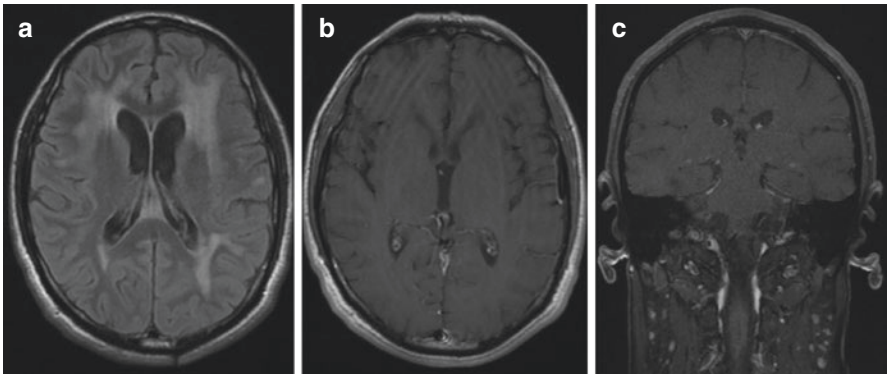


Fig. 5.1 A 41-year- old male with paraparesis, urinary incontinence and hearing loss for 1 year. In Cerebrospinal fluid (CSF) cell count was 20/mm^3 protein 565, and glucose 21 mg/dL. The Rose Bengal Test was positive in CSF, *Brucella* tube agglutination level in the CSF was 1/256, and 1/1024 with Coombs serum. (**a**) Images with magnetic resonance at bilateral cerebral hemispheres showed hyper intense regions in white substance with T2 section. (**b**) Contrast uptake in menengial structures which is more prominent in brain stem and medial temporal regions. (**c**) Contrast uptake in menengial structures, which is more prominent at the left side and at the cerebellopontine region

the main evidences of inflammation [6, 37, 38, 43]. However, the histopathological evidence of NB is limited in literature, because biopsy is rarely performed in patients with NB. Occasionally, the histopathological evaluation of intracranial mass lesions that are operated on can show marked nonnecrotizing granulomatous or non- granulomatous encephalitis with perivascular infiltration [86–88, 114]. Electromyography and electroencephalography can also provide additional evidence in the differentiating the involvement site of NB. Moreover, brain stem auditory evoked potentials (BAEPs) can display the dysfunction of the 8th cranial nerve in NB patients with hearing loss [115, 116]. On the other hand, BAEPs test is normal in patients with brucellosis and neurobrucellosis without any hearing loss complaints [117].

Differential Diagnosis

Wide variety of symptoms and signs of NB makes the diagnosis difficult with a long list of differential diagnosis. Differential diagnosis of NB includes various infectious diseases such as tuberculosis, neurosyphilis, neuroborreliosis, and vascular, autoimmune, and neoplastic diseases [14, 59, 87–89, 118]. In terma of imaging findings, differential diagnosis list includes other infectious disease, autoimmune disease, neurosarcoidosis, and neoplastic diseases [61, 86, 89].

Treatment

There is no randomized trial for the choices of antibiotic, dose, and duration of the treatment for neurobrucellosis. Triple combination therapies with doxycycline, rifampicin, trimethoprim- sulfamethaxazol (TMP-SMX), ceftriaxone, streptomycin, or gentamicin for more than 2 months were recommended [1, 14, 59, 66, 104, 119]. Doxycycline, rifampicin, ceftriaxone and TMP-SMX sufficiently can pass the blood-brain barrier (BBB), but streptomycin and gentamicin can pass in the presence of inflammation. The adverse events, including neurotoxicity and ototoxicity should be noted if an aminoglycoside was used. A major approach should be combination of doxycycline, rifampicin with ceftriaxone or TMP-SMX [1, 27, 28, 104]. Ceftriaxone-based regimens have been reported to be more successful and shorter than the oral standard treatment protocols [95].

The duration of treatment is another controversial issue in the treatment of NB. Although extreme examples of treatment durations like 19 months were reported in the literature, in many series antimicrobial treatment was continued for 4–9 months [29, 46, 55, 60, 67]. The cessation of treatment can be decided on the basis of normalization of the cell count and biochemical parameters in CSF and improvement in clinical findings [67, 104].

There are no adequate data for the use of corticosteroids in the treatment of neurobrucellosis. Lulu et al., reported that short-term corticosteroid therapy may be

effective in reducing the neurological deficit, especially in optic neuritis, arachnoiditis and demyelinating lesions [120]. In some case series and case reports, short-term steroid use have been reported in various situations such as myelitis, cranial nerve involvement, pseudotumor cerebri and hydrocephalus [69, 121–125].

Prognosis

Brucellar meningitis is considered to have a better prognosis than other meningitis, but mortality rates have been reported between 0% and 27% in neurobrucellosis cases [14, 58, 60]. The treatment reduced mortality, however neurologic sequelae were reported despite appropriate antibiotic therapy [14, 29, 46, 93]. Early diagnosis and treatment is important. The rate of neurologic sequelae is increased in case of myelitis, polyradiculopathy, cranial nerve involvement and underdiagnosed cases [29, 67, 104].

References

1. Gul HC, Erdem H. Brucellosis (*Brucella* species). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier Saunders; 2015. p. 2584–9.
2. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med. 2005;352:2325–36.
3. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis. 2007;7:775–86.
4. Wallach JC, Baldi PC, Fossati CA. Clinical and diagnostic aspects of relapsing meningoencephalitis due to Brucella suis. Eur J Clin Microbiol Infect Dis. 2002;21:760–2.
5. Kutlu M, Cevahir N, Erdenliğ-Gürbilek S, Akalın Ş, Uçar M, Sayın-Kutlu S. The first report of *Brucella suis* biovar 1 isolation in human in Turkey. J Infect Public Health. 2016;9:675–8.
6. Sohn AH, Probert WS, Glaser CA, Gupta N, Bollen AW, Wong JD, et al. Human neurobrucellosis with intracerebral granuloma caused by a marine mammal *Brucella* spp. Emerg Infect Dis. 2003;9:485–8.
7. Suárez-Esquivel M, Ruiz-Villalobos N, Jiménez-Rojas C, Barquero-Calvo E, Chacón-Díaz C, Víquez-Ruiz E, Rojas-Campos N, Baker KS, Oviedo-Sánchez G, Amuy E, Chaves-Olarte E, Thomson NR, Moreno E, Guzmán-Verri C. *Brucella neotomae* infection in humans, Costa Rica. Emerg Infect Dis. 2017;23:997–1000.
8. Dokuzoğuz B, Ergönül O, Baykam N, Esener H, Kiliç S, Celikbaş A, Eren S, Esen B. Characteristics of B. melitensis versus B. abortus bacteraemias. J Infect. 2005;50:41–5.
9. Troy SB, Rickman LS, Davis CE. Brucellosis in San Diego: epidemiology and species-related differences in acute clinical presentations. Medicine (Baltimore). 2005;84:174–87.
10. Madkour MM, Al-Moutarey KR, Al-Deep S, Al-Swailem R, Al-Okaily F. Neurobrucellosis. In: Madkour MM. editor. Madkour's brucellosis. Springer-Verlag: 2001. Berlin. P. 166–78.
11. Doganay M, Aygen B. Human brucellosis: an overview. Int J Infect Dis. 2003;7:173–82.
12. Solera J, Martinez-Alfaro E, Espinosa A. Recognition and optimum treatment of brucellosis. Drugs. 1997;53:245–56.
13. World Health Organization. 2006: Brucellosis in humans and animals. Available at: http://www.who.int/csr/resources/publications/Brucellosis.pdf. Accessed 17 Apr 2013.

14. McLean DR, Russell N, Khan MY. Neurobrucellosis: clinical and therapeutic features. Clin Infect Dis. 1992;15:582–90.
15. Zhang N, Huang D, Wu W, Liu J, Liang F, Zhou B, Guan P. Animal brucellosis control or eradication programs worldwide: a systematic review of experiences and lessons learned. Prev Vet Med. 2018;160:105–15.
16. Seleem MN, Boyle SM, Sriranganathan N. Brucellosis: a re-emerging zoonosis. Vet Microbiol. 2010;140:392–8.
17. Godfroid J. *Brucella* spp. at the wildlife-livestock Interface: an evolutionary trajectory through a livestock-to-wildlife "host jump"? Vet Sci. 2018;5:81.
18. Finn TB. Brucellosis. In: Cohen J, Powderly WG, editors. Infectious diseases. Elsevier; 2010. p.1238–40.
19. Young EJ. An overview of human brucellosis. Clin Infect Dis. 1995;21:283–9.
20. Al Dahouk S, Neubauer H, Hensel A, Schöneberg I, Nöckler K, Alpers K, Merzenich H, Stark K, Jansen A. Changing epidemiology of human brucellosis, Germany, 1962-2005. Emerg Infect Dis. 2007;13:1895–900.
21. Noviello S, Gallo R, Kelly M, Limberger RJ, DeAngelis K, Cain L, Wallace B, Dumas N. Laboratory-acquired brucellosis. Emerg Infect Dis. 2004;10:1848–50.
22. John K, Fitzpatrick J, French N, Kazwala R, Kambarage D, Mfinanga GS, MacMillan A, Cleaveland S. Quantifying risk factors for human brucellosis in rural northern Tanzania. PLoS One. 2010;5:e9968.
23. Sayin-Kutlu S, Kutlu M, Ergonul O, Akalin S, Guven T, Demiroglu YZ, Acicbe O, Akova M, Occupational Infectious Diseases Study Group. Laboratory-acquired brucellosis in Turkey. J Hosp Infect. 2012;80:326–30.
24. Kutlu M, Ergonul O, Sayin-Kutlu S, Guven T, Ustun C, Alp-Cavus S, Ozturk SB, Acicbe O, Akalin S, Tekin R, Tekin-Koruk S, Demiroglu YZ, Keskiner R, Gönen I, Sapmaz-Karabag S, Bosnak V, Kazak E. Risk factors for occupational brucellosis among veterinary personnel in Turkey. Prev Vet Med. 2014;117:52–8.
25. Proch V, Singh BB, Schemann K, Gill JPS, Ward MP, Dhand NK. Risk factors for occupational *Brucella* infection in veterinary personnel in India. Transbound Emerg Dis. 2018;65:791–8.
26. Dean AS, Crump L, Greter H, Hattendorf J, Schelling E, Zinsstag J. Clinical manifestations of human brucellosis: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2012;6:e1929.
27. Zhao S, Cheng Y, Liao Y, Zhang Z, Yin X, Shi S. Treatment efficacy and risk factors of neurobrucellosis. Med Sci Monit. 2016;22:1005–12.
28. Dreshaj S, Shala N, Dreshaj G, Ramadani N, Ponosheci A. Clinical manifestations in 82 neurobrucellosis patients from Kosovo. Mater Sociomed. 2016;28:408–11.
29. Guven T, Ugurlu K, Ergonul O, Celikbas AK, Gok SE, Comoglu S, Baykam N, Dokuzoguz B. Neurobrucellosis: clinical and diagnostic features. Clin Infect Dis. 2013;56:1407–12.
30. Percin D. Microbiology of Brucella. Recent Pat Antiinfect Drug Discov. 2013;8:13–7.
31. Ko J, Splitter GA. Molecular host-pathogen interaction in brucellosis: current understanding and future approaches to vaccine development for mice and humans. Clin Microbiol Rev. 2003;16:65–78.
32. Caron E, Peyrard T, Köhler S, Cabane S, Liautard JP, Dornand J. Live Brucella spp. fail to induce tumor necrosis factor alpha excretion upon infection of U937-derived phagocytes. Infect Immun. 1994;62:5267–74.
33. Jubier-Maurin V, Boigegrain RA, Cloeckaert A, Gross A, Alvarez-Martinez MT, Terraza A, Liautard J, Köhler S, Rouot B, Dornand J, Liautard JP. Major outer membrane protein Omp25 of Brucella suis is involved in inhibition of tumor necrosis factor alpha production during infection of human macrophages. Infect Immun. 2001;69:4823–30.
34. Billard E, Dornand J, Gross A. Brucella suis prevents human dendritic cell maturation and antigen presentation through regulation of tumor necrosis factor alpha secretion. Infect Immun. 2007;75:4980–9.
35. Miraglia MC, Rodriguez AM, Barrionuevo P, Rodriguez J, Kim KS, Dennis VA, Delpino MV, Giambartolomei GH. *Brucella abortus* traverses brain microvascular endothelial cells using ınfected monocytes as a Trojan horse. Front Cell Infect Microbiol. 2018;8:200.

36. Drevets DA, Leenen PJ, Greenfield RA. Invasion of the central nervous system by intracellular bacteria. Clin Microbiol Rev. 2004;17:323–47.
37. García Samartino C, Delpino MV, Pott Godoy C, Di Genaro MS, Pasquevich KA, Zwerdling A, Barrionuevo P, Mathieu P, Cassataro J, Pitossi F, Giambartolomei GH. Brucella abortus induces the secretion of pro-inflammatory mediators from glial cells leading to astrocyte apoptosis. Am J Pathol. 2010;176:1323–38.
38. Miraglia MC, Scian R, Samartino CG, Barrionuevo P, Rodriguez AM, Ibañez AE, Coria LM, Velásquez LN, Baldi PC, Cassataro J, Delpino MV, Giambartolomei GH. Brucella abortus induces TNF-α-dependent astroglial MMP-9 secretion through mitogen-activated protein kinases. J Neuroinflammation. 2013;10:47.
39. Miraglia MC, Costa Franco MM, Rodriguez AM, Bellozi PM, Ferrari CC, Farias MI, Dennis VA, Barrionuevo P, de Oliveira AC, Pitossi F, Kim KS, Delpino MV, Oliveira SC, Giambartolomei GH. Glial cell-elicited activation of brain microvasculature in response to Brucella abortus infection requires ASC inflammasome-dependent IL-1β production. J Immunol. 2016;196:3794–805.
40. Rodriguez AM, Delpino MV, Miraglia MC, Franco MMC, Barrionuevo P, Dennis VA, Oliveira SC, Giambartolomei GH. *Brucella abortus*-activated microglia induce neuronal death through primary phagocytosis. Glia. 2017;65:1137–51.
41. Lee KM, Chiu KB, Sansing HA, Didier PJ, Ficht TA, Arenas-Gamboa AM, Roy CJ, Maclean AG. Aerosol-induced brucellosis increases TLR-2 expression and increased complexity in the microanatomy of astroglia in rhesus macaques. Front Cell Infect Microbiol. 2013;3:86.
42. Baldi PC, Giambartolomei GH. Immunopathology of Brucella infection. Recent Pat Antiinfect Drug Discov. 2013;8:18–26.
43. Seidel G, Pardo CA, Newman-Toker D, Olivi A, Eberhart CG. Neurobrucellosis presenting as leukoencephalophaty. The role of cytotoxic T lymphocytes. Arch Pathol Lab Med. 2003;127:374–7.
44. Turkoglu SA, Halicioglu S, Sirmatel F, Yildiz M, Yildiz N, Yildiz S. Vasculitis and neurobrucellosis: evaluation of nine cases using radiologic findings. Brain Behav. 2018;8:e00947.
45. Ay S, Tur BS, Kutlay S. Cerebral infarct due to meningovascular neurobrucellosis: a case report. Int J Infect Dis. 2010;14 Suppl 3:e202–4.
46. Shakir RA, Al-Din AS, Araj GF, Lulu AR, Mousa AR, Saadah MA. Clinical categories of neurobrucellosis. A report on 19 cases. Brain. 1987;110:213–23.
47. Bussone G, La Mantia L, Grazzi L, Lamperti E, Salmaggi A, Strada L. Neurobrucellosis mimicking multiple sclerosis: a case report. Eur Neurol. 1989;29:238–40.
48. Watanabe K, Kim S, Nishiguchi M, Suzuki H, Watarai M. Brucella melitensis infection associated with Guillain-Barré syndrome through molecular mimicry of host structures. FEMS Immunol Med Microbiol. 2005;45:121–7.
49. Demiroğlu YZ, Turunç T, Karaca S, Arlıer Z, Alışkan H, Colakoğlu S, Arslan H. Neurological involvement in brucellosis; clinical classification, treatment and results. Mikrobiyol Bul. 2011;45:401–10.
50. Al Deeb SM, Yaqub BA, Sharif HS, Phadke JG. Neurobrucellosis: clinical characteristics, diagnosis, and outcome. Neurology. 1989;39:498–501.
51. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, Akdeniz H. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis. 2010;14:e469–78.
52. Sayin-Kutlu S, Kutlu M, Tuzun T, Ozdemir K. Spondylodiscitis: a common complication of brucellosis. J Infect Dev Ctries. 2018;12:550–6.
53. Pappas G, Akritidis N, Christou L. Treatment of neurobrucellosis: what is known and what remains to be answered. Expert Rev Anti-Infect Ther. 2007;5:983–90.
54. Gul HC, Erdem H, Bek S. Overview of neurobrucellosis: a pooled analysis of 187 cases. Int J Infect Dis. 2009;13:e339–43.
55. Yetkin MA, Bulut C, Erdinc FS, Oral B, Tulek N. Evaluation of the clinical presentations in neurobrucellosis. Int J Infect Dis. 2006;10:446–52.

56. Karaoglan I, Namiduru M, Akcali A, Cansel N. Different manifestations of nervous system involvement by neurobrucellosis. Neurosciences (Riyadh). 2008;13:283–7.
57. Gündüz T, Tektürk PT, Yapıcı Z, Kürtüncü M, Somer A, Törün SH, Eraksoy M. Characteristics of isolated spinal cord involvement in neurobrucellosis with no corresponding MRI activity: a case report and review of the literature. J Neurol Sci. 2017;372:305–6.
58. Shakir RA. Neurobrucellosis. Postgrad Med J. 1986;62:1077–9.
59. Akdeniz H, Irmak H, Anlar O, Demiroz AP. Central nervous system brucellosis: presentation, diagnosis and treatment. J Infect. 1998;36:297–301.
60. Ceran N, Turkoglu R, Erdem I, et al. Neurobrucellosis: clinical, diagnostic, therapeutic features and outcome: unusual clinical presentations in an endemic region. Braz J Infect Dis. 2011;15:52–9.
61. Al-Sous MW, Bohlega S, Al-Kawi MZ, Alwatban J, McLean DR. Neurobrucellosis: clinical and neuroimaging correlation. AJNR Am J Neuroradiol. 2004;25:395–401.
62. Karakurum Goksel B, Yerdelen D, Karatas M, Pelit A, Demiroglu YZ, Kizilkilic O, Tan M, Toygar O. Abducens nerve palsy and optic neuritis as initial manifestation in brucellosis. Scand J Infect Dis. 2006;38:721–5.
63. Sahin E, Yilmaz A, Ersöz G, Uğuz M, Kaya A. Multiple cranial nerve involvement caused by Brucella melitensis. South Med J. 2009;102:855–7.
64. Miyares FR, Deleu D, El Shafie SS, Equia F, Mesraoua B, Al Hail H, Salim K. Irreversible papillitis and ophthalmoparesis as a presenting manifestation of neurobrucellosis. Clin Neurol Neurosurg. 2007;109:439–41.
65. Işıkay S, Yılmaz K, Ölmez A. Neurobrucellosis developing unilateral oculomotor nerve paralysis. Am J Emerg Med. 2012;2085(30):e5–7.
66. Bahemuka M, Shemena AR, Panayiotopoulos CP, al-Aska AK, Obeid T, Daif AK. Neurological syndromes of brucellosis. J Neurol Neurosurg Psychiatry. 1988;51:1017–21.
67. Gul HC, Erdem H, Gorenek L, Ozdag MF, Kalpakci Y, Avci IY, Besirbellioglu BA, Eyigun CP. Management of neurobrucellosis: an assessment of 11 cases. Intern Med. 2008;47:995–1001.
68. Kochar DK, Agarwal N, Jain N, Sharma BV, Rastogi A, Meena CB. Clinical profile of neurobrucellosis--a report on 12 cases from Bikaner (north-west India). J Assoc Physicians India. 2000;48:376–80.
69. Kesav P, Modi M, Singla V, Khurana D, Prabhakar S. Kaleidoscopic presentation of neurobrucellosis. J Neurol Sci. 2013;331:165–7.
70. Eren S, Bayam G, Ergonul O, et al. Cognitive and emotional changes in neurobrucellosis. J Infect. 2006;53:184–9.
71. Shehata GA, Abdel-Baky L, Rashed H, Elamin H. Neuropsychiatric evaluation of patients with brucellosis. J Neurovirol. 2010;16:48–55.
72. Amiri RS, Hanif H, Ahmadi A, Amirjamshidi A. Brucella-related multiple cerebral aneurysms: report of a case and review of the literature. Surg Neurol Int. 2014;5:152.e.
73. Adaletli I, Albayram S, Gurses B, Ozer H, Yilmaz MH, Gulsen F, Sirikci A. Vasculopathic changes in the cerebral arterial system with neurobrucellosis. AJNR Am J Neuroradiol. 2006;27:384–6.
74. Goktepe AS, Alaca R, Mohur H, Coskun U. Neurobrucellosis and a demonstration of its involvement in spinal roots via magnetic resonance imaging. Spinal Cord. 2003;41:574–6.
75. Namiduru M, Karaoglan I, Yılmaz M. Guillian-Barre syndrome associated with acute neurobrucellosis. Int J Clin Pract. 2003;57:919–20.
76. Al-Eissa YA, Al-Herbis AS. Severe hypertension: an unusual presentation of Guillian-Barre syndrome in a child with brucellosis. Eur J Pediatr. 1996;155:53–5.
77. Aygul R, Deniz O, Guzelcik M, Kotan D. Guillain-Barré syndrome during active brucellosis. Eurasian J Med. 2010;42:157–9.
78. Babamahmoodi F, Babamahmoodi A. Brucellosis, presenting with guillain-barré syndrome. J Glob Infect Dis. 2011;3:390–2.

79. Elzein FE, Mursi M. Case report: Brucella induced Guillain-Barré syndrome. Am J Trop Med Hyg. 2014;91:1179–80.
80. García T, Sánchez JC, Maestre JF, Guisado F, Vilches RM, Morales B. Brucellosis and acute inflammatory polyradiculoneuropathy. Neurologia. 1989;4:145–7.
81. Ciftçi E, Erden I, Akyar S. Brucellosis of the pituitary region: MRI. Neuroradiology. 1998;40:383–4.
82. Novati R, Viganò MG, de Bona A, Nocita B, Finazzi R, Lazzarin A. Neurobrucellosis with spinal cord abscess of the dorsal tract: a case report. Int J Infect Dis. 2002;6:149–50.
83. Gündeş S, Meriç M, Willke A, Erdenliğ S, Koç K. A case of intracranial abscess due to *Brucella melitensis*. Int J Infect Dis. 2004;8:379–81.
84. Kizilkilic O, Turunc T, Yildirim T, Demiroglu YZ, Hurcan C, Uncu H. Successful medical treatment of intracranial abscess caused by Brucella spp. J Infect. 2005;51:77–80.
85. Daglioglu E, Bayazit N, Okay O, Dalgic A, Hatipoglu HG, Ergungor F. Lumbar epidural abscess caused by brucella species: report of two cases. Neurocirugia (Astur). 2009;20:159–62.
86. Alqwaifly M, Al-Ajlan FS, Al-Hindi H, Al Semari A. Central nervous system brucellosis granuloma and white matter disease in immunocompromised patient. Emerg Infect Dis. 2017;23:978–81.
87. Miguel PS, Fernández G, Vasallo FJ, Hortas M, Lorenzo JR, Rodríguez I, Ortiz-Rey JA, Antón I. Neurobrucellosis mimicking cerebral tumor: case report and literature review. Clin Neurol Neurosurg. 2006;108:404–6.
88. Erdem M, Namiduru M, Karaoglan I, Kecik VB, Aydin A, Tanriverdi M. Unusual presentation of neurobrucellosis: a solitary intracranial mass lesion mimicking a cerebral tumor: a case of encephalitis caused by Brucella melitensis. J Infect Chemother. 2012;18:767–70.
89. Algahtani H, Shirah B, Abdulghani D, Farhan R, Algahtani R. Occupational Neurobrucellosis mimicking a brain tumor: a case report and review of the literature. Case Rep Infect Dis. 2017;2017:1434051.
90. Karaoglan I, Akcali A, Ozkur A, Namiduru M. Neurobrucellosis mimicking demyelinizating disorders. Ann Saudi Med. 2008;28:148–9.
91. Tekeli O, Tomaç S, Gürsel E, Hasiripi H. Divergence paralysis & intracranial hypertension due to neurobrucellosis. A case report. Binocul Vis Strabismus Q. 1999;14:117–8.
92. Ozisik HI, Ersoy Y, Refik Tevfik M, Kizkin S, Ozcan C. Isolated intracranial hypertension: a rare presentation of neurobrucellosis. Microbes Infect. 2004;6:861–3.
93. Panagariya A, Sharma B, Mathew V. Pseudotumor--like presentation of neurobrucellosis. J Assoc Physicians India. 2007;55:301–2.
94. Yilmaz S, Serdaroglu G, Gokben S, Tekgul H. A case of neurobrucellosis presenting with isolated intracranial hypertension. J Child Neurol. 2011;26:1316–8.
95. Tugcu B, Nacaroglu SA, Coskun C, Kuscu DY, Onder F. Chronic meningitis complicating intracranial hypertension in neurobrucellosis: a case report. Semin Ophthalmol. 2015;30:429–31.
96. Yilmaz M, Ozaras R, Ozturk R, Mert A, Tabak F, Aktuglu Y. Epileptic seizure: an atypical presentation in an adolescent boy with neurobrucellosis. Scand J Infect Dis. 2002;34:623–5.
97. Trifiletti RR, Restivo DA, Pavone P, Giuffrida S, Parano E. Diabetes insipidus in neurobrucellosis. Clin Neurol Neurosurg. 2000;102:163–5.
98. Sturniolo G, Mondello P, Bruno S, Bonfatto OE, Frattima S, Albanese A, Restivo R, Liberti G, Pasquali P, Marianelli C. Neurobrucellosis associated with syndrome of inappropriate antidiuretic hormone with resultant diabetes insipidus and hypothyroidism. J Clin Microbiol. 2010;48:3806–9.
99. Sanchez-Sousa A, Torres C, Campello MG, et al. Serological diagnosis of neurobrucellosis. J Clin Pathol. 1990;43:79–81.
100. Tekin-Koruk S, Duygu F, Gursoy B, Karaagac L, Bayraktar M. A rare case of seronegative neurobrucellosis. Ann Saudi Med. 2010;30:412–4.

101. Pascual J, Combarros O, Polo JM, Berciano J. Localized CNS brucellosis: report of 7 cases. Acta Neurol Scand. 1988;78:282–9.
102. Young EJ. Utility of the enzyme-linked immunosorbent assay for diagnosing neurobrucellosis. Clin Infect Dis. 1998;26:1481.
103. Kochar DK, Kumawat BL, Agarwal N, et al. Meningoencephalitis in brucellosis. Neurol India. 2000;48:170–3.
104. Aygen B, Sumerkan B, Mırza M, Doganay M, Arman F. Treatment of neurobrucellosis with a combination of ceftriaxone, rifampicin and doxycycline (a study on ten cases). Med Mal Infect. 1996;26:1199–201.
105. Erdem H, Kilic S, Sener B, et al. Diagnosis of chronic brucellar meningitis and meningoencephalitis: the results of the Istanbul-2 study. Clin Microbiol Infect. 2013;19:E80–6.
106. Despotopoulos S, Akinosoglou K, Tzimas T, Akritidis N, Gogos C. Diagnosis of neurobrucellosis in resource-limited real-world settings: a case-series of 8 patients. J Neurol Sci. 2017;379:293–5.
107. Araj GF, Lulu AR, Saadah MA, Mousa AM, Strannegard IL, Shakir RA. Rapid diagnosis of central nervous system brucellosis by ELISA. J Neuroimmunol. 1986;12:173–82.
108. Araj GF, Lulu AR, Khateeb MI, Saadah MA, Shakir RA. ELISA versus routine tests in the diagnosis of patients with systemic and neurobrucellosis. APMIS. 1988;96:171–6.
109. Baldi PC, Araj GF, Racaro GC, Wallach JC, Fossati CA. Detection of antibodies to Brucella cytoplasmic proteins in the cerebrospinal fluid of patients with neurobrucellosis. Clin Diagn Lab Immunol. 1999;6:756–9.
110. Araj GF. Enzyme-linked immunosorbent assay, not agglutination, is the test of choice for the diagnosis of neurobrucellosis. Clin Infect Dis. 1997;25:28–32.
111. Colmenero JD, Queipo-Ortuño MI, Reguera JM, Baeza G, Salazar JA, Morata P. Real time polymerase chain reaction: a new powerful tool for the diagnosis of neurobrucellosis. J Neurol Neurosurg Psychiatry. 2005;76:1025–7.
112. Mongkolrattanothai K, Naccache SN, Bender JM, Samayoa E, Pham E, Yu G, Dien Bard J, Miller S, Aldrovandi G, Chiu CY. Neurobrucellosis: unexpected answer from metagenomic next-generation sequencing. J Pediatric Infect Dis Soc. 2017;6:393–8.
113. Fan S, Ren H, Wei Y, Mao C, Ma Z, Zhang L, Wang L, Ge Y, Li T, Cui L, Wu H, Guan H. Next-generation sequencing of the cerebrospinal fluid in the diagnosis of neurobrucellosis. Int J Infect Dis. 2018;67:20–4.
114. Martínez-Chamorro E, Muñoz A, Esparza J, Muñoz MJ, Giangaspro E. Focal cerebral involvement by neurobrucellosis: pathological and MRI findings. Eur J Radiol. 2002;43:28–30.
115. Khuraibet AJ, Shakir RA, Trontelj JV, Butinar D, al-Din AS. Brainstem auditory evoked potential (BAEP) abnormalities in brucellosis. J Neurol Sci. 1988;87:307–13.
116. Yaqub BA, Kabiraj MM, Shamena A, al-Bunyan M, Daif A, Tahan A. Diagnostic role of brainstem auditory evoked potentials in neurobrucellosis. Electroencephalogr Clin Neurophysiol. 1992;84:549–52.
117. Coskun O, Ertem GT, Ergun U, Kutlu G, Tulek N, Inan LE, Ozkan S. Evaluation of brainstem auditory potential in brucellosis patients with and without neurological involvement. Int J Neurosci. 2005;115:717–23.
118. Erdem H, Senbayrak S, Gencer S, et al. Tuberculous and brucellosis meningitis differential diagnosis. Travel Med Infect Dis. 2015;13:185–91.
119. Erdem H, Ulu-Kilic A, Kilic S, et al. Efficacy and tolerability of antibiotic combinations in neurobrucellosis: results of the Istanbul study. Antimicrob Agents Chemother. 2012;56:1523–8.
120. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF. Human brucellosis in Kuwait: a prospective study of 400 cases. Q J Med. 1988;66:39–54.
121. Haji-Abdolbagi M, Rasooli-Nejad M, Jafari S, Hasibi M, Soudbakhsh A. Clinical and laboratory findings in neurobrucellosis: review of 31 cases. Arch Iran Med. 2008;11:21–5.
122. Cagatay A, Karadeniz A, Ozsut H, Eraksoy H, Calangu S. Hearing loss in patient with neurobrucellosis. South Med J. 2006;99:1305–6.

123. Yilmaz M, Ozaras R, Mert A, Ozturk R, Tabak F. Abducent nerve palsy during treatment of brucellosis. Clin Neurol Neurosurg. 2003;105:218–20.
124. Jochum T, Kliesch U, Both R, Leonhardi J, Bär KJ. Neurobrucellosis with thalamic infarction: a case report. Neurol Sci. 2008;29:481–3.
125. Madjdinasab N, Naieni AR. Neurobrucellosis and steroid therapy. Iran J Clin Infect Dis. 2006;1:103–7.

Chapter 6
Neurological Complications of Syphilis

Deanna Saylor and Christina Marra

Syphilis is a sexually transmitted infection caused by the spirochete bacterium *Treponema pallidum* subspecies *pallidum.* It is an important public health problem worldwide with approximately 6 million new cases each year [1]. Syphilis is relevant to neurologists because it can be complicated by neurosyphilis, which can occur at any time after initial infection. Neurosyphilis can manifest with multiple neurological syndromes including meningitis, stroke, cranial neuropathies, sensory ataxia, and dementia. Due to diagnostic limitations, a high degree of suspicion must be maintained in order to recognize and appropriately treat neurosyphilis. Here, we review the epidemiology, clinical manifestations, diagnosis, management and pathophysiology of neurosyphilis.

Epidemiology

After the introduction of penicillin as effective treatment of syphilis in the early 20th century, much progress had been made in controlling syphilis in the United States (US). However, since the turn of the 21st century, syphilis rates in the US have risen steadily [2]. Much of this rise has been due to an increase in the number

D. Saylor (✉)
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Internal Medicine, John Hopkins Medicine, University Teaching Hospital, Lusaka, Zambia
e-mail: deanna@jhmi.edu

C. Marra
Department of Neurology and Internal Medicine, University of Washington School of Medicine, Seattle, WA, USA
e-mail: cmarra@uw.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_6

of syphilis cases among men who have sex with men, but a marked increase in syphilis has also been noted amongst women and heterosexual men since 2012 (Fig. 6.1). As a result of increasing infection rates amongst women, there has also been a sharp rise in rates of congenital syphilis, which is the second leading cause of stillborn deaths globally [2, 4]. Despite this increase in incidence, deaths from syphilis have decreased dramatically in the US over the past 50 years, with deaths from neurosyphilis decreasing six-fold [5]. Only congenital syphilis deaths have risen, with deaths increasing in proportion to the incidence of syphilis amongst women.

From a global perspective, regional syphilis rates vary drastically with Africa demonstrating the highest prevalence [6]. Furthermore, as in the US, local increases have been noted in several areas of the world since 2000, including Russia, China, Canada and England [6, 7]. In particular, increasing rates of syphilis have been observed among men who have sex with men in Europe and other high-income countries [8, 9]. As a result, a World Health Organization (WHO) analysis of global syphilis trends suggests a concerted reduction effort is needed before 2021 not only in order to achieve WHO target reduction goals but also in order to prevent a rise in the global incidence of syphilis [10].

The prevalence of neurosyphilis, however, is largely unknown for a variety of reasons. First, the diagnosis is often missed as patients may be minimally symptomatic and presentations can mimic many other neurological diseases, so a high clinical suspicion is required. In addition, guidelines vary on when screening for neurosyphilis is indicated, especially in regards to asymptomatic neurosyphilis which may become symptomatic if not detected early. Finally, the diagnosis requires cerebrospinal fluid (CSF) investigations, which are unobtainable in many parts of the world. As a result, most estimates of neurosyphilis prevalence are thought to underestimate the true prevalence of the condition. What is known is that, like syphilis in general, cases of neurosyphilis markedly decreased after the introduction of

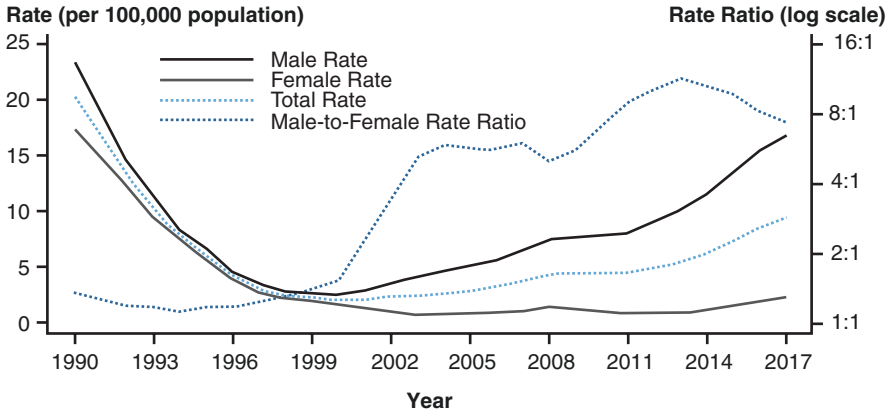
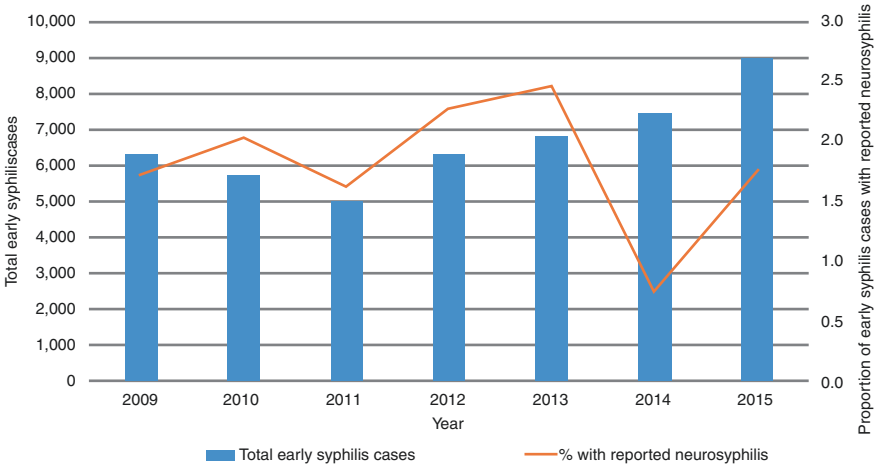


Fig. 6.1 Prevalence of syphilis infections by sex in the United States between 1990 and 2017. This graph illustrates the rising incidence of syphilis in the general population of the US since 2000 and the more recent increase in incidence rates amongst women since 2012. (From Centers for Disease Control and Prevention [3])

penicillin. However, a nearly tenfold increase of early neurosyphilis cases with meningeal or meningovascular involvement was seen after the introduction of penicillin, likely in patients with early neurosyphilis who were inadequately treated with standard penicillin regimens for uncomplicated syphilis [11]. In contrast, cases of late neurosyphilis (e.g. tabes dorsalis, general paresis) declined significantly after the introduction of penicillin [12, 13]. This suggests that partial treatment of neurosyphilis may affect the immune response to the infection in a way that increases the risk of early neurosyphilis. An increase in reported neurosyphilis cases, especially asymptomatic and early neurosyphilis, has been noted in individuals co-infected with human immunodeficiency virus (HIV) [14, 15].

Of the data that are available, most estimates of neurosyphilis from the US and Europe suggest that neurosyphilis occurs in approximately 1–3% of all cases of syphilis [16, 17]. A 2018 review of neurosyphilis cases reported to the Notifiable Diseases Surveillance System of the Centers for Disease Control and Prevention (CDC) found a reported prevalence of neurosyphilis amongst individuals diagnosed with syphilis in the US between 2009 and 2015 of 1.8% (Fig. 6.2) [18]. Of note, large regional and temporal variations were observed in the percentage of reported syphilis cases from which data on neurosyphilis were included, suggesting there is likely an under-ascertainment of neurosyphilis. As such, some studies have found higher prevalence rates of neurosyphilis. A review of syphilis cases from King County, Washington between 2012 and 2013 found a confirmed neurosyphilis prevalence of 3.5%. However, 7.9% of individuals reported either hearing or vision changes that could be consistent with neurosyphilis, not all of whom were investigated as such, again suggesting an ascertainment bias in the diagnosis [19]. A registry from sexually transmitted infections (STI) clinics in the Netherlands identified a 10–11% prevalence of neurosyphilis among patients with syphilis, but this was



[+] Includes 10 states (Delaware, Georgia, Hawaii, Indiana, Kentucky, Maine, South Dakota, Texas, Virginia, and west Virginia) that consistently reported a response for neurologic involvement for 70% of early syphilis cases from 2009–2015. Reporting percentage completeness ranged from 74% to 100% for these 10 states across the time period.

Fig. 6.2 Prevalence of neurosyphilis amongst patient with an early syphilis diagnosis in the United States between 2009 and 2015. (From de Voux et al. [18], with permission)

based on clinician reported diagnoses and no consistent case definitions were used [20]. Despite accounting for the highest prevalence of syphilis in the world, a paucity of data regarding the prevalence of neurosyphilis exists from Africa. A systematic review of neurosyphilis data from Africa found a limited number of studies available for inclusion, most of which demonstrated poor methodologic quality. Because of this, the strongest conclusion that could be drawn was that neurosyphilis accounted for approximately 3% of all meningitis cases and was a frequent cause of dementia in northern Africa [21]. Given the increasing rates of syphilis in key populations and in many areas of the world in conjunction with the potentially devastating consequences of neurosyphilis, more standardized approaches to screening and reporting of neurosyphilis are needed.

Clinical Characteristics

Neurosyphilis can develop at any time after acquisition of infection with *T. pallidum.* Animal models suggest *T. pallidum* invasion of the central nervous system (CNS) occurs within hours to days after primary infection [22], and human studies suggest CNS invasion is common [23], may be asymptomatic [24], may occur with or without concomitant CSF abnormalities [25], and may be either persistent or transient [24]. Early forms of neurosyphilis, occurring months to a few years after primary infection, primarily affect the meninges and cerebral blood vessels, while late forms, occurring decades after primary infection, primarily affect brain parenchyma and the spinal cord (Fig. 6.3).

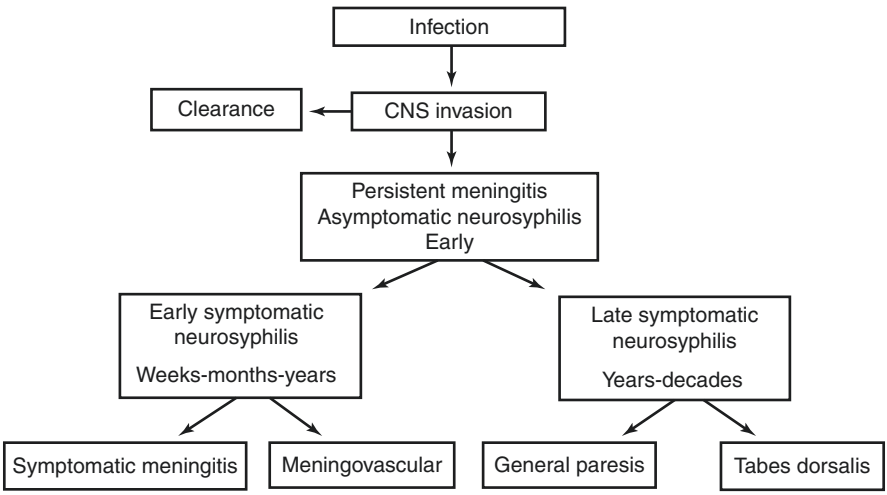


Fig. 6.3 Natural history of neurosyphilis. (From Marra [26], with permission.)

Clinical Syndromes

Asymptomatic Neurosyphilis

Asymptomatic neurosyphilis is defined as abnormal CSF studies meeting diagnostic criteria for neurosyphilis (see below) without associated neurological symptoms. The true prevalence of asymptomatic neurosyphilis is not known as CSF investigations are not routinely pursued in asymptomatic individuals with untreated syphilis. In addition, it is known that some people will have transient neuroinvasion by *T. pallidum,* which resolves without treatment and does not cause clinical symptoms [24, 25]. Risk factors for persistent neuroinvasion have not been identified, but some evidence suggests that it is independent of HIV status [23, 27]. Because it is unknown whether CNS invasion will be transient or persistent, most experts favor completing a treatment course for neurosyphilis in individuals identified to have asymptomatic neurosyphilis in order to prevent progression to symptomatic neurosyphilis. However, a study of neurologically asymptomatic persons living with HIV (PLWH) at high risk for neurosyphilis (defined by a high rapid plasma reagin (RPR) titer and/or low CD4 cell count) found only 1 of 59 patients had asymptomatic neurosyphilis after completing standard treatment for early syphilis [28]. This suggests that a single dose of penicillin (standard treatment for early syphilis) may be sufficient to treat early syphilis and prevent neurosyphilis even in individuals at high-risk of neurosyphilis. The small sample size in this study, however, and contradictory evidence suggesting PLWH are at higher risk of treatment failure after treatment for early syphilis [29] indicates the need for further research to define the optimal clinical approach to screening for and managing asymptomatic neurosyphilis, especially in individuals with HIV co-infection.

Symptomatic Meningitis and Meningovascular Syphilis

Symptomatic syphilitic meningitis presents identically to subacute meningitis from other causes with fevers, headache and neck stiffness. Confusion, seizures, and cranial neuropathies may also be present. Focal deficits may also be found, especially in individuals with gummas, focal mass lesions that usually arise from the pia mater (Fig. 6.4). Occasionally, the spinal cord may also be involved as part of meningomyelitis or with myelopathies secondary to spinal cord gummas. Meningeal syphilis can also cause an arteritis, which leads to meningovascular syphilis. This form of neurosyphilis presents with stroke, most commonly affecting the middle cerebral artery, and is often preceded by non-specific systemic prodromal symptoms such as headache, dizziness or confusion in the days to weeks prior to stroke onset.

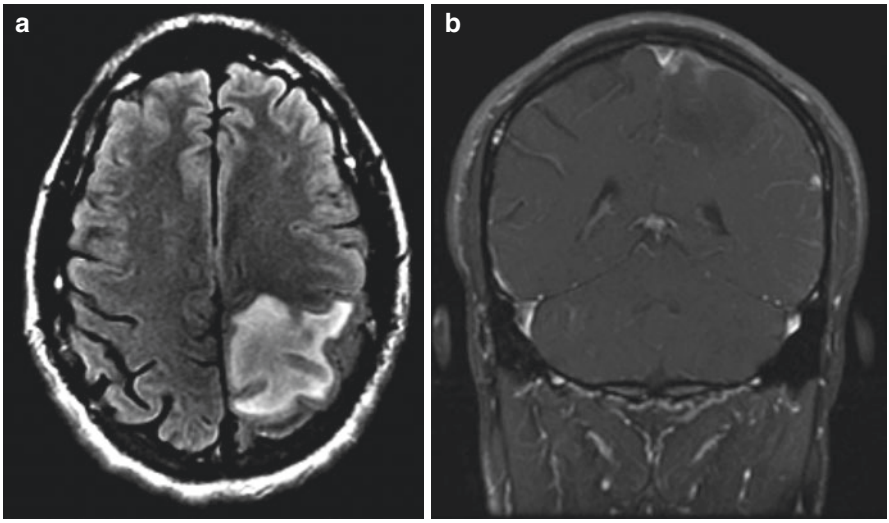


Fig. 6.4 Magnetic resonance image (MRI) showing an intracranial gumma. (**a**) Axial fluid attenuated inversion recovery (FLAIR) image showing vasogenic edema in the left fronto-parietal region. (**b**) Coronal post-contrast T1-weighted image showing the gumma as an enhancing dural-based mass with surrounding edema and mild mass effect. (Courtesy of the author, Dr. Marra)

General Paresis

Called by many names (e.g. syphilitic dementia, general paralysis of the insane, dementia paralytica), this syndrome most commonly develops 5–25 years after primary infection and has a wide variety of manifestations [26]. Initial manifestations are primarily memory impairment and personality changes, and, in most cases, these symptoms continue to progress to frank dementia. However, some individuals will develop a wide variety of psychiatric symptoms including psychosis, mania and depression. If untreated, general paresis can progress to seizures, immobility and incontinence [25]. Neurological examination is usually normal save for mental status early in the disease but can evolve to include pupillary and reflex abnormalities and intention tremor later in the disease course.

Tabes Dorsalis

Also called locomotor ataxia, tabes dorsalis was the most common form of neurosyphilis before the introduction of penicillin, but it is now uncommon [26]. Early symptoms may present as radicular paresthesias, which progress to vibration and proprioceptive loss in the lower extremities with progressive sensory ataxia. Bowel and bladder involvement is common, but involvement of the upper limbs is uncommon.

Ocular Syphilis

Like neurosyphilis, ocular syphilis can occur at any stage of syphilis, and its prevalence is largely unknown due to inconsistent screening and surveillance practices. However, in late 2014 and early 2015, several clusters of ocular syphilis were reported in the US suggesting that its incidence may be increasing and resulting in a clinical advisory being issued by the CDC [30]. Subsequent analysis of ocular syphilis prevalence in eight US jurisdictions during the same time period found a prevalence of 0.6% of ocular syphilis among individuals with syphilis, with five jurisdictions reporting increasing incidence [31]. The demographics of this population matched those of the overall syphilis epidemic in the US with most being men who have sex with men about half of whom were PLWH [31].

Ocular syphilis can involve almost any structure of the eye and may present as panuveitis, posterior uveitis, anterior uveitis, optic neuropathy, retinal vasculitis, and interstitial keratitis. The most common forms in most cohorts are panuveitis or posterior uveitis, and the majority of patients present with bilateral disease [32–36]. A 2009–2017 cohort from Israel, however, found that 78% of ocular syphilis cases were due to optic neuropathy with papilledema as the most common finding [37]. This was a retrospective cohort from a single center, and only 30% of the cohort were PLWH, which may account for some of the differences observed. Ocular syphilis may occur in association with or independent from neurosyphilis, with approximately one-third to two-thirds of individuals with ocular syphilis having CSF findings consistent with neurosyphilis [31, 33, 34, 36]. While ocular syphilis can result in permanent visual changes, including blindness, visual outcomes after appropriate antibiotic treatment are good in the majority of cases with earlier treatment initiation linked to improved visual outcomes [32, 33, 35, 38].

Atypical Manifestations

In recent years, there have been an increasing number of reports of neurosyphilis presenting with temporal lobe encephalitis complicated by seizures and mimicking herpes simplex virus encephalitis [39–42]. Several reports of neurosyphilis mimicking limbic and/or autoimmune encephalitis with prominent temporal lobe involvement have also emerged [43, 44]. In addition, a 2019 prospective study of patients with general paresis revealed that those with greater medial temporal lobe atrophy had both more severe cognitive impairment and a poorer cognitive outcome after antibiotic therapy [45]. Taken together, these findings suggest *T. pallidum* may have a predilection for the temporal lobes, a finding which should be further explored.

HIV Co-Infection

Much of the increase in neurosyphilis cases in recent decades has coincided with the HIV epidemic as HIV and syphilis co-infection is common. A 2018 review of 92 cases of neurosyphilis in PLWH in China found that nearly half were diagnosed with asymptomatic neurosyphilis, one-third of which were in individuals with ocular syphilis. Syphilitic meningitis and stroke accounted for the majority of the remaining cases, with late neurosyphilis making up only 14% of the diagnoses. In addition, the CSF profile of PLWH with neurosyphilis also varied depending on the diagnosis. Syphilitic meningitis was more likely to have a pleocytosis than other forms, and asymptomatic neurosyphilis was less likely to have an elevated protein [46].

Since early in the HIV epidemic, PLWH with syphilis were noted to develop neurosyphilis soon after completing antibiotic treatment regimens for early syphilis at much higher rates than HIV- individuals with early syphilis [15, 47]. Furthermore, some studies have found rates of symptomatic neurosyphilis are up to 3–4 times higher among PLWH than HIV- individuals [17, 48]. Failure rates of standard, uncomplicated, syphilis treatment are also much higher among PLWH than HIV- individuals [29]. This increased treatment failure may be due to higher rates of undiagnosed neurosyphilis that is inadequately treated with standard antibiotic regimens for uncomplicated syphilis. As noted above, this finding in particular suggests that regular screening for asymptomatic neurosyphilis may be indicated in HIV+ patients with early syphilis and, if found, likely warrants full treatment for neurosyphilis. However, the approach to asymptomatic neurosyphilis remains controversial.

Given the association between HIV infection and cognitive impairment and the high rates of syphilis co-infection amongst PLWH, the question of whether syphilis co-infection contributed to cognitive impairment was an open one. A study of 136 PLWH found that those with a history of syphilis had a greater degree of cognitive impairment than those with no history of syphilis, even after controlling for education and premorbid intelligence [49]. However, two contemporary studies revealed no association between neurosyphilis or syphilis and cognition in PLWH. In the first, 132 men with syphilis and HIV co-infection underwent CSF investigations and the mental alternation test as an assessment of cognitive impairment. While men with neurosyphilis had higher levels of HIV RNA and inflammatory CSF cytokines, they were not more cognitively impaired than those without neurosyphilis [50]. In a subsequent study of 623 PLWH and 246 HIV- controls, a history of syphilis was more common in PLWH (22%) than in HIV- (8%) individuals, but individuals with syphilis were not more likely to have cognitive impairment or depression [51]. Of note, this study did not limit participants to those with confirmed neurosyphilis; rather, it included anyone with a history of any form of syphilis. Still, its results are similar to the prior study and suggest neurosyphilis does not significantly contribute to cognitive impairment among PLWH.

Diagnosis

Diagnosis of neurosyphilis is based on clinical findings, serologic tests, CSF examinations, and, often, neuroimaging results.

Serologic Tests

Serologic tests for syphilis are divided into two types – nontreponemal and treponemal tests. Nontreponemal tests – which include RPR, VDRL, and the toluidine red unheated serum test (TRUST) – detect IgG and IgM antibodies to a synthetic cardiolipin- cholesterol-lecithin antigen and are expressed as titers. Higher titers are generally indicative of greater disease activity, and titers decline over time – even without treatment – so many individuals with late syphilis will have non-reactive results. In addition, titers should decrease with at least a four-fold reduction or reversion to non-reactive after successful syphilis treatment. False positive results can occur in the setting of certain autoimmune diseases, pregnancy, injection drug use and older age. False negative results can occur when antibody levels in the blood are so high that they greatly outnumber available antigen and flocculation does not occur, a phenomenon known as a prozone reaction.

Treponemal tests include the fluorescent treponemal antibody absorption (FTA-ABS), *Treponema pallidum* particle agglutination assay (TPPA) and the *Treponema pallidum* hemagglutination assay (TPHA), as well as a variety of chemiluminescent and enzyme immunoassays (EIAs and CIAs). These tests detect IgG and IgM antibodies to whole organisms or recombinant *T. pallidum* proteins, and they generally remain positive for the duration of an individual's life, even after treatment. The combination of treponemal and non-treponemal tests can help to determine an individual's syphilis and treatment status (Table 6.1).

CSF Investigations

Most individuals with neurosyphilis will have either a pleocytosis or elevated protein on basic CSF investigations. However, these abnormalities are more common in asymptomatic or early neurosyphilis while patients with tabes dorsalis may have entirely normal CSF. Non-treponemal tests, in particular the CSF VDRL, are often utilized for a diagnosis of neuroysphilis. In fact, a positive CSF-VDRL is considered the gold standard test for neurosyphilis, but its sensitivity, which ranges from 30% to 70%, limits its utility [26]. It is very specific, so a positive test establishes the diagnosis of neurosyphilis, but a negative test does not exclude the diagnosis.

Table 6.1 A combination of treponemal and non-treponemal tests are used to diagnose syphilis

	Treponemal test Negative	Treponemal test Positive
Non-Treponemal test Negative	No syphilis infection	Syphilis infection: Very early syphilis Treated syphilis Late stage untreated syphilis
Non-Treponemal test Positive	No syphilis infection False positive non-treponemal test	Syphilis infection: If non-treponemal test demonstrates high titers, this is indicative of active untreated syphilis If non-treponemal test demonstrates low titers, this is indicative of either previously treated syphilis or untreated late syphilis or very early syphilis

The various combinations of results are indicative of stage of syphilis infection and/or treatment status as shown in this figure. (Treponemal tests: FTA-ABS fluorescent treponemal antibody absorption; TPHA *Treponema* pallidum hemoagglutination assays; TPPA *Treponema pallidum* particle agglutination assay. Non-treponemal tests: RPR rapid plasma reagin; VDRL venereal disease research laboratory, TRUST toluidine red unheated serum test)

CSF-RPR and CSF-TRUST have also been investigated for neurosyphilis. While specific, they likely have even lower sensitivity with prior studies demonstrating that these assays miss up to one-third of CSF-VDRL-positive cases [52, 53]. However, a 2019 study from Brazil found CSF-RPR was in 100% agreement with CSF-VDRL in a series of 121 samples from individuals with confirmed neurosyphilis (CSF-VDRL reactive), suspected neurosyphilis (compatible clinical syndrome and CSF VDRL non-reactive), and controls (systemic syphilis but no suspicion of neurosyphilis and CSF VDRL non-reactive), suggesting the utility of CSF-RPR in the diagnosis of neurosyphilis needs further study [54]. CSF treponemal tests are sensitive but not specific and perform better in excluding asymptomatic than symptomatic neurosyphilis. High-titer CSF-TPHA and CSF-TPPA (greater than or equal to 1:640) have both shown promise as diagnostic tests for neurosyphilis with specificity similar to CSF-VDRL and the possibility that these assays may detect some cases of neurosyphilis missed by CSF-VDRL [55, 56]. In addition, several CSF PCR assays have also been developed to detect *T.* pallidum nucleic acid, but studies of their utility have largely been small and underpowered. A 2018 systematic review of these studies found sensitivity of CSF PCR assays varied between 40% and 70% when compared to CSF-VDRL with specificity ranging from 60% to 100% [57]. The lack of a sensitive and specific diagnostic gold standard makes such studies difficult, but the demonstrated low sensitivity of these assays suggests they likely have a limited role in the diagnosis of neurosyphilis.

As such, a diagnosis of neurosyphilis can be made based on a combination of serological treponemal and non-treponemal tests and CSF investigations for both asymptomatic and symptomatic neurosyphilis. However, criteria for asymptomatic neurosyphilis differ between HIV- individuals and PLWH and, amongst those with HIV co-infection, parameters of HIV control including CD4 T cell count, plasma viral load and antiretroviral therapy status (Table 6.2). In particular, because HIV infection itself can cause a pleocytosis, a higher CSF white blood cell count and a reactive CSF treponemal test are needed in order to make the diagnosis of

Table 6.2 Diagnostic criteria for neurosyphilis

	Asymptomatic neurosyphilis	Symptomatic neurosyphilis
Any HIV status	Reactive serum treponemal test Reactive CSF-VDRL	Reactive serum treponemal test Symptoms and signs of neurosyphilis Reactive CSF-VDRL
If CSF VDRL is negative…		
HIV-uninfected (HIV−)	Reactive serum treponemal test CSF WBC > 5 cells/μL or CSF protein >45 mg/dL	Reactive serum treponemal test Symptoms and signs of neurosyphilis CSF WBC > 5 cells/μL or CSF protein >45 m/dL
HIV-infected (HIV+) AND Plasma CD4 T cell count <200 cells/μL AND Undetectable plasma HIV RNA AND On antiretroviral therapy	Reactive serum treponemal test CSF WBC > 5 cells/ μL	
HIV-infected (HIV+) AND Plasma CD4 T cell count > 200 cells/ μL OR Detectable plasma HIV RNA OR Not on antiretroviral therapy	Reactive serum treponemal test Reactive CSF FTA-ABS CSF WBC > 20 cells/μL	

All criteria listed must be met for a diagnosis of either asymptomatic or symptomatic neurosyphilis *CSF* cerebrospinal fluid, *FTA-ABS* fluorescent treponemal antibody absorption, *VDRL* venereal disease research laboratory, *WBC* white blood cells

asymptomatic neurosyphilis in PLWH with CD4 T cell count >200 cells/μL, unsuppressed plasma HIV viral load, and not on antiretroviral therapy (i.e. those likely to demonstrate a CSF pleocytosis secondary to HIV itself).

Of note, evidence suggests that diagnostic criteria for neurosyphilis are inconsistently applied in a clinical setting. In one review of antibiotic therapy initiated after CSF analysis for suspicion of possible neurosyphilis, only 86% of patients with definite neurosyphilis (CSF VDRL reactive) were treated with an antibiotic regimen appropriate for neurosyphilis, and half of patients with CSF findings supportive of neurosyphilis were not treated with an antibiotic regimen for neurosyphilis. Furthermore, 17% of patients treated for neurosyphilis had no CSF findings suggestive of the diagnosis [58]. These findings reflect the complexity of making a diagnosis of neurosyphilis and the clinical practice heterogeneity that results.

Risk Factors

Given the complexities of confirming a diagnosis of neurosyphilis, it is imperative to both have a high clinical suspicion for and also to identify individuals at highest risk of developing neurosyphilis. Unfortunately, symptoms cannot be the only guide. In a study of 81 HIV- individuals and 385 PLWH with syphilis who underwent lumbar puncture (LP) and in which neurosyphilis was defined as a reactive

CSF-VDRL, absence of neurological symptoms did not exclude the diagnosis of neurosyphilis. Amongst PLWH, odds of neurosyphilis were higher with mild or greater photophobia, vision loss, and gait incoordination and moderate or greater hearing loss. While the specificity of these symptoms were high (92–100%), the sensitivity was very low (2–38%). Furthermore, no symptoms were more common amongst HIV- individuals with neurosyphilis [59]. Diplopia has recently been associated with several case reports of neurosyphilis with authors suggesting that it is often overlooked as a neurosyphilis symptom because it is a common symptom in other neurological disorders as well [60]. Furthermore, in a large multicenter study of CSF-VDRL reactive neurosyphilis, diplopia was the only symptom associated with a poor outcome after diagnosis [61]. Thus, it may serve as both a harbinger of the diagnosis and an indication for aggressive treatment and close monitoring after treatment.

In both PLWH and HIV- individuals, higher RPR titer is associated with increased risk of neurosyphilis [62, 63]. In one analysis, an RPR titer >1:32 was associated with a nearly 11-fold increased risk of neurosyphilis in HIV- individuals and a 6-fold increased risk in PLWH when both asymptomatic and symptomatic cases were included [62]. In another combined cohort of PLWH and HIV- individuals, an RPR titer >1:128 conferred twice the odds of neurosyphilis as a combined endpoint including both asymptomatic and symptomatic neurosyphilis [14]. An analysis of HIV- individuals with syphilis found those persons with RPR titers ≥1:4 or TPPA titers ≥1:2560 were much more likely to have neurosyphilis [64]. Elevated serum creatine kinase levels were also associated with increased risk of neurosyphilis in this study. Amongst PLWH, low CD4 count (particularly at or below 350 cells/μL), not taking antiretroviral therapy, and detectable plasma HIV RNA are also associated with risk of neurosyphilis [14, 62, 63, 65, 66]. Additionally, some experts believe that, despite the increased incidence of asymptomatic neurosyphilis, the majority of PLWH with neurosyphilis present with symptomatic rather than asymptomatic neurosyphilis. For example, one study found that 38 LPs would need to be performed amongst neurologically asymptomatic PLWH with syphilis in order to detect one case of asymptomatic neurosyphilis, suggesting that not every PLWH with syphilis needs to undergo an LP [63]. However, the participants in this study were not selected based on the aforementioned criteria that would have designated them as high-risk for neurosyphilis. Still, a study of PLWH at high-risk for neurosyphilis found that only 1 of 59 PLWH had evidence of asymptomatic neurosyphilis after completing treatment for uncomplicated systemic syphilis, again suggesting that LP's amongst all individuals with HIV co-infection may not be necessary as rates of asymptomatic neurosyphilis are low even after treatment for uncomplicated syphilis [28].

Treatment

Per CDC guidelines, standard treatment for neurosyphilis is with intravenous penicillin G for 10–14 days (i.e. 18–24 million units/day administered in six divided doses or a continuous influsion). Intramuscular procaine penicillin (2.4 million units daily) in combination with oral probenecid (500 mg four times daily) can also be

utilized for 10–14 days. In penicillin allergic patients, intravenous high-dose ceftriaxone (2 g intravenously daily x 14 days) can be employed, although the recommendation is based off of small studies and has less data to support their widespread use [67].

Treatment response is monitored with serial non-treponemal test titers, most commonly serum RPR titers. In early syphilis, titers should be obtained at 6 months and 12 months post-treatment in HIV- individuals and 6, 12, 18, and 24 months post-treatment in PLWH. In late syphilis, follow-up titers should be obtained 6, 12 and 24 months post-treatment in HIV- individuals and 3, 6, 9, 12, and 24 months post-treatment in PLWH. Treatment success is defined by at least a four-fold decrease in titers or reversion to non-reactive [67]. Treatment failure should be considered in any individual whose non-treponemal test titers fail to decline at least four-fold or revert to non-reactive after treatment. Any individual meeting these criteria after treatment for uncomplicated syphilis should be evaluated for neurosyphilis as unrecognized neurosyphilis, especially in early syphilis, may account for persistently high titers. For example, in one cohort of PLWH who did not achieve a four-fold reduction in their RPR titers one-year after treatment for uncomplicated syphilis, treatment failure was attributed to unrecognized neurosyphilis (based on CSF findings 12 months post-treatment) in 42%, with those with low CD4 counts, with high plasma HIV RNA, and not taking antiretroviral therapy most likely to have neurosyphilis [68]. In a cohort of 400 HIV- Chinese patients without an adequate reduction in RPR titer after treatment of uncomplicated syphilis, one-third were found to have asymptomatic neurosyphilis (based on post-treatment CSF studies) with middle age and high baseline RPR titers identified as risk factors [69].

In individuals with neurosyphilis who obtain at least a four-fold decrease or normalization of serum non-treponemal test titers, a repeat lumbar puncture may not be needed to confirm successful neurosyphilis treatment. Two studies have shown that normalization of serum RPR titers corresponds to normalization of CSF and clinical abnormalities in both PLWH and HIV- individuals after treatment for neurosyphilis [70, 71]. However, in the largest systematic study of PLWH, serum RPR normalization did not correctly predict CSF normalization after neurosyphilis treatment in those not taking antiretroviral therapy. As such, the CDC recommends that repeat CSF examinations be performed in all individuals treated for neurosyphilis every 6 months after completion of treatment until resolution of CSF abnormalities. If the CSF pleocytosis has not decreased after 6 months or if CSF abnormalities persist 2 years after treatment, re-treatment is recommended [67]. Of note, CSF white blood cell count is the most sensitive measure of therapy effectiveness. However, CSF-VDRL titers and protein levels should also normalize after therapy, but these changes generally occur more slowly [70, 72].

Pathophysiology

The striking differences in rates of neurosyphilis, types of CSF abnormalities, and response to treatment seen between PLWH who are virally suppressed and on antiretroviral therapy and those who are antiretroviral therapy-naïve illustrate the

importance of host immunity in the course of syphilis. Several studies have delineated the role of B cells and CXC chemokine ligand-13 (CXCL13), also called B lymphocyte chemoattracant (BLC) and B cell-attracting chemokine-1 (BCA-1), in the pathophysiology of neurosyphilis. A 2004 study of 46 PLWH and syphilis and 26 PLWH without syphilis found an elevated percentage of B cells in the CSF of those with neurosyphilis [73]. In a later study of CSF from individuals with neurosyphilis (defined by CSF abnormalities and including both asymptomatic and symptomatic neurosyphilis) and controls (individuals with syphilis but no evidence of neurosyphilis), CSF from individuals with neurosyphilis was found to be enriched in B cells with higher immunoglobulin indices compared to controls. Ectopic germinal centers were observed within an intracranial syphilitic gumma in one patient who underwent surgical resection. CXCL13 levels were higher in these CSF samples and mediated B cell migration and aggregation both *in vitro* and *in vivo* [74]. In a study of HIV- individuals with neurosyphilis defined by either CSF-VDRL or CSF-FTA-ABS positivity, uncomplicated syphilis and healthy controls, CXCL13 levels did not differ in the blood but were significantly higher among individuals with neurosyphilis than other groups. Furthermore, CSF CXCL13 levels were associated with increased CSF pleocytosis, protein levels, and IgG index as well as higher levels of CSF interleukin (IL)-6 and IL-10 and lower levels of IL-12. CSF CXCL13 levels then significantly reduced after treatment [75]. On the other hand, CSF CXCL13 levels in PLWH with neurosyphilis (defined by vision or hearing loss and/or CSF abnormalities) are independent of CSF pleocytosis, plasma HIV RNA, CD4 T cell count, and antiretroviral therapy use, and odds of neurosyphilis increased more than two-fold for each log increase in CSF CXCL13 concentration [76]. Taken together, these results indicate the humoral immune response of neurosyphilis is driven a least in part by CXCL13-mediated mechanisms, and CXCL13 may have utility as both a diagnostic indicator of neurosyphilis and a marker of therapeutic response.

Different strains of *T. pallidum* have been identified, and their role in the development of neurosyphilis has also been investigated. Initially, studies of six different *T. pallidum* strains in a rabbit model suggested strains varied in their neurovirulence with one strain not showing any evidence of CNS invasion and other strains differing markedly in the time to CNS invasion and the degree of CSF pleocytosis elicited [77]. An enhanced method of molecular phenotyping of samples from 158 individuals from the US, China, Ireland and Madagascar identified 25 unique strains, most of which had large regional overlap. One particular strain, subtype 14d/f, was more common in those with a reactive CSF-VDRL, with 50% of infected individuals having neurosyphilis compared to only 24% of individuals infected with all other strains [78]. However, these findings were not confirmed in a study of ocular syphilis in which no clear oculotropic strain of *T. pallidum* was identified [79]. Further investigation in larger and geographically diverse cohorts are needed to definitively understand the role of *T. pallidum* strains in the development of neurosyphilis, findings which may lead to improved understanding of neurosyphilis pathophysiology and, subsequently, diagnosis and management.

In addition to pathogen genetics, there is also emerging evidence that host genetics may play a role in the development of neurosyphilis. Common polymorphisms in toll-like receptors (TLRs) which impair cell signaling in response to *T. pallidum* lipoproteins have been identified *in vitro*. A study of single nucleotide polymorphisms (SNPs) in TLR genes amongst 456 white patients with syphilis identified a common TLR-1 polymorphism that was associated with increased risk of laboratory-confirmed neurosyphilis (CSF VDRL reactive) and common TLR2 and TLR6 polymorphisms that were associated with clinically defined neurosyphilis [66]. In another study, two IL-10 promoter polymorphisms were found to be associated with higher levels of CSF IL-10 and a higher risk of neurosyphilis [80]. Because IL-10 is a potent anti-inflammatory chemokine, it is possible that the lower levels of inflammation create a local environment in the CSF that facilitates *T. pallidum* persistence.

Future Work

While syphilis remains a major public health issue worldwide, the prevalence of neurosyphilis is largely unknown due to inconsistent screening practices and diagnostic criteria requiring CSF analysis. Lack of a true gold standard diagnostic test hinders neurosyphilis identification and leads to a body of research with heterogenous cohorts utilizing different definitions of the disease. Further work to identify a gold standard diagnostic assay with high sensitivity and specificity is urgently needed. In addition, further research is also needed to develop accurate screening protocols in order to identify patients at greatest risk of asymptomatic neurosyphilis or those who are minimally symptomatic who should undergo LP screening. Finally, better understanding the host and pathogen factors that lead to the development of neurosyphilis in some individuals but not others may lead to improved understanding of the pathophysiology of the disease and, subsequently, improved treatment regimens.

References

1. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10:e0143304.
2. Centers for Disease Control and Prevention. Sexually transmitted diseases surveillance [online]. Available at: https://www.cdc.gov/std/stats17/Syphilis.htm. Accessed 1 May.
3. Centers for Disease Control and Prevention. Figure 40 – Primary and secondary syphilis – rates of reported cases by sex and male-to-female ratios, United States, 1990–2017. [online]. Available at: https://www.cdc.gov/std/stats17/figures/40.htm. Accessed 1 July.
4. World Health Organization. Report on global sexually transmitted infection surveillance 2018. Geneva: World Health Organization; 2018.

5. Peterman TA, Kidd SE. Trends in deaths due to syphilis, United States, 1968-2015. Sex Transm Dis. 2019;46:37–40.
6. Smolak A, Rowley J, Nagelkerke N, et al. Trends and predictors of syphilis prevalence in the general population: global pooled analyses of 1103 prevalence measures including 136 million syphilis tests. Clin Infect Dis. 2018;66:1184–91.
7. Stamm LV. Global challenge of antibiotic-resistant Treponema pallidum. Antimicrob Agents Chemother. 2010;54:583–9.
8. Read P, Fairley CK, Chow EP. Increasing trends of syphilis among men who have sex with men in high income countries. Sex Health. 2015;12:155–63.
9. Spiteri G, Unemo M, Mardh O, Amato-Gauci AJ. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. Epidemiol Infect. 2019;147:e143.
10. World Health Organization. Global Health sector strategy on sexually transmitted infections 2016–2021: towards ending STIs. Geneva: World Health Organization; 2016.
11. Moore JE. The modern treatment of syphilis. Baltimore: Bailliere, Tindall, and Cox; 1943.
12. Tuddenham S, Ghanem KG. Neurosyphilis: knowledge gaps and controversies. Sex Transm Dis. 2018;45:147–51.
13. Perdrup A, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. Acta Derm Venereol Suppl (Stockh). 1981;96:1–14.
14. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS. 2008;22:1145–51.
15. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men – four cities, United States, January 2002–June 2004. MMWR Morb Mortal Wkly Rep. 2007;56:625–8.
16. Flood JM, Weinstock HS, Guroy ME, Bayne L, Simon RP, Bolan G. Neurosyphilis during the AIDS epidemic, San Francisco, 1985-1992. J Infect Dis. 1998;177:931–40.
17. Taylor MM, Aynalem G, Olea LM, He P, Smith LV, Kerndt PR. A consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001-2004. Sex Transm Dis. 2008;35:430–4.
18. de Voux A, Kidd S, Torrone EA. Reported cases of Neurosyphilis among early syphilis cases-United States, 2009 to 2015. Sex Transm Dis. 2018;45:39–41.
19. Dombrowski JC, Pedersen R, Marra CM, Kerani RP, Golden MR. Prevalence estimates of complicated syphilis. Sex Transm Dis. 2015;42:702–4.
20. Daey Ouwens IM, Koedijk FD, Fiolet AT, et al. Neurosyphilis in the mixed urban-rural community of the Netherlands. Acta Neuropsychiatr. 2014;26:186–92.
21. Marks M, Jarvis JN, Howlett W, Mabey DCW. Neurosyphilis in Africa: a systematic review. PLoS Negl Trop Dis. 2017;11:e0005880.
22. Collart P, Franceschini P, Durel P. Experimental rabbit syphilis. Br J Vener Dis. 1971;47:389–400.
23. Lukehart SA, Hook EW 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. Ann Intern Med. 1988;109:855–62.
24. Moore JE. Studies in asymptomatic neurosyphilis: the classification, treatment and prognosis of early asymptomatic neurosyphilis. Bull Johns Hopkins Hosp. 1922;33:231–46.
25. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford University Press; 1946.
26. Marra CM. Neurosyphilis. Continuum (Minneap Minn). 2015;21:1714–28.
27. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. N Engl J Med. 1997;337:307–14.
28. Tomkins A, Ahmad S, Cousins DE, Thng CM, Vilar FJ, Higgins SP. Screening for asymptomatic neurosyphilis in HIV patients after treatment of early syphilis: an observational study. Sex Transm Infect. 2018;94:337–9.

29. Blank LJ, Rompalo AM, Erbelding EJ, Zenilman JM, Ghanem KG. Treatment of syphilis in HIV-infected subjects: a systematic review of the literature. Sex Transm Infect. 2011;87:9–16.
30. Centers for Disease Control and Prevention. Clinical advisory: ocular syphilis in the United States [online]. Available at: https://www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm. Accessed 2 May.
31. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis – eight jurisdictions, United States, 2014-2015. MMWR Morb Mortal Wkly Rep. 2016;65:1185–8.
32. Bollemeijer JG, Wieringa WG, Missotten TO, et al. Clinical manifestations and outcome of syphilitic uveitis. Invest Ophthalmol Vis Sci. 2016;57:404–11.
33. Fonollosa A, Martinez-Indart L, Artaraz J, et al. Clinical manifestations and outcomes of syphilis-associated uveitis in northern Spain. Ocul Immunol Inflamm. 2016;24:147–52.
34. Furtado JM, Arantes TE, Nascimento H, et al. Clinical manifestations and ophthalmic outcomes of ocular syphilis at a time of re-emergence of the systemic infection. Sci Rep. 2018;8:12071.
35. Hoogewoud F, Frumholtz L, Loubet P, et al. Prognostic factors in syphilitic uveitis. Ophthalmology. 2017;124:1808–16.
36. Lapere S, Mustak H, Steffen J. Clinical manifestations and cerebrospinal fluid status in ocular syphilis. Ocul Immunol Inflamm. 2019;27:126–30.
37. Klein A, Fischer N, Goldstein M, Shulman S, Habot-Wilner Z. The great imitator on the rise: ocular and optic nerve manifestations in patients with newly diagnosed syphilis. Acta Ophthalmol. 2019;97:e641–7.
38. Mathew RG, Goh BT, Westcott MC. British ocular syphilis study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. Invest Ophthalmol Vis Sci. 2014;55:5394–400.
39. Jadeja N, Delfiner L, Zarnegar R, Milstein MJ. Infectious temporal lobe encephalitis-not just herpes! Neurohospitalist. 2018;8:156–7.
40. Szilak I, Marty F, Helft J, Soeiro R. Neurosyphilis presenting as herpes simplex encephalitis. Clin Infect Dis. 2001;32:1108–9.
41. Serrano-Cardenas KM, Sanchez-Rodriguez A, Pozueta A, Pelayo AL, Riancho J. Mesial encephalitis: an uncommon presentation of neurosyphilis: a case report and review of the literature. Neurol Sci. 2018;39:173–6.
42. Villar-Quiles RN, Gomez-Ruiz N, Jorquera-Moya M, Porta-Etessam J. The great imitator: mesial temporal alterations in MRI in an atypical case of neurosyphilis. Neurologia. 2020;35(1):59–61. https://doi.org/10.1016/j.nrl.2017.07.012. Epub 2017 Aug 31.
43. Beiruti K, Abu Awad A, Keigler G, Ryder CH, Shahien R. Atypical development of neurosyphilis mimicking limbic encephalitis. Int J STD AIDS. 2019;30:194–7.
44. Budhram A, Silverman M, Burneo JG. Neurosyphilis mimicking autoimmune encephalitis in a 52-year-old man. CMAJ. 2017;189:E962–5.
45. Chen B, Shi H, Hou L, et al. Medial temporal lobe atrophy as a predictor of poor cognitive outcomes in general paresis. Early Interv Psychiatry. 2019;13:30–8.
46. Wang Z, Liu L, Shen YZ, et al. The clinical and laboratory features of neurosyphilis in HIV-infected patients: a retrospective study in 92 patients. Medicine (Baltimore). 2018;97:e0078.
47. Musher DM. Syphilis, neurosyphilis, penicillin, and AIDS. J Infect Dis. 1991;163:1201–6.
48. Berger JR. Neurosyphilis in HIV-infected patients. Am J Med. 1993;95:664.
49. Marra CM, Deutsch R, Collier AC, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. Int J STD AIDS. 2013;24:351–5.
50. Ho EL, Maxwell CL, Dunaway SB, et al. Neurosyphilis increases human immunodeficiency virus (HIV)-associated central nervous system inflammation but does not explain cognitive impairment in HIV-infected individuals with syphilis. Clin Infect Dis. 2017;65:943–8.
51. De Francesco D, Winston A, Underwood J, et al. Cognitive function, depressive symptoms and syphilis in HIV-positive and HIV-negative individuals. Int J STD AIDS. 2019;30:440–6.
52. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis. 2012;39:453–7.

53. Gu W, Yang Y, Wu L, Yang S, Ng LK. Comparing the performance characteristics of CSF-TRUST and CSF-VDRL for syphilis: a cross-sectional study. BMJ Open. 2013;3(2):e002204. https://doi.org/10.1136/bmjopen-2012-002204.
54. Versiani I, Cabral-Castro MJ, Puccioni-Sohler M. A comparison of nontreponemal tests in cerebrospinal fluid for neurosyphilis diagnosis: equivalent detection of specific antibodies. Arq Neuropsiquiatr. 2019;77:91–5.
55. Marra CM, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC. Cerebrospinal fluid Treponema pallidum particle agglutination assay for neurosyphilis diagnosis. J Clin Microbiol. 2017;55:1865–70.
56. Luger AF, Schmidt BL, Kaulich M. Significance of laboratory findings for the diagnosis of neurosyphilis. Int J STD AIDS. 2000;11:224–34.
57. Marks M, Lawrence D, Kositz C, Mabey D. Diagnostic performance of PCR assays for the diagnosis of neurosyphilis: a systematic review. Sex Transm Infect. 2018;94:585–8.
58. Smibert OC, Abbinga S, Spelman DW, Jenney AWJ. Neurosyphilis: concordance between cerebrospinal fluid analysis and subsequent antibiotic strategy for patients undergoing evaluation of a diagnosis of neurosyphilis. Int J Infect Dis. 2019;82:73–6.
59. Davis AP, Stern J, Tantalo L, et al. How well do neurologic symptoms identify individuals with neurosyphilis? Clin Infect Dis. 2018;66:363–7.
60. Rolimpandoei SP, Sun X, Shi X, Leman RE, Xie L, Chen L. Diplopia: an overlooked feature in patients with neurosyphilis. Report of 2 cases and literature review. Sex Transm Dis. 2018;45:107–10.
61. Ozturk-Engin D, Erdem H, Hasbun R, et al. Predictors of unfavorable outcome in neurosyphilis: multicenter ID-IRI study. Eur J Clin Microbiol Infect Dis. 2019;38:125–34.
62. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis. 2004;189:369–76.
63. Rotman L, Luo X, Thompson A, Mackesy-Amiti ME, Young LR, Young JD. Risk of neurosyphilis in HIV-infected persons with syphilis lacking signs or symptoms of central nervous system infection. HIV Med. 2019;20:27–32.
64. Xiao Y, Tong ML, Liu LL, et al. Novel predictors of neurosyphilis among HIV-negative syphilis patients with neurological symptoms: an observational study. BMC Infect Dis. 2017;17:310.
65. Dumaresq J, Langevin S, Gagnon S, et al. Clinical prediction and diagnosis of neurosyphilis in HIV-infected patients with early syphilis. J Clin Microbiol. 2013;51:4060–6.
66. Marra CM, Sahi SK, Tantalo LC, et al. Toll-like receptor polymorphisms are associated with increased neurosyphilis risk. Sex Transm Dis. 2014;41:440–6.
67. Centers for Disease Control and Prevention. 2015 Sexually transmitted diseases treatment guidelines: Syphilis [online]. Available at: https://www.cdc.gov/std/tg2015/syphilis.htm. Accessed 3 May.
68. Pastuszczak M, Sitko M, Bociaga-Jasik M, Kucharz J, Wojas-Pelc A. Lack of antiretroviral therapy is associated with higher risk of neurosyphilis among HIV-infected patients who remain serofast after therapy for early syphilis. Medicine (Baltimore). 2018;97:e13171.
69. Cai SN, Long J, Chen C, Wan G, Lun WH. Incidence of asymptomatic neurosyphilis in serofast Chinese syphilis patients. Sci Rep. 2017;7:15456.
70. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis. 2008;47:893–9.
71. Xiao Y, Tong ML, Lin LR, et al. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. Sci Rep. 2017;7:9911.
72. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis. 2004;38:1001–6.
73. Marra CM, Tantalo LC, Maxwell CL, Dougherty K, Wood B. Alternative cerebrospinal fluid tests to diagnose neurosyphilis in HIV-infected individuals. Neurology. 2004;63:85–8.

74. Yu Q, Cheng Y, Wang Y, et al. Aberrant humoral immune responses in neurosyphilis: CXCL13/CXCR5 play a pivotal role for B-cell recruitment to the cerebrospinal fluid. J Infect Dis. 2017;216:534–44.
75. Yan Y, Wang J, Qu B, et al. CXCL13 and TH1/Th2 cytokines in the serum and cerebrospinal fluid of neurosyphilis patients. Medicine (Baltimore). 2017;96:e8850.
76. Marra CM, Tantalo LC, Sahi SK, Maxwell CL, Lukehart SA. CXCL13 as a cerebrospinal fluid marker for neurosyphilis in HIV-infected patients with syphilis. Sex Transm Dis. 2010;37:283–7.
77. Tantalo LC, Lukehart SA, Marra CM. Treponema pallidum strain-specific differences in neuroinvasion and clinical phenotype in a rabbit model. J Infect Dis. 2005;191:75–80.
78. Marra C, Sahi S, Tantalo L, et al. Enhanced molecular typing of treponema pallidum: geographical distribution of strain types and association with neurosyphilis. J Infect Dis. 2010;202:1380–8.
79. Oliver S, Sahi SK, Tantalo LC, et al. Molecular typing of Treponema pallidum in ocular syphilis. Sex Transm Dis. 2016;43:524–7.
80. Pastuszczak M, Jakiela B, Jaworek AK, Wypasek E, Zeman J, Wojas-Pelc A. Association of Interleukin-10 promoter polymorphisms with neurosyphilis. Hum Immunol. 2015;76:469–72.

Part III
Viral Infections

Chapter 7
Arboviral Central Nervous System Infections

Carolyn Gould and Marc Fischer

Arthropod-borne viruses (arboviruses) are transmitted to vertebrate hosts by certain types of insects and arachnids, including mosquitoes, sand flies, midges, and ticks [1]. These viruses typically are maintained in the environment between arthropod and vertebrate hosts through an enzootic cycle of transmission. With some important exceptions, humans are not the natural hosts for most arboviruses and do not develop a sufficient level of viremia to infect an arthropod and propagate transmission. Arboviral transmissions to humans most often result in asymptomatic infection. For persons who develop clinical disease, syndromes may include generalized febrile illness, neuroinvasive disease, polyarthralgia, or hemorrhagic fever. Neuroinvasive disease typically manifests as aseptic meningitis, encephalitis, or myelitis. Other neurologic complications, such as Guillain Barré syndrome, can result from some arboviral infections. Neuroinvasive disease is rare and is more likely to occur with certain viral pathogens as well as host factors such as age and underlying medical diseases, especially immunocompromising conditions. This chapter will discuss arboviruses that can cause acute central nervous system infection, with a focus on arboviruses transmitted locally in the United States (domestic arboviruses). These viruses are spread by various species of mosquitoes or ticks and belong to one of three virus families: *Flaviviridae*, *Peribunyaviridae*, and *Togaviridae*. A brief overview of non-domestic neurotropic arboviruses affecting travelers is provided.

C. Gould (✉) · M. Fischer
Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, USA
e-mail: cgould@cdc.gov; mfischer@cdc.gov

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_7

Domestic Arboviruses Causing Acute Central Nervous System Infections

Flaviviridae

West Nile Virus

West Nile virus is a single-stranded RNA virus in the family *Flaviviridae*, genus *Flavivirus*, related antigenically to other members of the Japanese encephalitis serogroup, including Japanese encephalitis, St. Louis encephalitis, and Murray Valley encephalitis viruses [2]. *Culex* species mosquitoes are the primary vectors for West Nile virus transmission, and birds are the natural amplification hosts. Although the vast majority of human infections are mosquito-borne, multiple non-vector modes of transmission of West Nile virus have been described, including blood transfusion, organ transplantation, breastfeeding, intrauterine, and percutaneous or conjunctival exposure in laboratory workers [2–7]. Because of its prevalence, West Nile virus is one of only two arboviruses (including Zika virus) for which blood donation screening is performed in the United States.

Distributed throughout much of the world, West Nile virus was first recognized in the western hemisphere when it caused an outbreak of meningitis and encephalitis in New York City in 1999 [8]. West Nile virus subsequently spread to all 48 contiguous states and became the leading cause of neuroinvasive arboviral disease in the United States, with large regional outbreaks in 2002, 2003, and 2012 [9]. From 1999–2017, >48,000 cases of West Nile virus disease were reported in the United States, including nearly 23,000 cases of neuroinvasive disease and > 2100 deaths. The average annual incidence of West Nile virus neuroinvasive disease increases with age, ranging from <0.1 per 100,000 in persons aged <20 years to 1.1 per 100,000 in persons aged ≥70 years [10]. Most human cases occur from July through September, although warmer regions of the United States have a longer season.

The incubation period for West Nile virus disease following a mosquito bite is typically 2–6 days but can be as long as 14 days [2]. Immunocompromised patients can have prolonged incubation periods; the longest documented duration from infection through organ transplantation to symptom onset was 37 days [3, 4]. The clinical spectrum of infection ranges from asymptomatic in 70–80% of cases to a non-specific febrile illness (“West Nile fever”) in 20–30% [11]. Fewer than 1% of infected people develop neuroinvasive disease, most commonly aseptic meningitis, encephalitis, or acute flaccid myelitis [12]. A less common neurologic complication is Guillain-Barré syndrome (GBS). The major risk factor for neuroinvasive disease is age ≥ 60 years [13]. Patients with immune suppression are at increased risk for West Nile virus encephalitis [4, 14]. Other risk factors for neuroinvasive disease include chronic kidney disease, cancer, hypertension, diabetes, and alcohol abuse [13].

Initial symptoms of West Nile virus disease include fever, headache, fatigue, myalgia, nausea, vomiting, and occasional rash. Patients with aseptic meningitis typically develop neck stiffness and photophobia. The clinical presentation of West Nile virus encephalitis may include confusion, lethargy, seizures, cranial nerve palsies, and movement disorders, such as tremor, parkinsonism, or cerebellar ataxia [15–18]. Acute flaccid myelitis is caused by viral infection of spinal cord anterior horn cells. Neurologic symptoms develop within 24–48 h after onset of fever. Patients develop limb weakness, which tends to be asymmetric, with an absence of sensory symptoms, although pain can occur in the affected limbs. Some patients develop paralysis of diaphragmatic and intercostal muscles due to viral involvement of the lower brainstem, leading to respiratory failure and need for emergent intubation [15]. GBS, an immune-mediated demyelinating peripheral neuropathy, is a less common presentation and is distinguished from acute flaccid myelitis by clinical, laboratory, and electrophysiologic features. The onset of GBS is typically later (1–8 weeks) following acute infection. Weakness is usually symmetric and ascending, involving the distal and proximal muscles. Sensory loss and painful paresthesias are characteristic [15].

The case fatality rate for West Nile virus neuroinvasive disease is approximately 10%, with higher mortality in patients with encephalitis or acute flaccid myelitis [16]. Immune suppression also is associated with higher morbidity and mortality [4, 13, 14]. Patients with encephalitis can have long-term neurologic sequelae, such as headaches, movement disorders, cognitive difficulties, and neuropsychiatric symptoms. Recovery from acute flaccid myelitis is variable, but the long-term functional outcome is often poor [15, 16].

St. Louis Encephalitis Virus

Like West Nile virus, St. Louis encephalitis virus is a single-stranded RNA virus in the family *Flaviviridae*, genus *Flavivirus*, and Japanese encephalitis serogroup. The clinical presentations of West Nile virus and St. Louis encephalitis virus disease are similar, and they share the same mosquito vectors. *Culex* spp. mosquitoes are the primary vectors, with birds as the main amplification hosts [19]. Possible transmission of St. Louis encephalitis virus through blood transfusion was documented during a concurrent outbreak of St. Louis encephalitis virus and West Nile virus disease in Arizona [20]. One case of St. Louis encephalitis virus disease has been reported as a result of accidental laboratory exposure [7].

In contrast to West Nile virus, St. Louis encephalitis virus is geographically limited to the Americas, from southern Canada to Argentina [21]. Following its recognition in 1933, St. Louis encephalitis virus caused periodic urban disease outbreaks in roughly 10-year cycles in the eastern and central United States. In the western United States, disease primarily occurred in rural, agricultural areas [19]. The incidence of St. Louis encephalitis virus disease has declined in recent decades. From

2008–2017, a total of 97 St. Louis encephalitis virus disease cases were reported to CDC, including 71 neuroinvasive disease cases associated with 5 (7%) deaths. An average of seven neuroinvasive disease cases were reported annually (range, 1–19 annual cases) [22]. Peak season is August and September, with cases occurring from June through October.

Most St. Louis encephalitis virus infections are asymptomatic. Neuroinvasive disease manifestations include aseptic meningitis and encephalitis, sometimes accompanied by hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [23]. After an incubation period of 4–14 days, illness onset may be abrupt or gradual in onset, with fever, headache, dizziness, and nausea. Findings of encephalitis include confusion, disorientation, ataxia, weakness, tremors, and coma [19]. The major risk factor for severe disease is older age. Case fatality associated with neuroinvasive disease is 5–20% but may be higher in elderly patients [19, 22, 24]. Depending on the age of the patient and severity of illness, patients can have long-term neurologic or psychiatric sequelae, such as irritability, memory loss, headaches, depression, or tremors [21].

Powassan Virus

Powassan virus is a single-stranded RNA virus in the family *Flaviviridae*, genus *Flavivirus*, and tick-borne encephalitis serogroup. There are two lineages of Powassan virus, lineage I and lineage II (also known as deer tick virus), which are clinically and serologically indistinguishable [25]. Powassan virus is transmitted by *Ixodes* spp. ticks, including *I. scapularis, I. cookei,* and *I. marxi* [25]. *I. scapularis* bites humans more frequently than the other species and also transmits multiple other pathogens, including the agents of Lyme disease, anaplasmosis, ehrlichiosis, and babesiosis. The range of the vector includes the eastern United States and Canada, and most cases of Powassan virus disease have been reported from the upper Midwest and northeastern United States [24]. The animal hosts include small- to medium-sized mammals (e.g., white-footed mice, woodchucks, squirrels) [25]. Probable transmission of Powassan virus through blood transfusion has been identified and a case of laboratory transmission has been reported [7, 26].

Human disease cases of Powassan virus have been reported in Russia, Canada, and the United States. Although still rare, the incidence of reported cases in the United States has increased in recent years [27]. From 2008–2017, a total of 125 cases of Powassan virus disease were reported to CDC, including 114 neuroinvasive disease cases associated with 9 (8%) deaths. An average of 11 neuroinvasive disease cases were reported annually (range, 2–33 annual cases) [28]. Because of the extended tick season relative to that of mosquitoes, the seasonal distribution of reported Powassan virus disease cases is longer; most cases have illness onset from May to September, with a peak in May and June [27].

Powassan virus infection can be asymptomatic or cause a non-specific febrile illness. Neuroinvasive disease can present as aseptic meningitis or encephalitis which can be severe. Following an incubation period of approximately 1–5 weeks,

illness may develop over several days with fever, headache, lethargy, generalized weakness, dizziness, vomiting, confusion, seizures, and focal neurologic deficits [25, 29–32]. A diffuse maculopapular rash may be present in some cases [30, 31]. Complications such as obstructive hydrocephalus and intra-parenchymal hemorrhage have been described [33–36]. Case fatality of encephalitis is approximately 10%, and about half of survivors have neurologic sequelae, such as headaches, cognitive and neurologic deficits, or functional disabilities [25, 27, 29–31, 34].

Peribunyaviridae

La Crosse Virus

La Crosse virus is a single-stranded RNA virus in the family *Peribunyaviridae*, genus *Orthobunyavirus*, and California encephalitis serogroup. The primary vector is *Aedes triseriatus* which breeds in root cavities of hardwood trees and water-collecting containers such as discarded tires. The animal hosts are small mammals, primarily squirrels and chipmunks [21].

Unlike most arboviruses, La Crosse virus disease occurs more commonly in children than adults, and it is the leading cause of pediatric arboviral neuroinvasive disease in the United States [37]. La Crosse virus has been found only in North America, with highest incidence in the Appalachian and Midwestern regions of the United States [37]. From 2008–2017, a total of 703 cases of La Crosse virus disease were reported to CDC, including 645 neuroinvasive disease cases associated with 9 (1%) deaths. An average of 65 neuroinvasive disease cases were reported annually (range, 31–116 annual cases) [38]. Peak season is July through September, but cases can occur from June through October.

The incubation period ranges from 5–15 days, and neurologic manifestations include aseptic meningitis and encephalitis. La Crosse virus infection has not been associated with acute flaccid paralysis [39]. La Crosse virus encephalitis is characterized by fever, headache, and vomiting; disorientation and seizures occur in almost half of cases [21, 40]. Hyponatremia, present in 20% of cases, and elevated body temperature are associated with clinical deterioration such as development of increased intracranial pressure [40]. Recovery is the general rule, with a case fatality <1%; neurologic sequelae, such as cognitive and behavioral difficulties, occur in 6–15% of survivors [40].

Jamestown Canyon Virus

Like La Crosse virus, Jamestown Canyon virus is a single-stranded RNA virus in the family *Peribunyaviridae*, genus *Orthobunyavirus*, and California encephalitis serogroup. Jamestown Canyon virus has been isolated from multiple mosquito species, but its primary vectors are believed to be *Aedes, Anopheles,* and *Culiseta*

species, depending on geographic region and time of year, and deer are the primary amplification hosts [41, 42].

Unlike La Crosse virus, Jamestown Canyon virus primarily affects adults (median age, 48 years) and has a wider geographic distribution, ranging throughout much of the United States and Canada [43]. From 2000–2013, a total of 31 cases of Jamestown Canyon virus disease, including 17 neuroinvasive disease cases, were identified in 13 states [43]. Although most cases have been reported from northern states, cases are distributed widely throughout the United States. A recent increase in reported cases (75 diseases cases reported in 2017) is likely related to increased awareness, surveillance, and routine testing for the virus [9]. Transmission of Jamestown Canyon virus begins as early as April, likely because of the hatching of vertically infected snowmelt mosquitoes. This is followed by a later peak transmission season of July through September attributed to horizontally infected mosquito species [41].

The incubation period for Jamestown Canyon virus disease is unknown. While most cases of infection are asymptomatic, neuroinvasive disease can occur. A respiratory prodrome, with sore throat, nasal congestion, and cough, beginning 2 days to 2 weeks prior to onset of neuroinvasive illness, has been described in case reports [44–46]. Patients can develop severe headaches with migraine-like features [47]. Although half of reported cases are hospitalized, fatalities are rare and have been primarily reported in immunocompromised patients [43].

Cache Valley Virus

Cache Valley virus is a single-stranded RNA virus in the family *Peribunyaviridae*, genus *Orthobunyavirus*, and Bunyamwera serogroup. Although the virus has been isolated from multiple different mosquito species (e.g., *Anopheles, Culiseta, Aedes* spp), the primary vector is unknown [48]. Its primary vertebrate amplifying hosts are likely large, hoofed animals such as deer, cattle, horses, and sheep [48].

First isolated from mosquitoes in Utah in 1956, the virus is widely distributed in the United States, Canada, and parts of the Caribbean [48]. Human cases, which are rarely reported, have occurred from May through November.

The incubation period is unknown. Disease cases initially present with a febrile illness, including headache, fatigue, myalgias, nausea, vomiting and, in some cases, rash. Patients who develop neurologic disease can present as aseptic meningitis or encephalitis. The first recognized human cases of Cache Valley disease occurred in three immunocompetent persons during the fall in 1995, 2003, and 2011, with disease ranging from aseptic meningitis to fatal encephalitis with multisystem organ failure [49–51]. While the aseptic meningitis cases were self-limited, residual headaches and memory loss were reported. A protracted clinical course presenting as a fatal, progressive meningoencephalitis over 3 years was described in a patient with X-linked agammaglobulinemia [52], and a fatal case of meningoencephalitis was reported in an immunocompromised patient receiving rituximab therapy [53].

Togaviridae

Eastern Equine Encephalitis Virus

Eastern equine encephalitis virus is a single-stranded RNA virus in the family *Togaviridae*, genus *Alphavirus* [54]. The virus circulates in an enzootic cycle between *Culiseta melanura* mosquitoes and birds in freshwater hardwood swamps [21, 54]. Bridging vectors — *Coquillettidia* and *Aedes* spp. mosquitoes — transmit the virus to humans and horses, which are dead-end hosts. In the southeastern United States, cycles involving several species of mosquitoes and wading birds, along with reptiles, might play a role in maintaining viral transmission during the winter months [55]. Eastern equine encephalitis virus can be transmitted through the aerosol route, as documented in accidental laboratory infections and animal studies, and through solid organ transplantation [7, 56, 57].

Since the first human outbreak was identified in Massachusetts in the 1930s, eastern equine encephalitis has become recognized as one of the most severe domestic arboviral encephalitides [24, 58, 59]. Eastern equine encephalitis virus is primarily distributed in North America, but a related virus (Madariaga virus) is found in Central and South America. Although Madariaga virus is generally thought to be less virulent it caused an outbreak of encephalitis among children in Panama in 2010 [60]. Most eastern equine encephalitis cases in the United States are reported from Atlantic and Gulf coast states, but cases also occur in areas bordering the Great Lakes. From 2008–2017, a total of 71 cases of eastern equine encephalitis virus disease were reported to CDC, including 70 neuroinvasive disease cases associated with 30 (43%) deaths. An average of seven neuroinvasive disease cases were reported annually (range, 3–15 annual cases) [61]. Most reported human cases of eastern equine encephalitis occur from July through September, although cases have occurred as early as June in Florida, where the virus circulates year-round [62].

The typical incubation period is 5–8 days [63]. Neuroinvasive disease is rare, occurring in <5% of infections based on limited, early seroprevalence surveys [64]. Risk factors for eastern equine encephalitis include close proximity to forested areas near swamps or marshes in endemic regions and age, with children aged <15 years and adults aged >55 years being at greatest risk [21, 64]. The clinical course of eastern equine encephalitis often involves a prodrome lasting several days, with fever, headache, nausea, vomiting, malaise and generalized weakness, followed by neurologic symptoms, including confusion, somnolence, movement disorders, meningeal signs, focal neurologic deficits, and seizures, with rapid deterioration to stupor and coma [58, 65]. Death typically occurs 2–10 days after neurological symptom onset. Case-fatality in those with neurological illness is typically 30–40% but was reported to be 50–75% during early outbreaks [21, 24, 37, 58, 61, 65]. Up to 90% of survivors have severe, debilitating neurologic sequelae, such as cognitive impairment, seizures, spastic hemiplegia, and cranial nerve deficits, and many die within several years [21, 65–67].

Western Equine Encephalitis Virus

Western equine encephalitis virus is a single-stranded RNA virus in the family *Togaviridae*, genus *Alphavirus* [68]. In the western United States, the virus amplification cycle involves *Culex tarsalis* mosquitoes and wild birds, primarily finches and sparrows [69]. During the summer, the mosquitoes shift to feeding on mammals, coinciding with the occurrence of cases among humans and equines, considered dead-end hosts [69]. Accidental transmission of western equine encephalitis virus to laboratory personnel has been described [7].

Western equine encephalitis virus historically caused large outbreaks of disease among horses and humans in the western United States and Canada, with cases peaking in the 1940s and 1950s [69]. The incidence of disease has since declined. From 1964–1989, a total of 636 cases were reported to CDC. Only four cases have been reported since 1990, the most recent case from Minnesota in 1999 [24]. The reason for the lack of recently identified cases is unknown [69–71]. The virus also is a rare cause of equine and human disease in South America.

The incubation period following western equine encephalitis virus infection is approximately 1 week. The clinical spectrum of symptomatic disease ranges from mild febrile illness to neurologic complications including aseptic meningitis and encephalitis. Infants and young children are at greatest risk of symptomatic and severe disease [69]. Onset of illness is abrupt and includes fever, chills, headache, drowsiness, nausea, vomiting, and sometimes respiratory symptoms. If illness progresses to neuroinvasive disease, patients may develop lethargy, stiff neck, photophobia, confusion, tremors, and seizures. Infants typically present with fever, irritability, seizures, rigidity, and neurologic deficits [72, 73]. The case fatality of neuroinvasive disease is relatively low at 3–4% but has been reported to be 8–15% during epidemics [69, 74]. Persistent neurologic sequelae, including cognitive and motor deficits, spastic paralysis, seizures, and psychological disorders, occur in 15–30% of patients and are more common among infants and young children [67, 73]. Some adults have developed parkinsonism [67, 75].

Non-domestic Arboviruses Causing Acute Central Nervous System Infections Among Travelers

Evaluation of a returned traveler with signs and symptoms of a central nervous system infection should take into account the clinical syndrome, timing of symptom onset in relation to exposure, location and duration of travel, the traveler's activities, and potential exposure to an arbovirus through the relevant vectors or other modes of transmission. The major international neurotropic arboviruses of concern (not including viruses that are also domestic) fall into three families, *Flaviviridae* (e.g., Japanese encephalitis, tick-borne encephalitis, Usutu, and Zika viruses), *Phenuiviridae* (e.g., Toscana virus), and *Togaviridae* (e.g., Venezuelan equine

encephalitis virus). These selected viruses are discussed briefly (Table 7.1) [76, 77]. Many arboviruses, such as dengue virus, can cause rare cases of neurologic disease [78, 79].

Japanese encephalitis virus is a flavivirus maintained in a cycle between mosquitoes and amplifying hosts, mainly pigs and wading birds, in Asia and parts of the western Pacific. It is transmitted to humans primary by *Culex* species mosquitoes, which breed in standing water and rice paddy habitats. The incidence of Japanese encephalitis among travelers from non-endemic countries to Asia is <1 case per 1 million. However, travelers who stay for prolonged periods in rural areas with active Japanese encephalitis virus transmission have a higher risk. Most infections are asymptomatic, but clinical symptoms range from a mild febrile illness to aseptic meningitis or encephalitis after an incubation period of 5–15 days. Encephalitis can be severe, with seizures in up to 85% of children and 10% of adults. The case fatality is 20–30%, and up to half of survivors have neurologic or psychiatric sequelae. A licensed Japanese encephalitis vaccine is available in the United States for travelers at risk (see section "Prevention") [80].

Table 7.1 Characteristics of selected arboviruses that cause central nervous system infections

Virus	Family	Vector	Animal hosts	Distribution	Peak months
Domestic[a]					
Cache Valley	*Peribunyaviridae*	Mosquito	Ungulates	North America	Sep–Nov
Eastern equine encephalitis	*Togaviridae*	Mosquito	Birds	Americas	Jul–Sep
Jamestown Canyon	*Peribunyaviridae*	Mosquito	Deer	North America	Jul–Sep
La Crosse	*Peribunyaviridae*	Mosquito	Rodents	United States	Jul–Sep
Powassan	*Flaviviridae*	Tick	Rodents	United States, Canada	May–Jun
St. Louis encephalitis	*Flaviviridae*	Mosquito	Birds	Americas	Aug–Sep
Western equine encephalitis	*Togaviridae*	Mosquito	Birds	Americas	Jul–Aug
West Nile	*Flaviviridae*	Mosquito	Birds	Worldwide	Aug–Sep
International					
Japanese encephalitis	*Flaviviridae*	Mosquito	Pigs, birds	Asia	May–Sep[b]
Tickborne encephalitis	*Flaviviridae*	Tick	Rodents	Europe, Asia	Jun–Jul
Toscana	*Phenuiviridae*	Sand fly	Unknown	Europe	Aug
Usutu	*Flaviviridae*	Mosquito	Birds	Africa, Europe	Jun–Oct
Venezuelan equine encephalitis	*Togaviridae*	Mosquito	Birds, rodents	Americas	Year round
Zika	*Flaviviridae*	Mosquito	Monkeys	Americas, Asia, Africa	Apr–Sep

[a]Peak months in the United States
[b]Year round in tropical areas

Tick-borne encephalitis virus, a flavivirus closely related to Powassan virus, includes three subtypes and is endemic in focal areas of Europe and Asia. *Ixodes* species ticks are the primary vector and reservoir, and small rodents are the main amplifying hosts. Tick-borne encephalitis virus can also be acquired by ingesting unpasteurized dairy products, such as milk and cheese, from infected goats, sheep, or cows. Less common routes of transmission include accidental laboratory exposure, slaughtering of viremic animals, blood transfusion, solid organ transplantation, and breastfeeding [7, 81, 82]. Most cases occur from April through November, with peaks in early and late summer when ticks are active. Travelers with exposure to forested areas through outdoor recreational or occupational activities are at greatest risk. The disease is unlikely in travelers who remain in urban or unforested areas and who do not consume unpasteurized dairy products [83]. From 2000 through 2017, only eight cases of tick-borne encephalitis among U.S. travelers to Europe and China were reported. Approximately one third of infected persons develop clinical illness following a median incubation period of 8 days (range, 4–28 days). The incubation period following ingestion of unpasteurized dairy products is shorter (3–4 days). Disease can present as a mild febrile illness with complete recovery or a biphasic illness with initial febrile illness that lasts several days and remits, followed by a second phase with central nervous system invasion that can present as aseptic meningitis, encephalitis, or myelitis. Disease severity increases with age and varies by viral subtype [83, 84].

Usutu virus was first identified as causing febrile rash illness in patients in Africa, but more recently has emerged and spread through parts of Europe where it has caused rare cases of neurologic disease. Similar to West Nile virus, Usutu virus is a flavivirus maintained in a cycle between *Culex* species mosquitoes and birds. While most infections are asymptomatic, clinical symptoms range from a febrile illness to aseptic meningitis or encephalitis. In Europe, Usutu virus infections have been identified in asymptomatic blood donors and patients with meningoencephalitis; no deaths have been reported [85–87].

Zika virus is a flavivirus that was first isolated from a monkey in the Zika forest in Uganda in 1947 and later caused sporadic cases in parts of Africa and Asia. In 2007, Zika virus emerged in the Pacific, causing outbreaks in Micronesia and later in French Polynesia. After being detected in Brazil in 2015, Zika virus rapidly spread throughout Central and South America. In the United States, limited local transmission of Zika virus occurred in south Florida and Texas in 2016. Zika virus is transmitted to humans by *Aedes* species mosquitoes. In contrast to most arboviruses, Zika virus infection can create a high enough level of viremia in humans to infect mosquito vectors, thus propagating transmission. Most infections with Zika virus are asymptomatic or lead to a mild, self-limited febrile illness. Intrauterine transmission leading to congenital infection can cause microcephaly and other congenital defects. In contrast to the developing fetus, children and adults are less susceptible to neuroinvasion with Zika virus infection; however, Zika virus infection has rarely been reported to cause meningitis, encephalitis, acute disseminated encephalomyelitis, myelitis, and sensory neuropathies [88]. Multiple studies during the epidemics in the Pacific and the Americas established an association between the immune-mediated disorder GBS and Zika virus infection. Zika virus-associated GBS is characterized by a more rapid onset (median 5–10 days) following a viral

prodrome, compared to the more classical form of GBS which tends to occur 2–4 weeks following infection. However, the severity of disease is similar to other forms of GBS [88, 89].

Toscana virus, in the family *Phenuiviridae*, genus *Phlebovirus*, is transmitted by sandflies in several European countries bordering the Mediterranean Sea, including Italy, France, Spain, Portugal, and Greece. Clinical course following Toscana virus infection varies from asymptomatic infection to meningitis or encephalitis. Disease occurs from May to October, with a peak incidence in August [90, 91].

Venezuelan equine encephalitis virus is in the family *Togaviridae*, genus *Alphavirus*, and is classified among the New World alphaviruses, along with eastern and western equine encephalitis viruses. The virus is transmitted in an enzootic cycle between mosquitoes and rodents, with spillover to humans. Horses can also serve as amplification hosts for epizootic strains of the virus, leading to further transmission by mosquitoes. Human and equine disease outbreaks have been reported in South and Central America and Mexico, with some cases occurring in southern Texas. Subtype II of the Venezuelan equine encephalitis complex (Everglades virus), is endemic in southern Florida and is a rare cause of human disease [92]. The clinical course of Venezuelan equine encephalitis virus infection ranges from asymptomatic infection or mild febrile illness to encephalitis, in some cases fatal (<1%). The incubation period is 2–5 days. Children have a higher risk of developing fatal encephalitis (case fatality up to 35% in children <5 years of age) and having permanent neurologic sequelae than adults [93–95].

Clinical Laboratory and Neuroimaging Findings

Cerebrospinal fluid (CSF) analysis in patients with arboviral infections of the central nervous system often demonstrates a lymphocyte-predominant pleocytosis, usually with <200 white blood cells/mm^3, although higher leukocyte counts have been reported, particularly for eastern equine encephalitis virus [15, 30, 40, 65]. Typically, the glucose is normal and protein is moderately elevated. Some patients might present with a peripheral leukocytosis and hyponatremia related to SIADH [23, 40, 65]. In contrast to patients with neuroinvasive disease, cerebrospinal fluid in patients with GBS typically shows an absence of cells but elevated protein (cytoalbuminologic dissociation) [15, 88].

Electroencephalographic patterns in patients with arboviral encephalitis are characterized by diffuse, non-specific slow-wave abnormalities, with periodic epileptiform discharges in some patients [15, 30, 40, 65]. Electrodiagnostics in patients with GBS are consistent with predominantly demyelinating polyneuropathy [15].

Computed tomography scan of the head in patients with encephalitis might show generalized or multifocal edema but often is normal and not helpful in diagnosis, except for excluding other possible etiologies of disease [15, 40]. Magnetic resonance imaging also can be normal, but the most common findings are increased signal intensity on T2-weighted-fluid-attenuated inversion recovery sequences in the basal ganglia, thalami, and cerebral cortex; less often, abnormalities are seen in the brain stem, cerebellum, meninges, or periventricular white matter [15, 30, 40,

65]. In severe cases, large lesions can lead to mass effect and obstructive hydrocephalus [34, 65].

Diagnosis of Arboviral Diseases

In the approach to the workup of central nervous system infection, the goal of the clinician should be to distinguish arboviral infection from disease caused by treatable organisms (i.e., bacteria, mycobacteria, fungi, and herpes viruses). Diagnosis of arboviral infection usually involves detection of virus-specific antibody in serum or CSF. Acute-phase serum specimens should first be tested for virus-specific immunoglobulin (Ig) M antibody, typically by enzyme-linked immunosorbent assays or microsphere immunoassays. IgM antibodies usually are detectable within the first week of illness and remain detectable for 30–90 days, but longer durations (months to years) have been documented for some arboviruses [96–98], making timing of infection difficult to determine in some cases. Patients with immunosuppression can have a delayed or reduced antibody response [99]. IgG antibody usually becomes detectable shortly after the IgM and persists for years. In patients with a positive IgM antibody test, virus-specific neutralizing antibodies should be evaluated using the plaque-reduction neutralization test (PRNT) to confirm the IgM antibody results and resolve cross-reactivity, particularly among flaviviruses [100]. A four-fold rise in neutralizing antibody titers between acute and convalescent serum samples also can help establish whether the infection was acquired recently.

Less commonly, viral culture and nucleic acid tests (NATs) can be performed on acute-phase serum, CSF, or tissue specimens from a biopsy or autopsy. However, most arboviruses (with the exception of some arboviruses that do not typically cause neuroinvasive disease) have a short duration of viremia, and testing for viral RNA is negative by the time the patient presents with symptoms. These tests are sometimes useful in immunocompromised patients who can have a delayed or reduced antibody response and prolonged viremia. Immunohistochemical staining can be performed to detect viral specific antigen in fixed tissue.

Most state public health laboratories and commercial laboratories can perform IgM antibody testing for the common domestic arboviruses. Confirmatory neutralizing antibody testing with PRNT, NATs, viral culture, immunohistochemical staining, and testing for less common domestic and international arboviruses are performed at the Centers for Disease Control and Prevention (CDC) and a few reference laboratories. The relevant state health departments should be consulted if arboviral testing at the state public health laboratory or CDC is needed.

Treatment

There are no proven specific treatments for arboviral infections, and management is supportive. Antipyretics and analgesics can be used in patients with fever and headache, and antiemetic therapy for associated nausea and vomiting.

Patients with encephalitis should be monitored closely and managed for elevated intracranial pressure and seizures, and patients with encephalitis or acute myelitis should be monitored for the need for airway protection and ventilatory support. Temporary reduction in immunosuppressive agents, when possible, is a common approach to management of immunosuppressed patients with neuroinvasive disease [4].

A review of the literature for healthcare providers of therapies evaluated or used empirically for West Nile virus disease was recently conducted [101]. The use of various products, such as polyclonal immune globulin, interferon, ribavirin, and corticosteroids, has been reported in case reports or case series, or evaluated in small clinical trials for infections due to West Nile virus or other related flaviviruses with no clear benefit shown. The National Institutes of Health also maintains a registry of clinical trials [102].

Prevention

Prevention of arboviral infection involves using personal protective measures to avoid exposure to the arthropod vectors, vaccination, blood donation screening, and community vector control measures.

Personal Protective Measures

Vector avoidance strategies include staying indoors during peak mosquito feeding times and avoiding walking through wooded, brushy areas with high grass and leaf litter where ticks live. The use of air conditioning or window and door screens and bed nets can reduce exposure to mosquitoes. If exposure is anticipated, Environmental Protection Agency-registered insect repellants should be used, and long-sleeved shirts and long pants worn. Clothing and gear also can be treated with permethrin. Clothing, skin, pets, and gear should be examined for ticks after being outdoors [103, 104].

Arboviral Vaccines

Human vaccines are available only for a limited number of neurotropic arboviruses. An inactivated Vero cell culture-derived Japanese encephalitis vaccine (Ixiaro) is licensed and available in the United States for use in adults and children aged ≥2 months. The CDC Advisory Committee on Immunization Practices recommends the use of this vaccine for certain travelers to Asia who have increased risk of exposure based on travel location, duration, frequency, season, activities, and accommodations [80].

Several inactivated tick-borne encephalitis virus vaccines are available in Europe, Russia, and China but none is licensed or available in the United States. Candidate vaccines against West Nile, eastern equine encephalitis, western equine encephalitis, and Venezuelan equine encephalitis viruses have been evaluated in clinical trials, but none is currently licensed for use in humans [105]. Several veterinary vaccines against arboviruses are licensed for use in horses, including West Nile virus and equine encephalitides viruses.

Blood Donation Screening

The use of screening assays for arboviruses to prevent transmission through blood and organ donation depends on the prevalence of the virus, utility and availability of screening assays, and potential risk to recipients. Beginning in 2003, the U.S. Food & Drug Administration (FDA) recommended routine screening of blood donations for West Nile virus RNA because of the endemicity of the virus and reports of transfusion-transmitted infections from asymptomatic, viremic donors [3, 106, 107]. In 2016, the FDA recommended screening of blood donations for Zika virus RNA, given reports of blood transmission of Zika virus in Brazil and the potential risk of congenital infections following transfusion to pregnant women or their sexual partners [108–110]. Other neurotropic arboviruses have been documented to be transmitted through blood transfusion, including St. Louis encephalitis, Powassan, tickborne encephalitis, and Japanese encephalitis viruses [20, 26, 82, 111]; however, blood donation screening is not performed in the United States given the low incidence of these infections and lack of available commercial NATs. Persons who have been infected with these viruses should be deferred from donating blood for 6 months after their illness.

West Nile, eastern equine encephalitis, and tick-borne encephalitis viruses have been transmitted through organ transplantation [4, 57, 81]. Although some organ procurement organizations screen potential organ donors for West Nile virus infection, there are no recommendations for routine screening for these pathogens because of limitations and lack of availability of screening assays and limited supply of available organs for transplant. Awareness and identification of possible infectious encephalitis among organ donors is critical for prevention of transmission [112].

References

1. Bres P. Impact of arboviruses on human and animal health. In: Monath TP, editor. The Arboviruses: epidemiology and ecology. Boca Raton, FL: CRC Press; 1988. p. 1–18.
2. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013;310(3):308–15.

3. Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med. 2003;349(13):1236–45.
4. Winston DJ, Vikram HR, Rabe IB, Dhillon G, Mulligan D, Hong JC, et al. Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. Transplantation. 2014;97(9):881–9.
5. Centers for Disease Control and Prevention. Possible West Nile virus transmission to an infant through breast-feeding--Michigan, 2002. MMWR Morb Mortal Wkly Rep. 2002;51(39):877–8.
6. Centers for Disease Control and Prevention. Intrauterine West Nile virus infection--New York, 2002. MMWR Morb Mortal Wkly Rep. 2002;51(50):1135–6.
7. Hanson RP, Sulkin SE, Beuscher EL, Hammon WM, McKinney RW, Work TH. Arbovirus infections of laboratory workers. Extent of problem emphasizes the need for more effective measures to reduce hazards. Science. 1967;158(3806):1283–6.
8. Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al. The outbreak of West Nile virus infection in the new York City area in 1999. N Engl J Med. 2001;344(24):1807–14.
9. Curren EJ, Lehman J, Kolsin J, Walker WL, Martin SW, Staples JE, et al. West Nile virus and other nationally notifiable arboviral diseases - United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(41):1137–42.
10. Centers for Disease Control and Prevention. West Nile virus final cumulative maps & data for 1999–2017. Available from: https://www.cdc.gov/westnile/statsmaps/cumMapsData.html.
11. Zou S, Foster GA, Dodd RY, Petersen LR, Stramer SL. West Nile fever characteristics among viremic persons identified through blood donor screening. J Infect Dis. 2010;202(9):1354–61.
12. Mostashari F, Bunning ML, Kitsutani PT, Singer DA, Nash D, Cooper MJ, et al. Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey. Lancet. 2001;358(9278):261–4.
13. Lindsey NP, Staples JE, Lehman JA, Fischer M. Medical risk factors for severe West Nile virus disease, United States, 2008-2010. Am J Trop Med Hyg. 2012;87(1):179–84.
14. Kleinschmidt-DeMasters BK, Marder BA, Levi ME, Laird SP, McNutt JT, Escott EJ, et al. Naturally acquired West Nile virus encephalomyelitis in transplant recipients: clinical, laboratory, diagnostic, and neuropathological features. Arch Neurol. 2004;61(8):1210–20.
15. Sejvar JJ, Marfin AA. Manifestations of West Nile neuroinvasive disease. Rev Med Virol. 2006;16(4):209–24.
16. Sejvar JJ. The long-term outcomes of human West Nile virus infection. Clin Infect Dis. 2007;44(12):1617–24.
17. Anninger WV, Lomeo MD, Dingle J, Epstein AD, Lubow M. West Nile virus-associated optic neuritis and chorioretinitis. Am J Ophthalmol. 2003;136(6):1183–5.
18. Vaispapir V, Blum A, Soboh S, Ashkenazi H. West Nile virus meningoencephalitis with optic neuritis. Arch Intern Med. 2002;162(5):606–7.
19. Tsai TF, Mitchell CJ. St. Louis encephalitis. In: Monath TP, editor. The Arboviruses: epidemiology and ecology. Boca Raton: CRC Press; 1988. p. 113–44.
20. Venkat H, Adams L, Sunenshine R, Krow-Lucal E, Levy C, Kafenbaum T, et al. St. Louis encephalitis virus possibly transmitted through blood transfusion-Arizona, 2015. Transfusion. 2017;57(12):2987–94.
21. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7(1):89–116.
22. Centers for Disease Control and Prevention. St. Louis encephalitis statistics & maps 2019. Available from: https://www.cdc.gov/sle/technical/epi.html.
23. White MG, Carter NW, Rector FC, Seldin DW, Drewry SJ, Sanford JP, et al. Pathophysiology of epidemic St. Louis encephalitis. I. Inappropriate secretion of antidiuretic hormone. II. Pituitary-adrenal function. III. Cerebral blood flow and metabolism. Ann Intern Med. 1969;71(4):691–702.

24. Reimann CA, Hayes EB, DiGuiseppi C, Hoffman R, Lehman JA, Lindsey NP, et al. Epidemiology of neuroinvasive arboviral disease in the United States, 1999-2007. Am J Trop Med Hyg. 2008;79(6):974–9.
25. Ebel GD. Update on Powassan virus: emergence of a north American tick-borne flavivirus. Annu Rev Entomol. 2010;55:95–110.
26. Stevens T, Taylor L, Annambhotla PD, Destrampe E, Gould CV, Groves J, et al. Probable transfusion-associated transmission of Powassan virus, 2018. CSTE Annual Conference; June 5, 2019; Raleigh, NC.
27. Krow-Lucal ER, Lindsey NP, Fischer M, Hills SL. Powassan virus disease in the United States, 2006-2016. Vector Borne Zoonotic Dis. 2018;18(6):286–90.
28. Centers for Disease Control and Prevention. Powassan virus statistics & maps. Available from: https://www.cdc.gov/powassan/statistics.html.
29. Centers for Disease C, Prevention. Outbreak of Powassan encephalitis--Maine and Vermont, 1999-2001. MMWR Morb Mortal Wkly Rep. 2001;50(35):761–4.
30. El Khoury MY, Camargo JF, White JL, Backenson BP, Dupuis AP 2nd, Escuyer KL, et al. Potential role of deer tick virus in Powassan encephalitis cases in Lyme disease-endemic areas of New York, U.S. Emerg Infect Dis. 2013;19(12):1926–33.
31. Piantadosi A, Rubin DB, McQuillen DP, Hsu L, Lederer PA, Ashbaugh CD, et al. Emerging cases of Powassan virus encephalitis in New England: clinical presentation, imaging, and review of the literature. Clin Infect Dis. 2016;62(6):707–13.
32. Smith R, Woodall JP, Whitney E, Deibel R, Gross MA, Smith V, et al. Powassan virus infection. A report of three human cases of encephalitis. Am J Dis Child. 1974;127(5):691–3.
33. Birge J, Sonnesyn S. Powassan virus encephalitis, Minnesota. USA Emerg Infect Dis. 2012;18(10):1669–71.
34. Zachary KC, LaRocque RC, Gonzalez RG, Branda JA. Case 3-2019: a 70-year-old woman with fever, headache, and progressive encephalopathy. N Engl J Med. 2019;380(4):380–7.
35. Choi EE, Taylor RA. A case of Powassan viral hemorrhagic encephalitis involving bilateral thalami. Clin Neurol Neurosurg. 2012;114(2):172–5.
36. Raval M, Singhal M, Guerrero D, Alonto A. Powassan virus infection: case series and literature review from a single institution. BMC Res Notes. 2012;5:594.
37. Gaensbauer JT, Lindsey NP, Messacar K, Staples JE, Fischer M. Neuroinvasive arboviral disease in the United States: 2003 to 2012. Pediatrics. 2014;134(3):e642–50.
38. Centers for Disease Control and Prevention. La Crosse encephalitis epidemiology & geographic distribution. Available from: https://www.cdc.gov/lac/tech/epi.html.
39. Hennessey MJ, Pastula DM, Machesky K, Fischer M, Lindsey NP, DiOrio M, et al. Investigation of acute flaccid paralysis reported with La Crosse virus infection, Ohio, USA, 2008-2014. Emerg Infect Dis. 2017;23(12):2075–7.
40. McJunkin JE, de los Reyes EC, Irazuzta JE, Caceres MJ, Khan RR, Minnich LL, et al. La Crosse encephalitis in children. N Engl J Med. 2001;344(11):801–7.
41. Andreadis TG, Anderson JF, Armstrong PM, Main AJ. Isolations of Jamestown canyon virus (Bunyaviridae: Orthobunyavirus) from field-collected mosquitoes (Diptera: Culicidae) in Connecticut, USA: a ten-year analysis, 1997-2006. Vector Borne Zoonotic Dis. 2008;8(2):175–88.
42. Kosoy O, Rabe I, Geissler A, Adjemian J, Panella A, Laven J, et al. Serological survey for antibodies to mosquito-borne bunyaviruses among US National Park Service and US Forest Service employees. Vector Borne Zoonotic Dis. 2016;16(3):191–8.
43. Pastula DM, Hoang Johnson DK, White JL, Dupuis AP 2nd, Fischer M, Staples JE. Jamestown Canyon virus disease in the United States-2000-2013. Am J Trop Med Hyg. 2015;93(2):384–9.
44. Grimstad PR, Shabino CL, Calisher CH, Waldman RJ. A case of encephalitis in a human associated with a serologic rise to Jamestown canyon virus. Am J Trop Med Hyg. 1982;31(6):1238–44.
45. Deibel R, Srihongse S, Grayson MA, Grimstad PR, Mahdy MS, Artsob H, et al. Jamestown canyon virus: the etiologic agent of an emerging human disease? Prog Clin Biol Res. 1983;123:313–25.

46. Grimstad PR. California group virus disease. In: Monath TP, editor. The arboviruses: epidemiology and ecology. Boca Raton: CRC Press; 1988. p. 99–136.
47. Centers for Disease Control and Prevention. Human Jamestown canyon virus infection --- Montana, 2009. MMWR Morb Mortal Wkly Rep. 2011;60(20):652–5.
48. Calisher CH, Francy DB, Smith GC, Muth DJ, Lazuick JS, Karabatsos N, et al. Distribution of Bunyamwera serogroup viruses in North America, 1956-1984. Am J Trop Med Hyg. 1986;35(2):429–43.
49. Campbell GL, Mataczynski JD, Reisdorf ES, Powell JW, Martin DA, Lambert AJ, et al. Second human case of Cache Valley virus disease. Emerg Infect Dis. 2006;12(5):854–6.
50. Nguyen NL, Zhao G, Hull R, Shelly MA, Wong SJ, Wu G, et al. Cache valley virus in a patient diagnosed with aseptic meningitis. J Clin Microbiol. 2013;51(6):1966–9.
51. Sexton DJ, Rollin PE, Breitschwerdt EB, Corey GR, Myers SA, Dumais MR, et al. Life-threatening Cache Valley virus infection. N Engl J Med. 1997;336(8):547–9.
52. Wilson MR, Suan D, Duggins A, Schubert RD, Khan LM, Sample HA, et al. A novel cause of chronic viral meningoencephalitis: Cache Valley virus. Ann Neurol. 2017;82(1):105–14.
53. Yang Y, Qiu J, Snyder-Keller A, Wu Y, Sun S, Sui H, et al. Fatal Cache Valley virus meningoencephalitis associated with rituximab maintenance therapy. Am J Hematol. 2018;93(4):590–4.
54. Morris CD. Eastern equine encephalomyelitis. In: Monath TP, editor. The arboviruses: epidemiology and ecology. Boca Raton: CRC Press; 1988. p. 1–20.
55. Bingham AM, Burkett-Cadena ND, Hassan HK, McClure CJ, Unnasch TR. Field investigations of winter transmission of eastern equine encephalitis virus in Florida. Am J Trop Med Hyg. 2014;91(4):685–93.
56. Roy CJ, Reed DS, Wilhelmsen CL, Hartings J, Norris S, Steele KE. Pathogenesis of aerosolized eastern equine encephalitis virus infection in guinea pigs. Virol J. 2009;6:170.
57. Pouch SM, Katugaha SB, Shieh WJ, Annambhotla P, Walker WL, Basavaraju SV, et al. Transmission of eastern equine encephalitis virus from an organ donor to three transplant recipients. Clin Infect Dis 2019;69(3);450–8.
58. Getting VA. Equine encephalomyelitis in Massachusetts. N Engl J Med. 1941;224(24):999–1006.
59. Goldfield M, Sussman O. The 1959 outbreak of eastern encephalitis in New Jersey. I. Introduction and description of outbreak. Am J Epidemiol. 1968;87(1):1–10.
60. Carrera JP, Forrester N, Wang E, Vittor AY, Haddow AD, Lopez-Verges S, et al. Eastern equine encephalitis in Latin America. N Engl J Med. 2013;369(8):732–44.
61. Centers for Disease Control and Prevention. Eastern equine encephalitis statistics & maps. Available from: https://www.cdc.gov/easternequineencephalitis/tech/epi.html.
62. Bigler WJ, Lassing EB, Buff EE, Prather EC, Beck EC, Hoff GL. Endemic eastern equine encephalomyelitis in Florida: a twenty-year analysis, 1955-1974. Am J Trop Med Hyg. 1976;25(6):884–90.
63. Sherwood JA, Oliver J. Eastern equine encephalitis incubation time periods of 5 and 8 days. Pediatr Infect Dis J. 2015;34(4):459–60.
64. Goldfield M, Welsh JN, Taylor BF. The 1959 outbreak of eastern encephalitis in New Jersey. 5. The inapparent infection:disease ratio. Am J Epidemiol. 1968;87(1):32–3.
65. Deresiewicz RL, Thaler SJ, Hsu L, Zamani AA. Clinical and neuroradiographic manifestations of eastern equine encephalitis. N Engl J Med. 1997;336(26):1867–74.
66. Ayres JC, Feemster RF. The sequelae of eastern equine encephalomyelitis. N Engl J Med. 1949;240(24):960–2.
67. Ronca SE, Dineley KT, Paessler S. Neurological sequelae resulting from encephalitic alphavirus infection. Front Microbiol. 2016;7:959.
68. Weaver SC, Kang W, Shirako Y, Rumenapf T, Strauss EG, Strauss JH. Recombinational history and molecular evolution of western equine encephalomyelitis complex alphaviruses. J Virol. 1997;71(1):613–23.
69. Reisen WK, Monath TP. Western equine encephalomyelitis. In: Monath TP, editor. The arboviruses: epidemiology and ecology. Boca Raton: CRC Press; 1988. p. 89–137.

70. Forrester NL, Kenney JL, Deardorff E, Wang E, Weaver SC. Western equine encephalitis submergence: lack of evidence for a decline in virus virulence. Virology. 2008;380(2):170–2.
71. Mossel EC, Ledermann JP, Phillips AT, Borland EM, Powers AM, Olson KE. Molecular determinants of mouse neurovirulence and mosquito infection for Western equine encephalitis virus. PLoS One. 2013;8(3):e60427.
72. Kokernot RH, Shinefield HR, Longshore WA Jr. The 1952 outbreak of encephalitis in California; differential diagnosis. Calif Med. 1953;79(2):73–7.
73. Medovy H. Western equine encephalomyelitis in infants. J Pediatr. 1943;22(3):308–18.
74. McGowan JE Jr, Bryan JA, Gregg MB. Surveillance of arboviral encephalitis in the United States, 1955-1971. Am J Epidemiol. 1973;97(3):199–207.
75. Schultz DR, Barthal JS, Garrett G. Western equine encephalitis with rapid onset of parkinsonism. Neurology. 1977;27(11):1095–6.
76. Centers for Disease Control and Prevention. CDC yellow book 2020: health information for international travel. Brunett GW, editor. New York: Oxford University Press; 2019.
77. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res. 2002;33(4):330–42.
78. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12(9):906–19.
79. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, et al. Neurological manifestations of dengue infection. Lancet. 2000;355(9209):1053–9.
80. Hills SL, Walter EB, Atmar RL, Fischer M. Japanese encephalitis vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep. 2019;68(2):1–33.
81. Lipowski D, Popiel M, Perlejewski K, Nakamura S, Bukowska-Osko I, Rzadkiewicz E, et al. A cluster of fatal tick-borne encephalitis virus infection in organ transplant setting. J Infect Dis. 2017;215(6):896–901.
82. Wahlberg P, Saikku P, Brummer-Korvenkontio M. Tick-borne viral encephalitis in Finland. The clinical features of Kumlinge disease during 1959-1987. J Intern Med. 1989;225(3):173–7.
83. Fischer M, Gould CV, Rollin PE. Tickborne encephalitis. In: Brunett GW, editor. CDC yellow book 2020: health information for international travel. New York: Oxford University Press; 2019.
84. Centers for Disease Control and Prevention. Tick-borne encephalitis among U.S. travelers to Europe and Asia - 2000-2009. MMWR Morb Mortal Wkly Rep. 2010;59(11):335–8.
85. Gaibani P, Rossini G. An overview of Usutu virus. Microbes Infect. 2017;19(7–8):382–7.
86. Roesch F, Fajardo A, Moratorio G, Vignuzzi M. Usutu virus: an arbovirus on the rise. Viruses. 2019;11:640–53.
87. Grottola A, Marcacci M, Taqliazucchi S, Gennari W, Di Gennaro A, Orsini M, et al. Usutu virus infections in humans: a retrospective analysis in the municipality of Modena. Italy Clin Microbiol Infect. 2017;23(1):33–7.
88. Munoz LS, Parra B, Pardo CA, Neuroviruses Emerging in the Americas Study. Neurological implications of Zika virus infection in adults. J Infect Dis. 2017;216(suppl_10):S897–905.
89. da Silva IRF, Frontera JA. Bispo de Filippis AM, Nascimento OJMD, Rio-GBS-ZIKV research group. Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017;74(10):1190–8.
90. Depaquit J, Grandadam M, Fouque F, Andry P, Peyrefitte C. Arthropod-borne viruses transmitted by Phlebotomine sandflies in Europe: a review. Euro Surveill. 2010;15(10):pii=19507.
91. Kay MK, Gibney KB, Riedo FX, Kosoy OL, Lanciotti RS, Lambert AJ. Toscana virus infection in American traveler returning from Sicily, 2009. Emerg Infect Dis. 2010;16(9):1498–500.
92. Hoyer IJ, Acevedo C, Wiggins K, Alto BW, Burkett-Cadena ND. Patterns of abundance, host use, and Everglades virus infection in Culex (Melanoconion) cedecei mosquitoes, Florida, USA. Emerg Infect Dis. 2019;25(6):1093–100.
93. Weaver SC, Ferro C, Barrera R, Boshell J, Navarro JC. Venezuelan equine encephalitis. Annu Rev Entomol. 2004;49:141–74.

94. Go YY, Balasuriya UB, Lee CK. Zoonotic encephalitides caused by arboviruses: transmission and epidemiology of alphaviruses and flaviviruses. Clin Exp Vaccine Res. 2014;3(1):58–77.
95. Aguilar PV, Estrada-Franco JG, Navarro-Lopez R, Ferro C, Haddow AD, Weaver SC. Endemic Venezuelan equine encephalitis in the Americas: hidden under the dengue umbrella. Future Virol. 2011;6(6):721–40.
96. Griffin I, Martin SW, Fischer M, Chambers TV, Kosoy O, Falise A, et al. Zika virus IgM detection and neutralizing antibody profiles 12-19 months after illness onset. Emerg Infect Dis. 2019;25(2):299–303.
97. Kapoor H, Signs K, Somsel P, Downes FP, Clark PA, Massey JP. Persistence of West Nile virus (WNV) IgM antibodies in cerebrospinal fluid from patients with CNS disease. J Clin Virol. 2004;31(4):289–91.
98. Roehrig JT, Nash D, Maldin B, Labowitz A, Martin DA, Lanciotti RS, et al. Persistence of virus-reactive serum immunoglobulin M antibody in confirmed West Nile virus encephalitis cases. Emerg Infect Dis. 2003;9(3):376–9.
99. Levi ME, Quan D, Ho JT, Kleinschmidt-Demasters BK, Tyler KL, Grazia TJ. Impact of rituximab-associated B-cell defects on West Nile virus meningoencephalitis in solid organ transplant recipients. Clin Transpl. 2010;24(2):223–8.
100. Calisher CH, Karabatsos N, Dalrymple JM, Shope RE, Porterfield JS, Westaway EG, et al. Antigenic relationships between flaviviruses as determined by cross-neutralization tests with polyclonal antisera. J Gen Virol. 1989;70(Pt 1):37–43.
101. Centers for Disease Control and Prevention. West Nile virus disease therapeutics: review of the literature for healthcare providers. Available from: https://www.cdc.gov/westnile/healthcareproviders/healthCareProviders-TreatmentPrevention.html.
102. National Institutes of Health. U.S. National Library of Medicine Clinical Trials.gov. Available from: https://clinicaltrials.gov/ct2/results?term=west+nile+virus&Search=Search.
103. Centers for Disease Control and Prevention. Prevent mosquito bites. Available from: https://www.cdc.gov/features/stopmosquitoes/index.html.
104. Centers for Disease Control and Prevention. Avoiding ticks. Available from: https://www.cdc.gov/ticks/avoid/index.html.
105. Brandler S, Tangy F. Vaccines in development against West Nile virus. Viruses. 2013;5(10):2384–409.
106. U.S. Food & Drug Administration. Use of nucleic acid tests to reduce the risk of transmission of West Nile virus from donors of whole blood and blood components intended for transfusion. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-nucleic-acid-tests-reduce-risk-transmission-west-nile-virus-donors-whole-blood-and-blood.
107. Busch MP, Kleinman SH, Tobler LH, Kamel HT, Norris PJ, Walsh I, et al. Virus and antibody dynamics in acute West Nile virus infection. J Infect Dis. 2008;198(7):984–93.
108. U.S. Food & Drug Administration. Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reducing-risk-zika-virus-transmission-blood-and-blood-components.
109. Barjas-Castro ML, Angerami RN, Cunha MS, Suzuki A, Nogueira JS, Rocco IM, et al. Probable transfusion-transmitted Zika virus in Brazil. Transfusion. 2016;56(7):1684–8.
110. Motta IJ, Spencer BR. Cordeiro da Silva SG, Arruda MB, dobbin JA, Gonzaga YB, et al. evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. 2016;375(11):1101–3.
111. Cheng VCC, Sridhar S, Wong SC, Wong SCY, Chan JFW, Yip CCY, et al. Japanese encephalitis virus transmitted via blood transfusion, Hong Kong, China. Emerg Infect Dis. 2018;24(1):49.
112. Basavaraju SV, Kuehnert MJ, Zaki SR, Sejvar JJ. Encephalitis caused by pathogens transmitted through organ transplants, United States, 2002-2013. Emerg Infect Dis. 2014;20(9):1443–51.

Chapter 8
Update on HSV and VZV Encephalitis in Adults

J. P. Stahl and A. Mailles

The Viruses

Types of Human Herpes Virus (HHV)

Eight different herpes viruses are known to be strict human pathogens [1]. All of them are neurotropic and can be responsible for encephalitis, although only a small proportion of those infected will develop this severe clinical presentation, and sometimes only under specific circumstances (HHV6, CMV, HHV8):

- *HHV-1 = HSV-1 (Herpes simplex virus 1)*
- *HHV-2 = HSV-2 (Herpes simplex virus 2)*
- *HHV-3 = VZV (Varicella Zoster virus)*
- *HHV-4 = EBV (Epstein-Barr virus)*
- *HHV-5 = CMV (Cytomegalovirus)*
- *HHV-6 = Roseolovirus*
- *HHV-7 = close to HHV6*
- *HHV 8 = KSHV (Kaposi's sarcoma-associated herpesvirus)*

J. P. Stahl (✉)
Department of Infectious Diseases, University and Hospital of Grenoble Alpes, Grenoble, France

European Study Group for the Infections of the Brain (ESGIB), Basel, Switzerland
e-mail: JPStahl@chu-grenoble.fr

A. Mailles
European Study Group for the Infections of the Brain (ESGIB), Basel, Switzerland

Infectious Diseases Department, Santé Publique France, Saint Maurice, France
e-mail: Alexandra.MAILLES@santepubliquefrance.fr

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_8

In this chapter, we will focus on HSV and VZV, as they are the most frequent viruses of this family responsible for encephalitis in western countries.

All HHV have the same structure: they carry an important genome (152-kbp), with linear double-stranded DNA, coding for 100–200 different genes. The DNA is inserted in an icosahedral capsid envelope, so-called virion. The complete genomic DNA sequence of HSV-1 was published in 1988 [2].

The evolutionary origins of human HSV have been investigated using phylogenetic and molecular dating analyses [3]. The models suggest that HSV-1 resulted from an ancient codivergence with its host during several million years, whereas HSV-2 might have arose from a spillover transmission event from the ancestor of modern chimpanzees to an extinct Hominid, ancestor of modern *Homo sapiens*, around 1.6 millions of years ago.

Pathophysiology

The viral envelope links to the membrane receptors of a cell of the host, and the virion is then transferred into the cell cytoplasm, where it is destructured. This makes possible the migration of viral DNA to the cell nucleus. In this nucleus, viral DNA duplicates and is transcribed to a limited number of latent viral genes. This explains the viral persistence in the human cell, during a long asymptomatic period. In case of reactivation, due to some independent aggressions toward the host (other infection, immunodeficiency, chemical or physical stimulation), the virus reassembles and comes back to its initial pathogenicity. This pathogenicity is related to the activation of lytic genes, leading most frequently to the cell death. Besides this common mechanism in cell, HSV and VZV have specific pathways explaining clinical neurological presentations.

HSV Encephalitis (HSVE)

After primary infection of the mucosal or skin epithelium, HSV interacts with cell-surface glycosaminoglycans and then infects sensory neurons [4]. It reaches the neuronal cell body in the dorsal root ganglion using a fast retrograde axonal transport. They are still hypothesis and debate about mechanisms of HSV access to the central nervous system. The most likely mechanisms are retrograde transport through the olfactory or trigeminal nerves, or viremia. Nevertheless, viremia is less credible as the orbitofrontal and mesiotemporal lobes infection are not in favor of this hypothesis.

The olfactory nerve pathways connect directly to the frontal and mesiotemporal lobes (including the limbic system) and do not go through the thalamus as other cranial nerves. Some clues support the hypothesis of viral spread to the CNS through the olfactory way, but this hypothesis is not fully demonstrated. Another route of

contamination of the brain could be the trigeminal nerve that innervates the meninges. The viral spread to the orbitofrontal and medial temporal lobes could also use this pathway.

HSVE results most frequently from reactivation of latent virus, but encephalitis following primary infection is possible as well. The most likely mechanism in case of reactivation is HSV multiplication in the trigeminal ganglia with subsequent spread of infection to the temporal and frontal lobes. In 50% of HSVE cases with documentation of the strains, the viral strain responsible for encephalitis is different from the strain isolated from herpetic skin lesions in the same patient.

HSV affects otherwise healthy patients and only a small minority of HSV-1–infected individuals develop encephalitis. Some genetic determinants have been identified as risk factors of HSVE, since some years after the initial publication [5]. These authors demonstrated a genetic predisposition for HSVE in two children presenting with autosomal recessive deficiency in the intracellular protein UNC-93B. This deficiency resulted in impaired cellular interferon-a/b and -l antiviral responses. This single-gene immunodeficiency does not compromise immunity to most pathogens, unlike most known primary immunodeficiencies. It explains it is undetectable in routine life.

A more recent study [6] used an *in vivo* chemical mutagenesis screen for HSV-1 susceptibility in mice. Authors identified the role of the Rel gene (RelC307X), encoding for the NF-κB transcription factor subunit c-Rel, in HSE disease susceptibility in mice. However, the identified genetic risk factors explain only a minority of cases.

VZV Encephalitis

Neurological presentation after VZV infection can be related to various mechanisms: parenchymatous encephalitis (with or without demyelination), microglial influx, small as well as large vessel vasculopathy inducing strokes, meningitis or necrotizing myelitis [7, 8]. The vascular as well as immunological involvement is crucial in this presentation.

Precise knowledge about VZV viruses responsible for encephalitis was provided in a study aiming at evaluating the genetic diversity of VZV recovered from the central nervous system (CNS; encephalitis or meningitis) and from non-CNS samples [9]. Viruses recovered from CSF of patients presenting with meningitis showed a similar diversity to those recovered from vesicular fluid. This finding suggests that self-limiting VZV meningitis might be caused by reactivation and replication of the virus from a limited number of neurons. VZV wild-type infections are probably due to few virions, with restricted genome diversity within vesicles. By contrast, in case of encephalitis, the authors demonstrated a wider genetic diversity of the viruses that might be related to accumulated mutations, perhaps under the control of the immune system. In this hypothesis, more severe cases, due to the virus spread into brain parenchyma, may be due to the failure of this same immune control, resulting

in the spread of multiple different viruses/virions. The results of this study suggest that VZV infection of the CNS is not related to single viral polymorphisms, and that immune control is of major importance in restricting infection as well as selecting more viruses.

Importance of Resistance to Viral Infection

Interferon Is of Major Importance in Fighting Viral Infection

The importance of a deficiency in interferon regulatory factors (IRF3 and IRF7) was evaluated in an HSVE model [10]. The case-fatality rates of infected IRF3 and IRF7 deficient mice were higher than those of controls. This finding was also associated with higher viral loads in animals' brain. After infection, negative IRF7 mice exhibited a deficit in IFN-β production. This finding suggests that interferon production might protect against poor outcome.

TLR3 is a sensor of double-stranded RNA. It is required for innate immune responses to HSV-1 in neurons and astrocytes [11]. It has been recently demonstrated that TLR3 recruited mTORC2, the metabolic checkpoint kinase complex leading to the induction of chemokines and trafficking of TLR3 to the cell periphery [12]. This trafficking activated molecules necessary for the induction of type I interferons. Authors showed that HSV-1 brain infection of animals was increased when TLR3 responses were impaired by an inhibitor. This underlines the final role of interferon in the defense against HSV infection of the brain, if needed.

Chemokines

CXCR3, a chemokine receptor, was previously identified as having an important impact on the course of HSV encephalitis in mouse models. Zimmermann et al. [13] compared CXCR3-deficient mice with controls. They demonstrated that CXCR3-deficient mice cleared HSV-1 more efficiently 14 days after infection. Moreover, inhibition of CXCR3 signalling reduced T cell infiltration and microglial activation. They concluded that interruption of the CXCR3 pathway leads paradoxically to an enhanced viral clearance after intranasal infection.

Epidemiology Worldwide

HSV 1 and 2 are the most frequently identified agent responsible for infectious encephalitis, except in the context of outbreaks (ex.: Japanese encephalitis, EV A71). In a French study HSV accounted for 42% of identified causes of encephalitis [14]. A US study [15] reported similar results, with HSV being accountable for 37%

of cases with an etiological diagnosis. In a UK study [16], the authors reported HSV as responsible of 19% of cases, but this study included all causes of encephalitis, including auto-immune encephalitis and inflammatory causes. Nevertheless, HSV was the most frequent pathogen.

Immunosuppression has been reported to be a concurrent disease of 31% of HSV E cases [17].

VZV is the second cause identified in patients presenting with infectious or suspected infectious encephalitis in the same western countries if using the same criteria for diagnosis (France, UK, US). Due to the pathophysiological features, VZV encephalitis is more likely to occur in patients with significant co-morbidities, including immunosuppression: 50% of proven VZV encephalitis in the French study [7].

However, in countries where domestically acquired arboviral infections occur, other causes might be more frequently identified, especially at a regional level. In South East Asia, Japanese encephalitis can be more locally more frequent than HSV.

Clinical and Imaging Presentations

HSV

HSV encephalitis involves most frequently temporal and frontal cerebral lobes and typical clinical presentation is linked to this localization: inappropriate behavior, dysexecutive syndrome, hallucinations of any type are typical symptoms, as well as language and memory disorders, at the very beginning. Nevertheless, there is no real specific clinical presentation of HSV encephalitis, making it impossible to confirm or rule out this causative agent without biological tests [17]. Finally, any clinical suspicion of encephalitis should lead to perform a lumbar puncture and test HSV in CSF by PCR, which is considered a "mandatory" first level of etiological investigation.

More precise information thanks to major improvements of imaging tools suggest the importance of vascular involvement [18]. In this recent review of the literature (from 2000 to January 2018), in cases of HSV encephalitis complicated with vascular involvement, intracerebral hemorrhage was identified as the most frequent lesion (89%). Hematoma was present on the first brain imaging in 32% of these cases. Infarction was frequently multifocal and preceded by hemorrhage in 20% of cases. Cerebral vasculitis exclusively located in large-sized vessels was present in 63% of these cases. HSV-1 was a most frequent cause of hemorrhagic complications, whereas HSV-2 was the most frequent in case of ischemic presentation. Authors of this review reported case-fatality rate of 21% in case of hemorrhage and 0% in case of infarction.

Nevertheless, some atypical cases are reported, and imaging can be normal or atypical, in case of proven HSV encephalitis [19]. The authors retrospectively

evaluated all consecutive PCR-proven HSV encephalitis cases (18 patients) treated in their hospital from January 1, 2013 to February 28, 2018. The most common clinical features were altered mental status (77.8%), focal neurologic deficits (72.2%) and fever (72.2%). Four of these patients (22.2%) had a normocellular cerebrospinal fluid (CSF) on admission. Initial CT scans were normal in 11 out of 16 patients (68.8%). These findings mean that treatment with acyclovir should be initiated early, even when the initial presentation is atypical [20].

VZV

In a study including 17 adult patients (among 20 VZV encephalitis including adults and pediatric cases), previous or concomitant cutaneous zoster was reported in eight cases only [7].

Nine adults presenting with VZV encephalitis had comorbidities, three of which could be considered having immunosuppressive comorbidities: osteosarcoma, recent heart–lung transplant and systemic lupus erythematosus with long-term corticosteroid treatment.

Six patients (30%) required admission to intensive care units, four were mechanically ventilated. The most frequent neurological symptoms were disorientation and confusion (70%), meningeal signs (60%), focal neurological signs (55%) and apathy (50%). Cranial nerve palsy was present in eight patients (40%), namely central facial nerve paralysis in seven cases and oculomotor nerve paralysis in one case.

In this cohort, all patients underwent brain imaging. Vascular lesions (MRI) were surprisingly demonstrated in only three cases, although VZV encephalitis is supposed to be most frequently due to vascular involvement. The other cases presented with non-specific images: non-vascular lesions; brainstem lesions suggesting rhombencephalitis; right-side temporal, parietal and occipital hypersignals; non-specific abnormalities (cortical atrophy). Seven patients had no visible abnormalities.

In conclusion, absence of cutaneous lesions or vascular lesions on MRI cannot rule out diagnosis of VZV encephalitis.

Biological Diagnosis

The current gold standard is PCR in CSF, for both viruses [20, 21]. Sensitivity and specificity are respectively 98% and 94%, with positive predictive value of 95% and negative predictive value of 98% [22].

In some cases, HSV PCR positivity is delayed from the onset of neurological symptoms, but no more than 4 days [20]. That means that, in case of negative result, one cannot rule out diagnosis of HSV encephalitis until the result of a PCR performed after this delay.

VZV PCR results should be interpreted according clinical presentation, as it is frequent to observe positive PCR in case of zoster without encephalitis. Diagnosis of encephalitis should meet clinical criteria as well as biological results [23].

Treatment

Antiviral Treatment

HSVE

Intravenous acyclovir is the standard treatment of HSV encephalitis. The acyclovir dosage for adult patients presenting with HSV encephalitis is 10 mg/kg every 8 h, with infusion of at least 1 h and IV saline final concentration < 5 mg/mL [20, 21]. The recommended treatment duration is 14 days in immunocompetent adults. A 21-day treatment is recommended for immuno-compromised patients only.

Acyclovir has been associated with a potential renal and neurological central toxicity, boosted by excessive doses, rapid infusion rate, high concentration of the infusion solution, combination with other nephrotoxic drugs, and older age. Decreasing the infusion rate reduces the renal toxicity. The use of nephrotoxic drugs during acyclovir treatment should be restricted to strictly necessary treatments. An adequate rehydration is needed, and doses should be adapted to the renal function.

There is no evidence-based data supporting the relation between a positive CSF HSV PCR at the end of treatment and the positive or negative outcome of encephalitis. In other words, the result of an HSV PCR at the end of the treatment is neither predictive of the outcome or the evolution of the patient, and its interpretation is impossible. It is difficult to report a reliable clearance of HSV in CSF, as LP is not usually performed in patients with a good outcome. Nevertheless, in one study, the authors reported positive PCRs up to 28 days [24]. In another study, 24% of patients with a correct treatment procedure presented with positive PCR in CSF 7 days after initiation of treatment [25]. These positive results were not correlated with a worse outcome. For these reasons, it is not recommended to check the CSF HSV PCR at the end of treatment in case of positive outcome.

In case of a non-favorable clinical outcome at the end of the 14-day treatment, a lumbar puncture with HSV PCR and autoantibodies detection in CSF should be performed. A positive result of the HSV PCR may lead to extend the acyclovir treatment to 21 days.

In this case, it is possible to investigate resistance to acyclovir and pharmacokinetic parameters (acyclovir concentration measurement in blood and CSF) after multidisciplinary evaluation. Acyclovir resistance has been demonstrated mostly in immunocompromised patients.

A delay in implementing the Acyclovir treatment has been proven to be independently associated with a negative outcome of HSV encephalitis. Acyclovir treatment must be rapidly initiated in patients with a suspected encephalitis, before

biological confirmation of the diagnosis, ideally within 6 h after hospital admission. In case of high clinical suspicion of HSV encephalitis, but unconfirmed with the first PCR test, acyclovir must be continued while waiting for a second CSF HSV PCR sampled at least 4 days after neurological signs onset.

VZV Encephalitis

VZV encephalitis is associated with a high case-fatality rate and with significant neurological sequelae in the absence of treatment, especially in elderlies and immunocompromised patients [7]. Treatment with acyclovir reduces VZV encephalitis-related case fatality and neurological sequelae. As for HSV, IV acyclovir is the standard treatment, with some modification of dosage. *In vitro*, VZV is less sensitive to acyclovir than HSV. The recommended dosage of acyclovir in the treatment of VZV encephalitis is 15 mg/kg for 1 h every 8 h [20, 21] The recommended treatment duration for VZV encephalitis is 14 days, even if no literature data helps in defining the optimal acyclovir treatment duration.

Foscarnet, ganciclovir, and cidofovir have been suggested in the second-line treatment of VZV encephalitis in immunocompromised patients, without any evidence of their benefit. There is currently no data on the use of these molecules in immunocompetent adults.

Supportive Treatment

Incidence of seizures during the acute phase of HSV encephalitis varies from 7% to 67% [26, 27]. Their clinical presentations range from subclinical and local seizures to status epilepticus [28]. Whenever subclinical seizures are suspected, EEG should be performed in order to confirm or rule out their diagnosis and adapt the treatment [29]. The presence of seizures at eh onset of encephalitis is a risk factor for the persistence of seizures as sequels, after the recovery from the infection [26]. Seizure are also related to worse outcome, with case-fatality rate of 30%, combined with severe initial coma and failure of anticonvulsants [26, 30]. Risk factors for seizures during encephalitis are age < 15 years, coma, cortical involvement, MRI images and HSV.

There is no data demonstrating the benefit of anticonvulsants at the initial phase of encephalitis, for prevention of seizures [31], thus it is not recommended to prescribe them. In case of seizure, there is no evidence of superiority of any drug, and they should be treated according to standard recommendations.

VZV encephalitis can be complicated by cerebral vasculopathy, and so adjuvant corticoid therapy could be considered, but clinical studies are scarce and poorly convincing. So far it is not recommended to administer an adjuvant corticoid therapy in the treatment of VZV encephalitis [20].

Outcome

Case Fatality Rate

Before the generalization of acyclovir, up to 70% of patients experiencing HSVE died. Case-fatality rate of HSVE now ranges from 5% to 20% according studies, the discrepancies being related to the selection criteria of studied populations [15–17, 32, 33].

The case-fatality ratio of VZV encephalitis was evaluated to 15% and related to co-morbidities and/or age [7, 34].

Outcome and Sequelae Following HSE Et VZV Encephalitis

Sequelae following HSVE have been known for long to be frequent and severe, and to be a cause of major cognitive impairment and behavioral disorders in surviving patients [35, 36].

In a more recent study focused on encephalitis sequelae, authors reported that only 42% of patients presenting with HSVE experienced a favorable outcome, compared with 68% in other encephalitis patients. Moreover, only 14% of HSVE patients had fully recovered at follow-up, compared with 49% in other encephalitis patients. Compared with other patients, patients with HSE more frequently experienced concentration and behavioral disorders, especially disinhibition, but the frequencies of memory impairment and speech disorders did not differ significantly [37].

VZV encephalitis sequelae have been less studied. In the same cohort study, moderate to severe sequelae (Glasgow outcome scale 3 or 4) were reported in 41% of patients with VZV encephalitis patients, 3 years after the onset of the infection [7, 34]. Like HSVE, VZV encephalitis can results in long-term memory disorders Speech disorders are reported in up to 30% of patients [34, 37].

Auto-Immune Disorders Following HSVE

The awareness on auto-immune encephalitis due to antibodies targeting some receptors of neurons membrane arose in 2006. Since the first publications, numerous cases have been diagnosed and could benefit from a targeted treatment. Limbic auto-immune encephalitis are now considered a major differential diagnosis if HSVE [38, 39].

Various studies recently confirmed the importance of auto-immune encephalitis triggered by HSE. The most recent study concluded that there is a predictable time frame of approximately 5 weeks in which 27% of patients with HSE develop

immune responses against NMDAR and other neuronal surface proteins, with neurological symptoms [39]. Among the remaining patients, 30% developed autoantibodies in serum (and some in CSF) without symptoms.

As a consequence, recent guidelines recommend looking for autoantibody secretion in CSF in case of failure of the antiviral treatment or recurrence of symptoms despite an early appropriate management [20].

The physiopathological explanation of this auto-immune disorder is still unclear, but some hypothesis could be raised [40]: molecular mimicry, release of antigenic proteins from neuronal injury becoming autoimmune targets, host autoinflammatory responses specific to herpesvirus infection, genetic risk factors, role of some degree of immunodeficiency. A recent case-report demonstrated a TLR3 deficiency in a patient experiencing auto-immune encephalitis following HSVE [41]. This finding opens the way to more research to understand, and possibly propose early interventions to prevent these severe complications of HSVE.

Conclusion

HSV and VZV encephalitis are severe diseases with a high case-fatality rate, and moreover a very high frequency of post-encephalitis sequelae. Acyclovir I.V., together with nonspecific neurological care, is the standard of care.

HSV is a trigger for auto-immune encephalitis as a complication of the infection, but the mechanisms still need to be uncovered.

Better knowledge about inflammatory process could lead to additional treatments such as steroids to prevent complications and limit the acute brain parenchyma necrosis (that are not currently recommended) of monoclonal antibodies and possibly predictive scores.

References

1. Everett RD. HSV-1 biology and life cycle methods. Mol Biol. 2014;1144:1–17.
2. McGeoch DJ, Dalrymple MA, Davison AJ, Dolan A, Frame MC, McNab D, Perry LJ, Scott JE, Taylor P. The complete DNA sequence of the long unique region in the genome of herpes simplex virus type 1. J Gen Virol. 1988;69:1531–74.
3. Wertheim JO, Smith MD, Smith DM, Scheffler K, Kosakovsky Pond SL. Evolutionary origins of human herpes simplex viruses 1 and 2. Mol Biol Evol. 2014;3:2356–64.
4. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics. 2016;13:493–508.
5. Casrouge A, Zhang S-Y, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science. 2006;314:308–12.
6. Mancini M, Caignard G, Charbonneau B, Dumaine A, Wu N, Leiva-Torres GA, Gerondakis S, Pearson A, Qureshi ST, Sladek R, Vidal SM. Rel-dependent immune and central nervous system mechanisms control viral replication and inflammation during mouse herpes simplex encephalitis. J Immunol. 2019;202:1479–93.

7. De Broucker T, Mailles A, Chabrier S, Morand P, Stahl J-P. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. Clin Microbiol Infect. 2012;18:808–19.
8. Kleinschmidt-DeMasters BK, Gilden DH. Varicella-Zoster virus infections of the nervous system: clinical and pathologic correlates. Arch Pathol Lab Med. 2001;125:770–80.
9. Depledge DP, Cudini J, Kundu S, Atkinson C, Brown JR, Haque T, Houldcroft CJ, et al. High viral diversity and mixed infections in cerebral spinal fluid from cases of Varicella Zoster virus encephalitis. J Infect Dis. 2018;218:1592–601.
10. Canivet C, Rhéaume C, Lebel M, Piret J, Gosselin J, Boivin G. Both IRF3 and especially IRF7 play a key role to orchestrate an effective cerebral inflammatory response in a mouse model of herpes simplex virus encephalitis. J Neurol. 2018;24:761–8.
11. Mielcarska MB, Bossowska-Nowicka M, Ngosa TF. Functional failure of TLR3 and its signaling components contribute to herpes simplex encephalitis. J Neuroimmunol. 2018;316:65–73.
12. Sato R, Kato A, Chimura T, Saitoh SI, Shibata T, Murakami Y, Fukui R, et al. Combating herpesvirus encephalitis by potentiating a TLR3-mTORC2 axis. Nat Immunol. 2018;19:1071–82.
13. Zimmermann J, Hafezi W, Dockhorn A, Lorentzen EU, Krauthausen M, Getts DR, Müller M, et al. Enhanced viral clearance and reduced leukocyte infiltration in experimental herpes encephalitis after intranasal infection of CXCR3-deficient mice. J Neurovirol. 2017;23:394–403.
14. Mailles A, Stahl JP. Infectious encephalitis in France in 2007: a National Prospective Study. Clin Infect Dis. 2009;49:1838–47.
15. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, Schuster FL, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43:1565–77.
16. Granerod J, Ambrose HE, Davies NWS, Clewley JP, Walsh AL, Morgan D, Cunningham R, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835–44.
17. Stahl JP, Mailles A, De Broucker T. Herpes simplex encephalitis and management of acyclovir in encephalitis patients in France. Epidemiol Infect. 2012;140:372–81.
18. Hauer L, Pikija S, Schulte EC, Sztriha LK, Nardone R, Sellner J. Cerebrovascular manifestations of herpes simplex virus infection of the central nervous system: a systematic review. J Neuroinflammation. 2019;16:19. https://doi.org/10.1186/s12974-019-1409-4.
19. Bewersdorf JP, Koedel U, Patzig M, Dimitriadis K, Paerschke G, Pfister HW, Klein M. Challenges in HSV encephalitis: normocellular CSF, unremarkable CCT, and atypical MRI findings. Infection. 2019;47:267–73.
20. Stahl JP, Azouvi P, Bruneel F, De Broucker T, Duval X, Fantin B, Girard N, et al. Guidelines on the management of infectious encephalitis in adults. Med Mal Infect. 2017;47:179–94.
21. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47:303–27.
22. Tebas P, Nease RF, Storch GA. Use of the polymerase chain reaction in the diagnosis of herpes simplex encephalitis: a decision analysis model. Clin Microbiol Rev. 2004;17:903–25.
23. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, Stahl J-P, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57:1114–28.
24. Kamei S, Takasu T, Morishima T, Mizutani T. Serial changes of intrathecal viral loads evaluated by chemiluminescence assay and nested PCR with acyclovir treatment in herpes simplex virus encephalitis. Intern Med. 2004;43:796–801.
25. Kleines M, Scheithauer S, Schiefer J, Häusler M. Clinical application of viral cerebrospinal fluid PCR testing for diagnosis of central nervous system disorders: a retrospective 11-year experience. Diagn Microbiol Infect Dis. 2014;80:207–15.
26. Misra UK, Tan CT, Kalita J. Viral encephalitis and epilepsy. Epilepsia. 2008;49(Suppl 6):13–8.
27. Solomon T, Dung NM, Kneen R, le TT T, Gainsborough M, Nisalak A, et al. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. Brain. 2002;125(Pt 5):1084–93.

28. Singh G, Prabhakar S, Modi M. Central nervous system infections and epilepsy. Epilepsia. 2008;49(Suppl 6):1.
29. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician's guide. Pract Neurol. 2007;7(5):288–305.
30. Nair PP, Kalita J, Misra UK. Role of cranial imaging in epileptic status. Eur J Radiol. 2009;70(3):475–80.
31. Pandey S, Rathore C, Michael BD. Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis. Cochrane Database Syst Rev. 2014;10:CD010247.
32. Davison KL, Crowcroft NS, Ramsay ME, Brown DWG, Andrews NJ. Viral encephalitis in England, 1989–1998: what did we miss? Emerg Infect Dis. 2003;9(2):234–40.
33. Hjalmarsson A, Blomqvist P, Sköldenberg B. Herpes simplex encephalitis in Sweden, 1990–2001: incidence, morbidity, and mortality. Clin Infect Dis. 2007;45(7):875–80.
34. Grahn A, Nilsson S, Nordlund A, Lindén T, Studahl M. Cognitive impairment 3 years after neurological Varicella-zoster virus infection: a long-term case control study. J Neurol. 2013;260(11):2761–9.
35. McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J Neurol Neurosurg Psychiatry. 1997;63(3):321–6.
36. Utley TF, Ogden JA, Gibb A, McGrath N, Anderson NE. The long-term neuropsychological outcome of herpes simplex encephalitis in a series of unselected survivors. Neuropsychiatry Neuropsychol Behav Neurol. 1997;10(3):180–9.
37. Mailles A, De Broucker T, Costanzo P, Martinez-Almoyna L, Vaillant V, Stahl JP. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France Clin. Infect Dis. 2012;54:1455–64.
38. Westman G, Sohrabian A, Aurelius E, Ahlm C, Schliamser S, Sund F, Studahl M, et al. Clinical significance of IgM and IgA class anti-NMDAR antibodies in herpes simplex encephalitis. J Clin Virol. 2018;103:75–80.
39. Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, Llufriu S, et al. Autoimmune encephalitis post-herpes simplex encephalitis: frequency, syndromes, risk factors, and outcome. Lancet Neurol. 2018;17:760–72.
40. Gelfand JM. Autoimmune encephalitis after herpes simplex encephalitis: insights into pathogenesis. Lancet Neurol. 2018;17:733–5.
41. Armangue T, Baucells BJ, Vlagea A, Petit-Pedrol M, Esteve-Solé A, Deyà-Martínez A, Ruiz-García R, et al. Toll-like receptor 3 deficiency in autoimmune encephalitis post-herpes simplex encephalitis. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e611.

Chapter 9
Neurologic Disease in HIV Infection

Eric A. Goethe, Naomi R. Kass, and Joseph S. Kass

Human Immunodeficiency Virus

First described in 1981 [1], acquired immunodeficiency syndrome (AIDS) presents as a constellation of signs, symptoms, and opportunistic diseases reflecting the human immunodeficiency virus's (HIV) infection, dysregulation, and destruction of immune cells involved primarily in the cellular immune response such as CD4+ T lymphocytes but also including members of the monocyte/macrophage lineage such as central nervous system (CNS) microglia. The Centers for Disease Control and Prevention (CDC) defined AIDS as a CD4+ T-lymphocyte count below 200 cells/microliter and also identified a number of AIDS-defining conditions, both opportunistic diseases arising from a devastated cellular immune as well as conditions manifesting as a direct consequence of the immune dysregulation characteristic of HIV infection. The entire neuroaxis is susceptible to the HIV-related damage, and many AIDS-defining conditions manifest in the central nervous system (CNS). Immune status, comorbid conditions, environmental exposures, and cART efficacy, adherence, and side effects all modulate the susceptibility of the nervous system to HIV-related complications.

Even in the cART era, treatment naïve or nonadherent HIV-infected patients may still present with a fulminant AIDS defining nervous system condition such as

E. A. Goethe
Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA
e-mail: Eric.Goethe@bcm.edu

N. R. Kass
Rice University, Houston, TX, USA
e-mail: kass@bcm.edu

J. S. Kass (✉)
Department of Neurology, Baylor College of Medicine, Houston, TX, USA
e-mail: kass@bcm.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_9

cerebral toxoplasmosis, primary central nervous system lymphoma (PCNSL), progressive multifocal leukoencephalopathy (PML), cytomegatlovirus (CMV) encephalitis or polyradicultis, a fungal meningitis, most commonly due to cryptococcus infection, tuberculosis meningitis, HIV-associated dementia, or even HIV-associated vascular myelopathy. With cART initiation, these patients become susceptible to Immune Reconstitution Inflamattory Syndrome (IRIS), which may result in serious neurological morbidity and even death. However, patients adherent to cART whose CD4+ T-lymphocyte level remain above 200 cells/microliter remain susceptible to peripheral neuropathy, HIV-associated neurocognitive disorder (HAND), and even rarer conditions such as CD8+ encephalitis. This chapter describes common complications of HIV infection including nervous system AIDS-defining conditions and other direct or opportunistic processes that damage the neuroaxis.

Neuropathogenesis

Shortly after systemic HIV infection, CCR5+/CD4+T-lymphocytes and CCR5+/CD4+ monocytes traffic HIV across the blood-brain barrier (BBB) into the central nervous system (CNS), releasing virus, viral particles such as vpr, tat, nef, and gp120, and a plethora of cytokines and chemokines and unleashing a cascade of inflammation and apoptosis in both microglia and astrocytes [2]. Initially, systemic and CNS HIV strains remain the same, but as infection progresses T-trophic virus, preferentially infecting CCR5+ /CD4+ T-cells, drives meningeal infection, whereas the M-trophic virus strain, preferentially infecting CCR5+/CD4+ perivascular macrophages and microglia, evolves along its own trajectory within the brain and spinal cord [3]. Perivascular macrophages and microglia are the only CNS cell types productively infected with HIV, transforming these cells into unique sources of viral production within the CNS [4]. Infected microglia aggregate to form multinucleated giant cells, the pathologic hallmark of HIV encephalitis. Infected microglia damage the brain and spinal cord by not only serving as reservoirs of viral production but also producing many excitotoxic molecules that damage adjacent neurons and glial cells and induce synaptic dysfunction [5]. These excitotoxic species also kill off adjacent cells, although with less potency than infected peripheral CD4+ T lymphocytes [6]. In response to this explosion of excitotoxicty and inflammation, the brain upregulates neuroprotective and regenerative proteins in an attempt to repair damage, although neither the patient's immune system nor cART can eradicate the virus from the brain [7].

Although HIV infects neither neurons nor oligodendrocytes, the virus does infect the astrocyte, the most abundant CNS cell type, through CD4 receptor independent mechanisms [8]. Unlike microglial infection, astrocytic infection does not yield a productive source of viral replication but nonetheless damages infected astrocytes and other adjacent glial cells and neurons by undermining the astrocyte's critical ability to maintain homeostasis, by, among other mechanisms, dampening astrocytes' ability to dampen locally generated excitotoxicity [5]. Additionally, because

astrocytes form an integral part of the blood-brain barrier (BBB), dysfunctionalinfected astrocytes damage BBB endothelial cells, inducing apoptosis in local, uninfected astrocytes [9]. Along with microglia, astrocytes do remain HIV viral reservoirs, and a viral strain can exist for a long time within the CNS because both astrocytes and microglia turn over very slowly. The unique biology of these glial cells also offers at least a partial explanation for the continued damage HIV wrecks on the brain despite appropriately targeted systemic cART therapy [10].

HIV-Associated Neurocognitive Disorder

Diagnostic Criteria

Before combination antiretrovial therapy (cART) transformed the natural history of HIV infection into a survivable, chronic disease, the single most common CNS AIDS-defining condition was the rapidly progressive subcortical dementia initially called AIDS Dementia Complex (ADC) [11–13]. The pathological substrate of this condition, HIV encephalitis, is characterized by cortical atrophy, leukoencephalopathy, microglial nodules, and multinucleated giant cells [14]. ADC underwent its first nomenclature revision in 1991 with the American Academy of Neurology (AAN) criteria dividing the condition into the milder Minor Cognitive Motor Disorder (MCMD) and more advanced and inexorably fatal HIV-Associated Dementia (HAD) (AAN 1991). The 2007 Frascati criteria established a new nosology for what is now called HIV-Associated Neurocognitive Disorder (HAND) in recognition of the changes in this condition in the cART era [15].

The Frascati criteria divide HAND into three stages: (1) asymptomatic neurocognitive impairment (ANI); (2) mild neurocognitive disorder (MND); and (3) HIV-associated dementia (HAD). An ANI diagnosis requires an acquired impairment (defined as scoring more than 1 standard deviation below the mean, adjusted for age and educational) in two or more cognitive domains on neuropsychological testing, but these deficits should not impact daily function. MND patients experience the same degree of acquired cognitive deficit on neuropsychological testing as ANI patients, but patients are diagnosed with MND when they report mild functional impairment due to these deficits. HAD patients experience severe functional impairment as a result of their severe acquired deficit in at least two cognitive domains on neuropsychological testing (defined as more than 2 standard deviations below the mean, adjusted for age and education). However, HAD typically impacts more than two cognitive domains [15]. The Frascati criteria do not establish a specific battery of tests with which to diagnose HAND but do require assessment of at least five of the following domains normed appropriately for patient demographic factors such as age and education: (1) attention-information processing; (2) language; (3) abstraction-executive function; (4) complex perceptual motor skills; (5) memory, including learning and recall; (6) simple motor skills; and (7) sensory perceptual skills. Other causes of dementia as well as

psychiatric and substance-related confounders must be excluded. Functional impact may be typically assessed either by self-report or by using self-administered questionnaires [15, 16].

HAND Demographics

Along with a change in disease phenotype, the demographics of HAND have changed over time. Before cART, HIV-infected individuals experiencing cognitive dysfunction passed rather quickly through mild stages of HAND, progressing to HAD and death over several months. In the pre-cART era, 20% of subjects in the Multicenter AIDS Cohort Study (MACS) developed HAD, making HAD the most common AIDS-defining CNS condition at the time. In the cART era, HAND itself is no less common than before, but the milder forms of HAND are considerly more common than HAD. Depending on the cohort studied, among cART-treated individuals, approximately 30% have ANI, 10–30% have MND, and only 2–8% have HAD [17]. However, regardless of treatment era, cognitive impairment appears to increase with advancing immunosuppression, and low CD4+ T lymphocyte count nadir is the single most critical HAND risk factor. A patient's current level of immunosuppression, estimated duration of infection, and CSF viral suppression are predictors of impairment in untreated patients only [18]. Therefore, an evaluation of a patient who has experienced an appropriate immune and virologic response to cART presenting with a cognitive complaint must include a determination of the patient's most profound level of immunocomprimise, because for the treatment experienced patient, a CD4+ T-lymphocyte count nadir below 200 cells/microliter is the most critical HAND risk factor.

Effective antiretroviral therapy has changed not only the prevalence but also the natural history of HAND. An untreated HIV seropositive patient who remains untreated once presenting with a mild cognitive complain will progress to a bedridden, akinetic mute, and incontent state and then to death over several months [19]. In patinets who respond as expected to cART, HAND stage remains stable in majority of individuals over several years. Both the Longitudinal CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Study [20] and the Multicenter AIDS Cohort Study [19] sought to describe the natural history of HAND in these large cohorts. CHARTER investigators studied both the incidence and predictors of neurocognitive change over a mean of 35 months in 436 the people living with HIV who were members of an ethnically diverse, predominantly male, predominantly cART treated cohort. Members of this cohort experienced a variety of non-HIV comorbidities that potentially affected cognitive outcomes. The CHARTER investigators found that 22.7% declined, 60.8% remained stable, and 16.5% improved. In multivariate analysis significant risk factors for earlier cognitive decline were Hispanic ethnicity (reflecting that population's late presentation to diagnosis and difficulties accessing healthcare), high impact comorbidities confounding a HAND diagnosis, low albumin and hematocrit values (factors associated with poor health

status), lack of cART treatment, a lifetime diagnosis of methamphetamine use, and a high burden of depressive symptoms. Having a higher premorbid IQ, lower total protein and AST levels, and no lifetime diagnosis of major depressive disorder predited cognitive improvement. In the Multicenter AIDS Cohort (MACS), a study of HIV infection in men who have sex with men, investigators found that depending on the time period studied, between 25% and 33% of their cohort met HAND criteria, lower than the 47% reported in the CHARTER cohort. Also, whereas in the CHARTER cohort 60.8% of subjects experienced no neurocognitive change over a mean of 3 years, in the MACS cohort 77% of 197 HIV-infected subjects had no change in cognitive status over 4 years, with only 13% deteriorating and 10% improving. Similar to the CHARTER findings, those with ANI were twice as likely to develop symptomatic HAND compared to those who were cognitively normal at baseline. The MACS study identified hypercholesterolemia as a predictor of cognitive decline, possibly reflecting an impact of cerebrovascular disease on cognitive change. Differences between MACS and CHARTER likely reflect the demographic differences between the two cohorts, since MACS subjects were generally better educated, healthier, more likely to be on cART, less ethnically diverse, and exclusively male.

Comorbidities and HAND

The CHARTER study examined the impact of comorbidities on HAND diagnosis by applying the Franscati criteria to over 1555 HIV-infected individuals at four university-based HIV clinics, determining whether comorbities were incidental to (54.2%, n = 843), contributed to (30.4%, n = 473), or confounded (15.4%, n = 239) a HAND diagnosis. Overall, 52% of subjects experienced cognitive impairment, and those with a greater comorbidity burden experienced higher rates of impairment (40% incidental vs. 83% confounding). Comorbities commonly encountered were low baseline reading level, placement in special education classes, current psychiatric disease—in particular major depressive disorder, a psychotic disorder, or a substance use disorder—and a medical history of traumatic brain injury, seizures, systemic medical illness, or CNS opportunistic infections. Excluding severely confounded cases, 33% of subjects were diagnosed with ANI, 12% with MND, and only 2% with HAD. Consistent with previous studies, CHARTER found that a history of a low CD4+ T lymphocyte count nadir was associated with a greater risk of HAND, even in patients who at the time of the study had responsed to cART with appropriate immune system recovery and viral suppression [21]. In addition to CHARTER, a number of other studies have found a strong correlation between CD4+ cell count nadir and the risk of HAND [22]. In addition to the CHARTER-identified comorbidities, comorbidities increasing the risk of cerebrovascular disease have been found to affect cognition in HIV-infected patients. One study found that hypertension and hyperlipidemia correlate better with baseline neuropsychological testing performance than current CD4+ T lymphocyte count and viral load

in middle aged men [23]. Other studies have found that central obesity, systemic inflammation, and diabetes mellitus (at least for older HIV-infected patients), were also associated with worse cognition [24, 25]. As mentioned earlier, the MACS study found hypercholesterolemia to be a risk factor for cognitive decline [19].

Patient Presentation: History and Examination

Diagnosing HAND begins with the patient's cognitive complaint and continues with a thorough history. The patient and, if at all possible, an informant should be asked to elaborate on the nature of the cognitive complaint, asking for specific examples of cognitive changes and the time course over which the cognitive deficit has evolved. HAND evolves insidiously and in virologically and immune optimized patients, progresses slowly if at all. Patients may initially complain of memory loss but rather than the frank anterograde amnesia typical of Alzheimer's disease, HAND patients will typically describe difficulty with information retrieval and multitasking. They may lose track of a conversation or the goal of a task part way through. However, given time or reminders, patients can typically re-engage with the task at hand. Some patients may also report symptoms that may mimic depression such as irritability, apathy, and social withdrawal. They may also notice subtle changes in fine motor skills and increased clumsiness [26]. Either an acute onset of a cognitive change or a rapid decline from normal to impaired demands a rapid evaluation for an opportunistic CNS condition or other non-HIV related disease impairing cognition such as acute cerebrovascular disease [27].

The clinician should establish the patient's cognitive baseline by inquiring about the highest level of educational and professional attainment and any history of scholastic difficulty and should also assess the impact of cognitive changes on the patient's performance of both instrumental activities of daily living (IADLs) and basic activities of daily living (ADLs). IADLs include higher order functions critical for independent living such as shopping, managing finances, cleaning, cooking, and finding ones way around the community. ADLs include more basic tasks such as bathing, grooming, dressing, and feeding. Even early MND patients are at increased risk of unemployment, medication non-adherence, and difficulty driving, and they may need to rely on others for help with IADLs [26]. A full cognitive history must include screening for changes in both mood and behavior, and patients should be screened for depressive and psychotic symptoms. The clinician should also inquire about a history of traumatic brain injury, cerebrovascular disease, CNS opportunistic disease, seizures, and significant psychiatric disease as well as current and past alcohol and substance use. Because cognitive dysfunction can impact a patient's ability to earn an income and live independently, the social history should include an assessment of the patient's overall economic and physical safety, including domicilary status and ability to access food and transportation relaibly. These medical, psychological, and social comborbidities may influence baseline cognitive

status independently of HAND and may also render the brain more susceptible to the affects of HIV-related insults.

The next step in diagnosing HAND is performing a thorough examination, beginning with a bedside cognitive assessment. HAND typically creates a "subcortical" pattern of cognitive dysfunction, with impairments in attention and speed of information processing, abstraction and executive function, and working memory [28]. However, some investigators have found evidence that in the cART era patients are experiencing a shift from a predominantly subcortical to a more cortical pattern of cognitive dysfunction. Unfortunately, when compared to the gold standard of formal neuropsychological testing, bedside cognitive tests typicaly used to assess cognitive function in HIV patients (e.g., the International HIV Dementia Screen, the HIV Dementia Scale, Z scores of several brief neuropsychological tests used in the AIDS Clinical Trials Group, or the Montreal Cognitive Assessment) are insensitive to the more subtle neuropsychological changes patients with ANI and MND experience. Furthermore, they do not possess adequately benchmarked norms for the diverse HIV-infected populations. These psychometric challenges may affect the sensitivity and specificity of a HAND diagnosis and complicate treatment monitoring. Using patients as their own controls may get around the issue of inadequate norms, but that choice creates its own pitfalls because of a practice effect from repeated testing [29–31].

After the bedside assessment of cognitive function, the patient should undergo a thorough physical examination, including a neurological exam, looking for evidence of extrapyramidal features (i.e., Parkinsonism) as well as focal neurological signs. Extrapyramidal features have long been recognized in patients with HAND, well before the cART era. The Hawaii Aging With HIV Cohort found that even in cART treated men, having three extrapyramidal signs was associated with cognitive impairment and a HAND diagnosis, an association even stronger in the older seropositive cohort. The extrapyramidal signs with the best predictive value were slowness of hand movements, body bradykinesia, action/postural tremor, and hypomimia, and the least useful sign was resting tremor. This correlation between increasing number of extrapyramidal signs and worsening cognition correlates with findings from neuroimaging studies demonstrating that both cognitive and motor impairments are associated with reductions in basal ganglia volume as well as with atrophy of nigro-striatal and fronto-striatal circuits [32, 33], areas of the brain in which dysfunction results in extrapyramidal signs and cognitive slowing.

Focal neurological findings are not part of HAND and should prompt an investigation for an alternative cause of cognitive dysfunction, such as a opportunisitic CNS condition or other focal disease process such as cerebrovascular disease. HIV infection increases stroke risk, and cerebrovascular disease and cerebrovascular risk factors may cause cognitive and behavioral dysfunction [23, 25, 34]. Although patients with HAND and no current or previous history of brain injury (regardless of etiology) should not demonstrate focal neurological deficits, they may have signs of generalized pyramidal tract dysfunction in the form of symmetric hyperreflexia (although Achilles reflex may be depressed due to HIV-associated distal symmetric

polyneuropathy) along with frontal release signs, especially in patients with HAD. In fact, as was typical in the pre-cART era, HAD may often evolve into an illness of not only profound cognitive dysfunction but also progressive myelopathy with spastic paraparesis, dorsal column dysfunction, and incontince but without a spinal sensory level typically seen in myelopathy from a compressive spinal lesion. These additional myelopathic findings are identical to those of vacuolar myelopathy, since both HAD and vacuolar myelopathy are thought have a smilar neuropathogenesis [26].

Patient Work-Up: Serum, CSF & Neuroimaging

Every HIV-infected patient presenting with a cognitive deficit should undergo a basic laboratory work, neuroimaging evaluation, and cerebrospinal fluid analysis. In addition to the typical serologic work recommended by the American Academy of Neurlogy Practice Guideline for the evaluation of dementia (i.e. complete blood count, electrolytes, renal, and hepatic function, glucose, thyroid function tests, and B12 level), all HIV seropositive patients should also be screened for syphilis and should undergo both cerebrospinal fluid analysis and neuroimaging to exclude HAND mimics such as an opportunistic CNS infection, PCNSL, or non-HIV-related CNS conditions such as cerebrovascular disease or non PCNSL brain tumors [27].

The CSF profile in HAND ranges from a normal white blood cell count to a mild mononuclear pleocytosis of up to 20 cells/microliter, although cART treated patients as well as those with severe immunosuppression tend to have lower CSF white blood cell counts. Protein level may be mildly elevated, indicating BBB disruption. Some patients also demonstrate intrathecal antibody production with the presence of oligoclonal bands and an elevated IgG index [27]. If there is concern about CSF HIV viral escape as a cause of cognitive decline (see below for more details), then CSF HIV viral load and genotype for resistence pattern, if available, may help guide therapy to address the different resistance pattern that has developed within the CNS as compared to the periphery. Concern for either leptomeningeal neoplasm or CD8+ encephalitis should prompt CSF analysis for cytology and flow cytometry.

A gadolinium-enhanced brain MRI is the neuroimaging modality of choice in the evaluation of all patients with cognitive dysfunction, regardless of HIV status. If gadolinium is contraindicated due impaired renal function, than an unenhanced MRI may be adequate to rule out a HAND mmic. If MRI itself is contraindicated, then a contrast-enhanced CT would be the next best imaging choice, followed by a non-contrast head CT, the least sensitive neuroimaging test to evaluate for HAND mimics. Brain MRI findings in HAND patients may range from mild cortical and white matter atrophy without significant white matter changes to significant generalized atrophy, enlarged ventricles, and significant periventricular subcortical white matter as well as the basal ganglia hyperintensities on T2 sequences that do not enhance on a T1 with gadolinium sequence. In contrast to PML, HAND white matter hyperintensities typically spare the cortical U-fibers [27]. Neither atrophy nor

white matter hyperintensity are unique to HAND, and therefore the radiologist should be made aware of the patient's HIV history to interpretate these findings in the appropriate clinical context. However, changes due to cerebrovascular disease may be difficult to distinguish from HAND-related changes, especially in older patients and those with co-morbid cerebrovascular risk factors. In fact, in cART-treated patients in the Hawaii Aging with HIV cohort, the extent of white matter hyperintensity correlated with age and blood pressure rather than with virologic and immune status [35].

The cortical atrophy detected on MRI may reflect neuronal and myelin loss [36]. Findings from volumetric MRI studies in HIV-infected individuals demonstrate smaller thalamic volumes and enlarged frontal sulci [37]. Futhermore, reduced brain basal ganglia, caudate, corpus callosum, cerebral cortex, and hippocampal volumes correlate with neuropsychological testing deficits [38–43].

HIV seropositivity may accelerate brain aging. HIV-related atrophy occurs independently of age-related atrophy in cART treated individuals when compared to age-matched seronegative individuals. For example, cART responsive HIV seropositive men demonstrated significant atrophy of the anterior regions of the caudate and putamen as compared to age-matched seronegative men. Basal ganglia volume was inversely associated with the time since initial seropositivity, suggesting that either a chronic subclinical process continues to damage the brain despite appropriate immune and virologic response to cART or a pre-treatment brain effect determines the extent of atrophy [44]. Studies examining the brains of acutely infected individuals lend support to the theory that early HIV infection leaves an early structural and functional impact on the brain. For example, one study examing 15 untreated subjects within 100 days of HIV infection compared to 20 uninfected controls found that seropositive subjects already demonstrated reduced brain parenchymal volume, expansion of third ventricle, and brainstem enlargement [45].

Other Neuroimaging Biomarkers

In addition to structural MRI, other imaging modalities also offer insight into the pathophysiology of HAND. For example, magnetic resonance spectroscopy (MRS) studies consistently find that cART-naïve patients demonstrate reductions in N-acetylaspartate, a signature of neuronal injury, along with an increase in myoinositol and choline levels, indicative of glial proliferation, especially in the frontal white matter and basal ganglia, areas that also show changes on volumetric MRI analyses. These elevations of myoinositol and choline may normalize after 6–9 months of cART [46]. Diffusion tensor imaging (DTI) has demonstrated reduced white matter integrity of the corpus callosum and alterations in the caudate. Cognitive impairment has also been associated with reduction in the integrity of cortical white matter, the corpus callosum, and the corona radiata. Blood oxygen level dependent (BOLD) fMRI studies have demonstrated variable findings depending on the type of tasks subjects were asked to perform [47]. Compared with control

subjects, patients with HIV demonstrated greater brain activation than seronegative controls in the lateral prefrontal cortex despite normal performance during fMRI on a neuropsychological assessment [48]. Such findings suggest that brains of HIV seropositive individuals must deploy additional metabolic resources compared to seronegative controls to carry out normal cognitive processes. Resting state functional connectivity MRI (rs-fcMRI) changes in the salience and default networks in HIV-infected patients are similar to those that deteriorate in normal aging [49]. 18-FDG PET studies have revealed both cortical hypometabolism and basal ganglia hypermetabolism [50].

Plasma and CSF Biomarkers

Because current CD4+ cell count and plasma viral load do not correlate with the risk of cognitive impairment for patients on cART, researchers have sought plasma, CSF, and neuroimaging biomarkers for HAND. Plasma biomarkers have included markers of activated monocytes and macrophages (e.g. increased plasma-soluble CD14 linked to impairment in attention and learning), and CSF biomarkers have focused on markers of inflammation (e.g. increased CSF neopterin, MCP-1), neuronal injury (e.g, increased neurofilament) as well as on CSF viral escape (presence of virus in CSF despite systemic viral suppression) and viral genomics [51–54].

Treatment

The HAND diagnosis does not distinguish between two types of HIV infected individuals: treatment naïve versus cART-treated individuals. For treatment naïve patients, cART offers a treatment target by either reversing the disease or arresting the cognitive decline. For those developing HAD despite an effective systemic virologic and immune response to cART, the approach to treatment is much less clear [7]. Discovering a biological target for treating either ANI or MND in cART treated individuals is especially difficult because neither ANI nor MND is associated with specific neuropathological correlates [29, 53], although ANI patients are between 2 and 6 times more likely to progress to either MND or HAD than HIV infected patients without ANI [55].

HAND may be preventable with early virologic control and prevention of a CD4+ cell nadir below 200 cells/microliter [56, 57]. The only effective treatment for HAND remains cART. By 48 weeks after cART initiation, 41% of patients with mild to moderate cognitive impairment experience clinically meaningful and sustained cognitive improvement [58]. Yet even on cART, a large percentage of HIV-infected patients continue to experience cognitive impairment [21]. Because the BBB does not allow all anti-retroviral agents (ARV) to penetrate the brain in equal measure, HIV may evolve independently in the CNS. Despite systemic suppression of viral replication, even low-level CNS viremia may perpetuate a deleterious

inflammatory, excitotoxic, and ultimately degenerative effect on the brain. Neuropathological studies have supported this hypothesis, finding that despite plasma viral suppression, high levels of microglial activation is found in the basal ganglia and hippocampus [59]. In fact, while 50% of patients had no detectable HIV RNA in examined brain regions, among those with evidence of HIV RNA, the lowest levels were identified in the CSF and the highest in the caudate, even in patients on cART [60].

By studying the CSF pharmacokinetics of the different AVRs, a CNS penetration effectiveness ranking system has been validated [61]. More penetrant cART leads to more prolonged CSF viral suppression. However, the impact on cognitive performance of more penetrant cART regimens is variable. Although some studies have shown that more penetrant cART positively affects neuropsychological test performance [62], other studies have suggested that more penetrant cART may have a deliterioius impact on cognitive function since those with more penetrant cART experienced a greater risk of HAD but not of other opportunistic processes [63].

Aside from cART, no other pharmacologic interventions have proven effective in improving cognitive function in HAND patients. Trials have studied medications targeing microglial activation, cytotoxic elements, NMDA levels, and variety of neurotransmitter levels. The studies medications include nimodipine, selegiline, minocycline, rivastigmine, and memantine, among others [64–69]. Although a small pilot study demonstrated improved processing speed with rivastigmine, no adjunctive strategy has been proven effective in improving cognitive function in a large, controlled study.

CD8+ Encephalitis

Background

CD8+ Encephalitis (CD8+E) is a neurocognitive manifestation of HIV characterized by massive perivascular infiltration of CD8+ lymphocytes [70]. This is a unique manifestation of HIV classically affecting patients with well-controlled disease and is often associated with viral escape [71]. Patients with CD8+E typically present with acute to subacute, nonspecific symptoms of encephalitis such as seizures, confusion, or focal deficits [70]. The overall prognosis of CD8+E is poor; even with appropriate treatment, less than a third of patients can be expected to return to neurologic baseline [70]. Without treatment, CD8+E is typically fatal [71].

Diagnosis and Treatment

The differential diagnosis of encephalopathic signs and symptoms in an HIV patient is broad, and the initial workup of such patients may be nonspecific [71, 72]. However, as the common culprits which cause such presentations are unlikely to do

so in patients with well-controlled disease, clinicians should maintain a high degree of suspicion for CD8+E in patients with well-controlled HIV disease [70–72]. While imaging findings may be nonspecific, MRI spin-echo sequences can demonstrate foci of post-contrast perivascular enhancement [70]. CSF studies show a CD8+ lymphocytic pleocytosis [70].

Lescure et al. [70] observed an inverse relationship between time to treatment and mortality in a series of patients with CD8+E, again highlighting the importance of clinical suspicion. The standard treatment for CD8+E is high-dose corticosteroids [70, 72], but Salam et al. [71] report a case of CD8+E successfully treated with mycophenolate.

Myelopathic Manifestations of HIV

HIV may affect any spinal cord segment or its exiting nerve root [73]. Data regarding spinal cord disease in HIV are sparse, owing to the widespread use of cART, though viral escape may induce a pro-inflammatory state inside the spinal cord even with perpetually well-controlled disease [73]. The differential diagnosis of myelopathy in HIV patients is broad and includes HIV-associated transverse myelitis, vacuolar myelopathy, other infections such as HTLV-1 or VZV myelopathy [73]. In addtion, patients with HIV may develop myelopathy from disease states typical of the HIV seronegative population, such as trauma, degenerative disc disease, and neoplasms.

HIV-Associated Acute Transverse Myelitis

Background

HIV-associated acute transverse myelitis (HIV-ATM) generally occurs at the time of seroconversion or in very early stage disease (and thus in patients with normal CD4+ counts), though it is exceedingly rare in patients receiving cART [73]. HIV-infected peripheral monocytes cross the blood-CNS barrier, fusing with microglial cells to form multinucleated giant cells that secrete inflammatory mediators, causing HIV-ATM [73]. Patients present with acute segmental spinal cord inflammation with resulting motor, sensory, and autonomic dysfunction [74].

Diagnosis

The first step in the workup of any progressive myelopathy is an MRI to rule out an indication for neurosurgical intervention from a compressive spinal cord lesion [75]. MRI may be normal in HIV-ATM [73], transverse T2 hyperintensity may

also be present, similar to findings in non-HIV ATM [73, 76]. CSF examination is also essential to rule out other autoimmune and infectious etiologies; studies show HIV RNA, normal to elevated protein, and a lymphocytic pleocytosis [73, 75].

Treatment

The treatment for HIV-ATM consists of cART initiation and corticosteroids [73, 75]. Although data on HIV-ATM are sparse, this regimen has been documented to lead to clinical recovery [74, 75].

HIV Vacuolar Myelopathy

Background

HIV vacuolar myelopathy (VM) is a rare myelopathic manifestation of AIDS, strongly associated with the presence of other AIDS-defining illnesses [77], that has grown less common in cART-treated patients [73]. VM is characterized by myelin vacuolization in both afferent and efferent tracts and invasion of the cord by lipid-filled macrophages [73, 78]. Lesions may ultimately progress to areas of complete demyelination or axon destruction [73]. Patients thus present with a subacute paraparesis that eventually progresses to bladder and bowel dysfunction and gait ataxia [73, 77]. Co findings are the results of corticospinal track, dorsal columns, and autonomic involvement. However, patients are often asymptomatic with one study [77] finding that only 28.6% of autopsy-proven VM cases exhibited symptoms during life.

Diagnosis

Spine MRI of VM patients may be nonspecific and can show cord atrophy, pathologic cord signal change, or no abnormal findings at all [78]. As with HIV-ATM, CSF analysis is critical for ruling out infectious etiologies of myelopathy, though results are generally nonspecific and may only demonstrate elevated protein and a mild lymphocytic pleocytosis [73, 79]. While HIV-ATM manifests as HIV translocates into the spinal canal, there is no association between VM and the presence of HIV RNA in CSF [73, 78]. Somatosensory-evoked potentials may demonstrate delayed conduction times, [73] but this finding is nonspecific [78]. HAND often occurs concurrently with VM, likely due to a shared pathophysiology between HAD and VM. Patients with HAND, especially HAD, often have physical exam findings of pyramidal tract injury that open spares the upper extremities (lower extremity weakness with hyperreflexia at the patellas, spasticity, and an extensor plantar response) as well as autonomic and dorsal column dysfunction (impaired vibration

and proprioception) with superimposed neuropathy from HIV-associated distal symmetric polyneuropathy (stocking distribution lower extremity numbness or parasthesias with depressed Achilles reflexes). Thus, patents presenting with HAD should be evaluated for myelopathic findings and those with findings of VM should be assessed for cognitive decline [78].

Treatment

Unlike the treatment of HIV-ATM, the treatment for VM is incompletely defined [73, 77]. Some patients experience symptomatic improvement with cART initiation, but neither randomized nor prospective data exist [73, 77, 80, 81]. In addition to cART, symptomatic management is also critical. Spasticity can be treated with baclofen, tizanadine, or botulinum toxin and incontinence with bladder training or anticholinergics [82].

Immune Reconstitution Related Syndrome in the Nervous System

Immune Reconstitution Inflammatory Syndrome manifesting in the nervous system, NeuroIRIS, results from immune recovery rather than immune deficiency. Risk factors for developing NeuroIRIS include a low CD4 T-lymphocyte nadir, infection with an opportunistic process at the time of cART initiation, as well as a rapid immune recovery rate, indicated by the speed of either plasma viral load decline or CD4+ T lymphocyte cell count rise [83]. IRIS-related immune activation may propagate ongoing damage even in settings of chronic, low-level infection [84].

CSF Escape

Patients with detectable HIV plasma viral loads are expected to have a CSF viral load 10% of the plasma viral load, whereas patients with undetectable plasma HIV viral loads should also have undetectable CSF viral loads [3]. However, between 4% and 21% of cART treated individuals experience "CSF escape," a rise in CSF viral load from expected baseline despite no change in the plasma HIV viral load [85]. CSF escape may be asymptomatic, neuro-symptomatic, or secondary [3]. Asymptomatic CSF escape, the CSF equivalent of a brief, clinically insignificant rise in plasma HIV viral load, does not impair patients neurologically, and patients do not experience a detectable plasma viral loads or a CSF pleocytosis. The CSF viral loads ranges between 50 and 200 copies/mL. Patients with simplified

antiretroviral regimens who experience asymptomatic escape should undergo cART intensification [3]. Secondary CSF escapte, likely the rarest form, occurs when a secondary non-HIV related infection results in a rise in CSF HIV replication but without neurological symptoms [3].

Neuro-symptomatic patients experience CNS virologic failure despite a median plasma CD4+ T-lymphocyte count of 520 cells/ uL (range 106–660) and present with neurological symptoms, a CSF lymphocytic pleocytosis, elevated CD8+ T-lymphocyte levels, a mean CSF viral load of approximately 1000 copies/mL, and a marked reversal in the typical CSF:plasma viral load ratio. These patients typically have a past history of severe immunocomprimise, with a median CD4+ T-lymphocyte nadir of 55 cells/ uL (range 2–250). Some cases of neuro-symptomatic CSF escape have demonstrated CD8+ T-cell encephalitis, characterized by infiltration of CD8+ T-cells into the perivascular and parenchymal infiltration. This entity is discussed in more detail in the following section [3].

Symptoms reported in patients with neurosymptomatic CSF escape range from a subacutely progressive dementia syndrome with cognitive, behavioral, long-track, and brainstem signs to a more acute meningoencephalitis with seizures, headache, stiff neck, and diminished consciousness [54]. MRI findings vary. MRI in patients with the CSF escape-related acute meningoencephalitis are reported to reveal leptomeningeal thickening and gadolinium enhancement as well as focal T1 gadolinium-enhancing lesions, whereas those with a subacute dementia with motor and brainstem signs demonstrate hyperintense signal on T2-weighted images in the subcortical white matter, the basal ganglia, cerebellum, and brainstem either without or with only subtle gadolinium enhancement. Because these MRI findings are not specific and may overlap with HAND, HIV CSF escapte must remain high on the differential diagnosis, and spinal fluid should be analyzed early on to diagnose and manage these patients appropriately [3].

CSF escape likely results from two interconnected processes. Many cART regimens penetrate the BBB poorly. In addition, because of the relatively protected nature of the CNS, HIV strains within the CNS may develop drug resistance independently of systemic HIV strains. Given these findings, CNS escape can be treated by modifying antiretroviral therapy to account for both the plasma and CSF resistance genotype [3]. To address the issue of poor CNS penetrance, antiretroviral clinical penetration effectiveness (CPE) scores were developed to identify the CNS penetration of antiretroviral drugs based on a drug's specific molecular structure, pharmacokinetics, and pharmacodynamics. However, the clinical utility of CPE score-guided therapy to combact CSF escape has been more difficult to prove. The development of CSF:plasma viral load discordance (viral load [VL] in CSF 0.5 log10 copies HIV-1 RNA greater than plasma VL) was associated with CD4+ T lymphocyte count nadir rather than CPE scores [86]. Thus, focusing on drug penetration alone provides an inadequate account of the reason for and appropriate treatment of CSF escape.

CD8+ T-Cell Encephalitis

CD8+ T lymphocyte encephalitis (CD8+ encephalitis) is a severe, often treatable condition presenting with symptoms of a subacute encephalopathy—progressive cognitive decline with headache and seizures—thought to arise from autoreactive CD8+ cells attacking HIV-infected CD4+ lymphocytes and causing diffuse perivascular and intraparenchymal lymphocytic CD8+ T-cell and CD68+ macrophage infiltration with reactive astrocytosis [71]. CSF analysis reveals a CD8+ lymphocytic pleocytosis with marked CSF:plasma HIV viral load discordance. MRI findings include T2 hyperintensities in the white matter greater than gray matter with multiple gadolinium enhancing perivascular lesions on T1 spin echo that also demonstrate restricted diffusion [87]. Definitive diagnosis is made through brain biopsy, and corticosteroid treatment appears to yield variable results. Rare patients have been treated successfully by changing antiretroviral therapy to account for the CSF genetic resistance pattern without the use of corticosteroids, just like in neuro-symptomatic CSF escape [88].

CD8+ encephalitis occurs both in patients recently started on cART, those on stable cART, and in those with neuro-symptomatic CSF escape. Previously stable cART-treated patients may report either a brief lapse in cART adherence or a recent infection and have a mean duration of cART treatment of 4.2 years with a CD4 cell count > 200/uL during the 6 months prior to onset of symptoms [70]. In a series of 14 CD8+ encephalitis patients, 5 recovered completely, and 5 died within an average of 9 months. Although CD8+ encephalitis is generally steroid responsive but not steroid dependent, at least one patient experienced relapsing disease when steroids were tapered and therefore required a chronic steroid sparing agents to treat the condition definitively [71].

Toxoplasmosis

Background

Cerebral toxoplasmosis, caused by the protozoan *toxoplasma gondii*, is an opportunistic infection that for unclear reasons is more common in AIDS patients than in those with other immune deficiencies. Patients are at increased risk for toxoplasma infection once their CD4+ T-lymphoctyte count falls below 100 cells/microliter. Patients on trimethoprim-sulfamethoxazole (TMP/SMZ) for *pneumocystis jiroveci* prophylaxis are relatively protected from cerebral toxoplasmosis [89, 90]. While the incidence of cerebral toxoplasmosis has decreased with cART, this condition remains a significant cause of morbidity and mortality [89] and is the most common space-occupying lesion in individuals with AIDS [91].

Cats are the only hosts in which toxoplasma can complete its full reproductive cycle [90]. Humans ingest bradyzoite-containing cysts by

ingesting infected undercooked meat, handling infected cat feces, such as when cleaning cat litter, via organ transplantation, or via transplacental transmission [90]. These bradyzoites proliferate inside intestinal epithelial cells, and in the setting of immune compromise, they convert to tachyzoites and cause active infection in neural and muscular tissue. The immune-mediated response to this infection ultimately results in tissue necrosis [89]. While infection in the general population is usually subclinical, up to 30% of AIDS patients not on TMP/SMZ prophylaxis will experience reactivation of this infection.

Presentation

Toxoplasma can infect any neural tissue and can thus present quite variably. Therefore, it should be on the differential diagnosis for any HIV-positive patient who presents with neurologic signs or symptoms [89, 90]. Most commonly, patients will present with one or more intracranial abscesses [89]. Between 67% and 83% of patients will have more than one ring-enhancing mass on MR or CT imaging [90]. These masses are typically hypometabolic on positron emission tomography (PET) [92] and have decreased blood flow on single photon emission computed tomography (SPECT) [93], as opposed to the hypermetabolic lesions of primary CNS lymphoma. Symptoms are initially nonspecific but over weeks progress to focal deficits corresponding to the locations of the toxoplasma abscesses [89]. Toxoplasma has a predilection for the basal ganglia, so patients may present with corresponding movement disorders like hemiparkinsonism or hemiballism [89].

Other CNS manifestations of toxoplasma are much less common. Toxoplasma may rarely cause a diffuse encephalitis, which should be suspected in patients presenting with nonspecific findings like altered mental status and seizure. It may also cause chorioretinitis, which is typically unilateral, with scattered gray or yellow lesions and hemorrhages of various ages [89].

Diagnosis

The mainstay of molecular testing involves Polymerase Chain Reaction (PCR) of CSF [89], but, while this test is nearly 100% specific, it is only 44–65% sensitive [90]. Serum toxoplasma IgG is generally evaluated and should be tested routinely. Ayoade et al. [90] suggest that a presumptive diagnosis of toxoplasmosis can be made in 90% of cases if the following four criteria are met:

1. CD4+ count is <100, and patient is not on either TMP/SMZ or atovaquone prophylaxis
2. Compatible clinical syndrome
3. Seropositivity for toxoplasma IgG
4. Mass lesions present on imaging

Treatment

Pyrimethamine and sulfadiazine taken in combination are the first line treatment for CNS toxoplasmosis [89, 90]. Treatment response is often rapid and dramatic, with 50% of patients showing improvement by day 3 [90]. Patients can be treated empirically unless on routine prophylaxis, with TMP/SMZ or atovaquone, in which case patients likely are infected with a different organism and can be harmed by a delay in appropriate treatment [89]. Because of its invasiveness, brain biopsy should not be an initial test but should be reserved for patients who are strongly suspected of having toxoplasmosis but have negative serology [89] or for patients whose symptoms persist after 10–14 days of appropriate therapy and who may have PCNSL [90].

IRIS is a feared complication of initiating cART during treatment for any opportunistic infection. The rates of IRIS in CNS toxoplasmosis are much lower than those seen in patients with tuberculous or cryptococcal infections, so cART should not be unduly delayed in these patients [90].

Primary CNS Lymphoma

Background

Immunocompromised patients are more than 3000 times more likely than the general population to develop primary CNS lymphoma (PCNSL), an extranodal form of non-Hodgkin's disease [94]. While often confined to the CNS, systemic disease has been found in up to 8% of patients [95]. Though classically considered an AIDS-defining illness, with the advent and spread of cART, most patients with PCNSL are HIVseronegative, immunocompetent individuals [96].

Presentation

Patients with PCNSL develop signs and symptoms over a subacute period—most commonly focal neurologic signs, though approximately a third may have either altered mental status or signs of increased intracranial pressure (ICP) [97]. In contrast to CNS toxoplasmosis, most PCNSL presents as a single, supratentorial, homogenously-enhancing mass lesion [89, 97]. The eyes may be involved in up to a quarter of cases, and spinal cord involvement is rare [97]. The classic "B symptoms" of lymphoma are rare in PCNSL and have been observed in as few as 2% of patients [95].

Diagnosis

The PCNSL Collaborative has published guidelines regarding the clinical, laboratory, imaging, and histologic workup of patients with suspected PCNSL. Clinical examination should be conducted with particular attention to neurologic findings, mental

status and cognition, and lymph nodes. Patients should also have a dilated fundoscopic exam to assess for retinal involvement. In addition to routine labs, serum LDH should be drawn, as levels have demonstrated prognostic value. Contrast-enhanced MRI of the brain should be obtained, and CSF should be sent for analysis [95].

CSF cytology and routine studies are of questionable yield in PCNSL, as cell counts have been found to be normal in more than half of patients with lymphoma with CNS involvement, rendering CSF cytology only 2–32% sensitive for detecting malignant cells. CSF glucose may be low, but this finding has a sensitivity of 27%. CSF protein may be normal in more than half of patients [98]. Given the association of PCNSL with Epstein-Barr Virus, CSF EBV PCR is a more appropriate test. This test has been shown to have 87.5% sensitivity and 100% specificity by DeLuca et al. [99]. Flow cytometry has a reported sensitivity of 80% in identifying lymphoma cells in CSF [98]. Because of the high prevalence of extracranial disease, the PCNSL Collaborative also recommends that every patient undergo a bone marrow biopsy and a contrast-enhanced CT of the chest, abdomen and pelvis. All patients should also undergo stereotaxic brain biopsy to confirm diagnosis [95].

Treatment

In contrast with other intracranial neoplasms, surgical resection of PCNSL yields no clinical benefit and merely increases the rate of complications [95, 97]. Instead, the mainstay of treatment is chemotherapy, administered in an induction and a consolidation phase. Typically, induction is conducted with high-dose methotrexate and rituximab, along with other agents (which vary depending on geography and provider preference), including vincristine and procarbazine [97]. Consolidation is typically conducted with radiation, cytarabine-based regimens, high-dose chemotherapy with stem-cell rescue, or, in the elderly, observation. There is no survival benefit to the addition of intrathecal chemotherapy, the administration of which may increase the risk of neurotoxicity and infectious complications [97]. Despite treatment, relapse can occur in up to 50% of patients, usually within 2 years of diagnosis. No consensus exists regarding treatment of refractory disease, though some investigators have observed high response rates with methotrexate rechallenge [97]. IRIS seems to be of minimal concern when initiating ART in patients being treated for PCNSL; in a series of 51 consecutive patients with AIDS-related PCNSL there were no instances of IRIS [100].

Cytomegalovirus

Background

While up to 90% of the general population has antibodies to cytomegalovirus (CMV), [101] nervous system infection, which is almost universally devastating, typically arises only in patients with profound immune suppression [89, 102] (typically with CD4+ counts <50 cells/microliter) and is therefore rarely seen in cART

treated patients [103]. CMV nervous system infection can present as a retinitis, transverse myelitis, polyradiculitis, meningitis, ventriculitis, or encephalitis [89, 101, 102]. Retinitis is the most common neurological manifestation of CMV infection (up to 25% of cases); patients may complain of either floaters or decreased vision [89]. Patients with CMV meningitis, ventriculitis, or encephalitis may either have a fulminant meningoenecephalitic presentation or present with a rapidly progressive cognitive decline. CMV transverse myelitis presents with an acute myelopathy, and CMV polyradiculitis presents with a rapidly progressive cauda equina syndrome of painful ascending flaccid paraparesis, lower extremity pain and numbness, and sphincter and sexual dysfunction. Pathology shows inflammatory necrosis of the caudal nerve roots.

Diagnosis

Imaging findings in patients with CNS involvement of CMV are highly variable. Typically, patients with brain involvement have scattered foci of periventricular T2 hyperintensity, though lesions may occur anywhere in the CNS and may be either ring-enhancing or nodular [101]. Ependymal and meningeal enhancement may be seen in ventriculitis and meningitis, respectively [101]. Given the relative non-specificity of MRI, CMV CSF PCR should be ordered in patients suspected of having a nervous system CMV infection, since this test has a sensitivity of 95% and specificity of 85% [89, 102–105]. CSF demonstrates a lymphocytic pleocytosis in patients with meningits, encephalitis, or ventriculitis but a polymorphonuclear pleocytosis in patients wth CMV polyradiculaitis. Patients with suspected CMV retinitis should additionally undergo fundoscopy, which typically shows hemorrhage and opacification of the retina [89].

Treatment

CMV infection in HIV patients is treated with intravenous ganciclovir and foscarnet (or prolonged foscarnet if ganciclovir resistance is encountered) [89]. Once patients demonstrate clinical response (as guided by CSF titers), maintenance therapy with oral valganciclovir is initiated [89]. Patients with isolated CMV retinitis can be treated either with oral valganciclovir alone or with intravitreal injection for more centrally-located lesions (though this is controversial) [89]. In spite of available treatments, CNS infection with CMV is still deadly: Silva et al. [103] report at 38% mortality rate in patients receiving antiviral treatment. As with any opportunistic infection, the mainstay of treatment is initiation of ART [89, 105]. Maintenance therapy may be ceased if CD4+ counts remain >100 for 6 months [105].

Varicella Zoster Virus

Background

Varicella zoster virus (VZV) is a herpesvirus with significant neurotropism [106]. After causing primary infection (chicken pox), the virus remains latent in ganglion cells, and re-activation can take on a number of different forms [106, 107]. Perhaps the most commonly-known manifestation is shingles, which can cause significant and chronic neuropathic pain, but the entire neuroaxis and its supporting vasculature are at risk [106, 107]. In HIV patients, VZV infection can cause encephalitis, ventriculitis, myelitis, radiculitis, vasculitis, aneurysm formation, and infarction—both ischemic and hemorrhagic [106, 108–110]. VZV tends to affect the nervous system in patients with low CD4+ T-lymphocyte counts but may still present in those with counts above 200 cells/mm^3 [111]. Presenting symptoms depend on specific manifestations and may include altered mental status, focal neurologic deficits, radiculopathy, or meningismus [107, 111].

Diagnosis

CSF will typically demonstrate a nonspecific lymphocytic pleocytosis with elevated protein [108, 112]. A virologic diagnosis of VZV-associated CNS disease can be made by a positive CSF VZV PCR or the detection of intrathecal anti-VZV IgG [112]. Because VZV DNA levels drop off within 1–3 weeks of acute neurological symptoms, a patients presenting with an acute VZV-related CNS disease such as either meningitis or encephalitis who is evaluated rapidly is more likely to have a positive CSF VZV PCR result; however, for conditions such as VZV vasculopathy, where the delay form VZV reactivation to neurological symptoms may be on the order of months, the PCR is likely to be negative. However, intrathecal anti-VZV antibody production is more likely to be detected [112]. Imaging findings are nonspecific and vary depending on the presentation [111]. Patients with vasculopathy may have segmental arterial stenoses or aneurysms on angiographic studies [107, 109]. MRI may demonstrate meningeal enhancement, focal hyperintensity, or nonspecific white matter changes [111].

Treatment

CNS VZV in HIV patients is treated with IV acyclovir, which has been shown to lead to recovery in most patients [111]. Prompt treatment is essential, as acyclovir administration within 48 hours has been shown to decrease the risk of adverse outcomes [113].

Progressive Multifocal Leukoencephalopathy

Background

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that results from infection of the CNS with the John Cuningham (JC) virus [114–117]. It remains the second most common cause of death in HIV patients [115]. While it has been reported in other immunocompromised populations like patients taking monoclonal antibodies, multiple sclerosis therapies, or those with hematalogic malignancies, PML is most commonly associated with HIV infection [114, 115, 117]. The incidence of PML has declined significantly in the cART era, though it may rarely occur in HIV patients with CD4+ counts above 200 cells/mm^3 or even those stabilized on cART [114, 115, 118]. Patients typically present with focal neurologic deficits, such as hemiparesis, ataxia, cortical visual field disturbances, aphasia, ataxia as well as with seizures or dementia [114, 115, 119]. The propensity of PML to cause focal deficits (80% of cases) may help to differentiate it from other causes of encephalopathy in HIV patients [115].

Diagnosis

The gold standard for diagnosis of PML is brain biopsy, with sensitivity as high as 96% and a specificity of nearly 100%, though the invasiveness and complications of the procedure must be considered [115]. In the cART era, JC virus PCR remains very specific (98%) but may be inadequately sensitive (as low at 76% if viral levels are low due to immune reconstitution and increased JC virus DNA clearance from CSF) [89, 115]. On MRI, PML presents with T1 non- enhancing hypointense, T2 hyperintense white matter lesions involving the subcoritical U-fibers but without mass effect or edema [114, 115]. A diagnosis of PML is considered definite with histopathologic evidence of infection with JC virus protein identification or with a combination of classic MRI findings and positive JC virus PCR [114].

Treatment

There is no specific therapy available for PML, though treatment with cART can lead to clinical stabilization in approximately half of affected patients [15, 115]. Without cART, PML is rapidly and nearly always fatal [114]. However, cART initiation can lead to paradoxical worsening due to IRIS, a significantly augmented inflammatory response driven by CD8+ T cells [114, 115, 119]. The risk of PML IRIS is increased in cART naïve patients and in those with a CD4+ T-lymphocyte count below 50 cells/mm^3 [119]. On MRI, PML IRIS may demonstrate contrast enhancement and vasogenic edema [114]. Shahani et al. [119] report resolution of PML IRIS in a patient treated with CCR5 antagonist maraviroc. Although no specific therapy exists, coritosteroids may be used if the patient's clinical condition warrants.

Cryptococcal Infection

Background

Cryptococcosis, caused by the yeasts *Cryptococcus neoformans* or *Cryptococcus gattii*., is one of the most common opportunistic infections in HIV patients [120, 121]. Despite its association with late-stage disease (i.e. CD4+ counts <50 cells/mm^3), even during the cART era [122] cryptococcosis is still responsible for up to 20% of the infection-related HIV deaths worldwide [89]. Infection is acquired through inhalation of spores from either the soil or bird droppings [89, 122, 123]. Once inside the body, cryptococcus has a predilection for the CNS, explaining why meningitis is the most common presentation of infection, although cryptococcus may less commonly cause pulmonary and disseminated infections [89, 120, 123]. In addition to meningitis, patients may also develop cryptococcomas within the brain parenchyma [120]. Only 25% of patients present with classic meningeal signs, with the rest experiencing subacute, nonspecific symptoms such as headache, fever, altered mental status, and malaise [89, 120]. Patients with cryptococcomas (up to a quarter of patients with cryptococcal infection) [89] may experience seizures and develop focal neurologic deficits [120]. Another hallmark of cryptococcal infection is its ability to substantially raise intracranial pressure, further contributing to both morbidity and mortality [120].

Diagnosis

Cryptococcal CNS infections may be diagnosed in several ways. Cryptococcal antigen detection in CSF has a reported sensitivity of over 90% [89, 122]. CSF India ink staining is reported to have a sensitivity of up to 86% [89, 120]. In resource-poor settings, either latex agglutination assays or lateral flow immunochromatographic assays are used with sensitivities of over 99% [89]. CSF may demonstrate mononuclear pleocytosis and increased protein [89]. A lumbar puncture has the added benefit of relieving intracranial hypertension [120].

MRI is the preferred imaging modality in cryptococcal infection, though results may be normal in up to 8% of patients [89]. In addition to meningitis, MRI may also demonstrate lacunar cortical and subcortical infarcts, dilated Virchow-Robin spaces, or, in the case of cryptococcomas, enhancing mass lesions.

Treatment

Even with appropriate treatment, cryptococcosis remains a devastating disease, with mortality rates for patients receiving appropriate therapy of 20% in North America and up to 70% in Sub-Saharan Africa [124]. Treatment of CNS cryptococcal infections in HIV involves an induction-consolidation-maintenance antifungal therapy model [89, 122, 124]. Typically, induction includes 2 weeks of intravenous

liposomal amphotericin B and flucytosine [89, 122, 124]. The addition of flucytosine has been shown to improve mortality over amphotericin B alone [89, 122]. Longer consolidation phases should be instituted in patients failing to show clinical improvement after 2 weeks [120]. An 8-week consolidation phase with oral fluconazole follows, with maintenance therapy consisting of 12 months of low-dose oral fluconazole [89]. Maintenance therapy may be safely discontinued when patients have CD4+ T-lymphocyte counts above 100 cells/mm^3 and a suppressed viral load [89]. Management of increased intracranial pressure is of special concern, as intracranial hypertension is associated with increased mortality from cryptococcal meningitis [124]. Some studies have demonstrated an improvement in survival with therapeutic lumbar puncture even among patients with normal ICP [89, 120, 124]. Treatment guidelines for managing cryptococcal disease state that if CSF pressure is 25 cm of CSF or greater, and the patient is experiencing symptoms of intracranial hypertension (e.g., headache, altered mental status, nausea, vomiting, diplopia, vision loss) then daily CSF drainage by lumbar puncture is recommended. In patients with severally elevated ICP, pressure should be reduced by 50% of opening pressure. For others with elevated ICP, pressure should be reduced to a normal pressure of below 20 cm of CSF. Daily CSF drainage should be continued until CSF pressure and symptoms have stabilized for at least 2 consecutive days. Furthermore, mannitol, acetazolamide, and corticosteroids should be avoided in managing intracranial hypertension in these patients. Patients receiving treatment whose intracranial hypertension cannot be managed with daily CSF drainage may be candidates for ventriculoperitoneal shunt placement, even if complete sterilization of CSF has not yet been accomplished [125].

Special Considerations: IRIS and Drug Interactions

The predilection of cryptococcus for patients with advanced disease raises questions about the appropriate timing for the initiation of cART because early initiation of ART in patients with cryptococcosis can lead to IRIS. IRIS may result in clinical worsening in patients with an established diagnosis or a new presentation of the disease through an "unmasking" phenomenon [122, 126]. Between 20% and 45% of AIDS patients with cryptococcosis develop IRIS, [89] and cryptococcus IRIS carries the highest morality rate of any other IRIS, approximately 20% [126]. However, an inappropriately long delay in cART initiation can predispose patients to other opportunistic pathogens [120]. Recent recommendations are that cART be initiated between 2 and 10 weeks after the initiation of antifungal therapy [120, 126], although 30% of patients receiving ART within 4 weeks have been found to develop IRIS [126].

Several cART-antifungal drug interactions must be considered when simultaneously treating cryptococcus and HIV. Fluconazole can decrease clearance of both nevirapine and potentiate zidovudine [126]; it can also increase serum concentrations of NNRTIs and protease inhibitors [120]. Flucytosine and zidovudine in combination can lead to life-threatening bone marrow suppression [126]. Thus, caution must be exercised when selecting appropriate antifungal and antiretroviral regimens.

Peripheral Nervous System Disorders in HIV

HIV infected individuals are susceptible to a wide range of peripheral nervous system disorders, manifesting at all stages of HIV disease and often simultaneously with central nervous system disorders. Peripheral neuropathy remains common in HIV seropositive individuals because of a range of factors: the neurotoxicity of some anti-retrovirals, inflammatory conditions associated with HIV-associated immune activation, opportunistic infections, vasculitides, and neoplasms [127]. Co-morbidities such as older age, diabetes mellitus, and advanced immunodeficiency also increase the risk of neuropathy significantly [128]. Diagnosing the correct type of neuropathy, determined by determining the pattern of peripheral nerve involvement clinically and electrophysiologically, is vital to targeting treatment appropriately. Distal sensory polyneuropathy, sensorimotor polyneuropathy, polyradiculopathy, and mononeuropathy are the most common subtypes of peripheral neuropathy among HIV infected individuals.

Distal sensory polyneuropathy (DSP) is the most prevalent HIV-associated sensory neuropathy, and patients present with symptoms of numbness, burning, and paresthesia arising symmetrically in the distal lower extremities and progressing in a distal to proximal distribution. DPS is the end result of Schwann cell and macrophage release of inflammatory factors that induce apoptosis and axonal degeneration of small myelinated and unmyelinated nerve fibers [129]. Electrodiagnostic studies may show either normal or diminished sensory action potentials. Normal results suggest involvement is limited to unmyelinated small nerve fibers whose dysfunction is not appreciated through electrodiagnosis. Nerve biopsy is not required for diagnosis but shows reduced intraepidermal nerve fiber density. Treatment first involves managing co-morbidities, withdrawing neurotoxic agents, followed by administration of medication to treat the pain. Symptoms may improve with withdrawal of neurotoxic ART [128]. Clinical trials of neuropathic pain agents in DSP have generally failed to demonstrate benefit. However, most clinicians use the agents used to treat neuropathic pain in non-HIV associate neuropathies.

DSP has also been attributed to certain nucleoside reverse transcriptase inhibitors (NRTIs) specifically, didanosine, stavudine, and zalcitabine [130]. Metabolic factors such as cyanocobalamin and pyridoxine deficiencies may play a role in selected cases, and HTLV co-infection may also promote development of a mixed axonal and demyelinating distal, symmetric, sensory neuropathy [127].

Sensorimotor polyneuropathy initially presents like DSP; however, the etiologies are distinct and crucial to differentiate clinically. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), also known as Guillain Barre Syndrome (GBS), is an ascending polyradiculoneuropathy progressing over several hours to days and nadiring in intensity by 28 days. Exam findings classically show symmetric weakness with few sensory symptoms. In HIV patients, AIDP can develop in several settings including in the setting of seroconversion. In addition to clinical signs, electrodiagnostic findings show delayed or absent F-waves and prolonged distal latencies with slowed conduction velocities, the same criteria as for seronegative

AIDP patients. Cerebrospinal fluid (CSF) analysis reveals elevated protein but in contrast to those without HIV, HIV-infected individuals may have a CSF lymphocytic pleocytosis of up to 50 lymphocytes/uL. If symptoms either progress for greater than 8 weeks or relapse, the patient is diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP presents with symmetric, four-limb, proximal and distal motor involvement. Although sensory symptoms are not typically as prominent as the motor symptoms, sensory symptoms are more pronounced in CIDP than in AIDP. AIDP and CIDP both produce diminished or absent reflexes. In addition to flaccid weakness, patients may report dyesthesias even in the absence of significant sensory loss. Among HIV-infected patients, CIDP is more common than AIDP and is seen in both early HIV infection and advanced disease [127]. Just as with HIV seronegative patients, HIV infected patients with both AIDP and CIDP should be treated with either intravenous immunoglobulin (IVIG) or plasmapheresis [131].

Another cause of sensorimotor polyneuropathy among HIV patients is diffuse infiltrative lymphocytosis syndrome (DILS). Pain is the hallmark feature of DILS-related sensorimotor polyneuropathy. Although DILS was originally described in the setting of Sjogren syndrome, that condition is not a requisite. Patients will have hyperlymphocytosis with CD8 > 1000 cells/uL with typically no change in CD4 count. Electrodiagnostic studies show axonal involvement, and nerve biopsy demonstrates perivascular CD8+ T-cell infiltration in the neural fiber layers without necrosis [132]. Although most DILS patients develop a distal, length dependent, symmetric polyneuropathy, one third do develop focal, progressive findings [133]. Treatment involves both prednisone and cART in the treatment naïve.

Vasculitic neuropathy also presents with pain, but it typically arises as a mononeuritis multiplex that may worsen to mimic a symmetric polyneuropathy. Nerve biopsy is required to establish the diagnosis, and treatment is with corticosteroids, other immunotherapies, and cART in the treatment naïve. Lumbosacral polyradiculitis in both HIV seropositive and seronegative patients may arise from reactivation of the herpes simplex virus type 2 (HSV-2) and represents an acute ascending, necrotizing vasculitic neuropathy.

References

1. Gottlieb GJ, Ragaz A, Vogel JV, Friedman-Kien A, Rywlin AM, Weiner EA, et al. A preliminary communication on extensively disseminated Kaposi's sarcoma in young homosexual men. Am J Dermatopathol. 1981;3(2):111–4.
2. Desplats P, Dumaop W, Smith D, Adame A, Everall I, Letendre S, et al. Molecular and pathologic insights from latent HIV-1 infection in the human brain. Neurology. 2013;80(15):1415–23.
3. Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal fluid HIV escape from antiretroviral therapy. Curr HIV/AIDS Rep. 2015;12(2):280–8.
4. Ozdener H. Molecular mechanisms of HIV-1 associated neurodegeneration. J Biosci. 2005;30(3):391–405.

5. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. Nat Rev Immunol. 2005;5(1):69–81.
6. Masliah E, Ge N, Mucke L. Pathogenesis of HIV-1 associated neurodegeneration. Crit Rev Neurobiol. 1996;10(1):57–67.
7. Kass JS, Parker AS, Samudralwar RD. Infectious diseases of the central nervous system. Textbook of neuropsychiatry and clinical neurosciences. 6th ed. Washington, DC: American Psychiatric Association Publishing; 2018. p. 303–32.
8. Luo X, He JJ. Cell-cell contact viral transfer contributes to HIV infection and persistence in astrocytes. J Neurovirol. 2015;21(1):66–80.
9. Brew B, Chan P. Update on HIV dementia and HIV-associated neurocognitive disorders. Curr Neurol Neurosci Rep. 2014;14(8):1–7.
10. Dahl V, Peterson J, Fuchs D, Gisslen M, Palmer S, Price RW. Low levels of HIV-1 RNA detected in the cerebrospinal fluid after up to 10 years of suppressive therapy are associated with local immune activation. AIDS. 2014;28(15):2251–8.
11. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex: II. Neuropathology. Ann Neurol. 1986;19(6):525–35.
12. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Ann Neurol. 1986;19(6):517–24.
13. Beresford TP, Blow FC, Hall RC. AIDS encephalitis mimicking alcohol dementia and depression. Biol Psychiatry. 1986;21(4):394–7.
14. Bissel SJ, Wiley CA. Human immunodeficiency virus infection of the brain: pitfalls in evaluating infected/affected cell populations. Brain Pathol. 2004;14(1):97–108.
15. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69(18):1789–99.
16. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Gill H, Attali M, Asher I. HIV-associated neurocognitive disorders (HAND). Isr Med Assoc J. 2015;17(1):54–9.
17. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol. 2010;67(6):699–714.
18. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011;17(1):3–16.
19. Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, et al. Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. Neurology. 2016;86(4):334–40.
20. Heaton RK, Franklin DR, Deutsch R, Letendre S, Ellis RJ, Casaletto K, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. Clin Infect Dis. 2015;60(3):473–80.
21. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. Neurology. 2010;75(23):2087–96.
22. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 2011;25(14):1747–51.
23. Becker JT, Kingsley L, Mullen J, Cohen B, Martin E, Miller EN, et al. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology. 2009;73(16):1292–9.
24. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, Letendre SL, Ellis RJ, Heaton RK, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology. 2012;78(7):485–92.
25. Sattler FR, He J, Letendre S, Wilson C, Sanders C, Heaton R, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr. 2015;68(3):281–8.

26. Small RC, Brew BJ. HIV-associated neuro cognitive disorder. In: Brew BJ, editor. Handbook of clinical neurology, vol. 152; 2018. p. 75–98.
27. Eggers C, Arendt G, Hahn K, Husstedt IW, Maschke M, Neuen-Jacob E, et al. HIV-1-associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis, and treatment. J Neurol. 2017;264(8):1715–27.
28. Cysique LA, Maruff P, Brew BJ. The neuropsychological profile of symptomatic AIDS and ADC patients in the pre-HAART era: a meta-analysis. J Int Neuropsychol Soc. 2006;12(3):368–82.
29. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013;13(11):976–86.
30. Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, et al. The international HIV dementia scale: a new rapid screening test for HIV dementia. AIDS. 2005;19(13):1367–74.
31. Overton ET, Azad TD, Parker N, Demarco Shaw D, Frain J, Spitz T, et al. The Alzheimer's disease-8 and Montreal Cognitive Assessment as screening tools for neurocognitive impairment in HIV-infected persons. J Neurovirol. 2013;19(1):109–16.
32. Steinbrink F, Evers S, Buerke B, Young P, Arendt G, Koutsilieri E, et al. Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. Eur J Neurol. 2013;20(3):420–8.
33. Kuper M, Rabe K, Esser S, Gizewski ER, Husstedt IW, Maschke M, et al. Structural gray and white matter changes in patients with HIV. J Neurol. 2011;258(6):1066–75.
34. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology. 2011;76(5):444–50.
35. McMurtray A, Nakamoto B, Shikuma C, Valcour V. Small-vessel vascular disease in human immunodeficiency virus infection: the Hawaii aging with HIV cohort study. Cerebrovasc Dis. 2007;24(2–3):236–41.
36. Archibald SL, Masliah E, Fennema-Notestine C, Marcotte TD, Ellis RJ, McCutchan JA, et al. Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss. Arch Neurol. 2004;61(3):369–76.
37. Pfefferbaum A, Rosenbloom MJ, Sassoon SA, Kemper CA, Deresinski S, Rohlfing T, et al. Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. Biol Psychiatry. 2012;72(5):361–70.
38. Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J Neurovirol. 2004;10(6):350–7.
39. Hall M, Whaley R, Robertson K, Hamby S, Wilkins J, Hall C. The correlation between neuropsychological and neuroanatomic changes over time in asymptomatic and symptomatic HIV-1-infected individuals. Neurology. 1996;46(6):1697–702.
40. Jakobsen J, Gyldensted C, Brun B, Bruhn P, Helweg-Larsen S, Arlien-Søborg P. Cerebral ventricular enlargement relates to neuropsychological measures in unselected AIDS patients. Acta Neurol Scand. 1989;79(1):59–62.
41. Paul R, Cohen R, Navia B, Tashima K. Relationships between cognition and structural neuroimaging findings in adults with human immunodeficiency virus type-1. Neurosci Biobehav Rev. 2002;26(3):353–9.
42. Thompson PM, Dutton RA, Hayashi KM, Lu A, Lee SE, Lee JY, et al. 3D mapping of ventricular and corpus callosum abnormalities in HIV/AIDS. NeuroImage. 2006;31(1):12–23.
43. Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. Proc Natl Acad Sci U S A. 2005;102(43):15647–52.
44. Becker JT, Sanders J, Madsen SK, Ragin A, Kingsley L, Maruca V, et al. Subcortical brain atrophy persists even in HAART-regulated HIV disease. Brain Imaging Behav. 2011;5(2):77–85.
45. Ragin AB, Du H, Ochs R, Wu Y, Sammet CL, Shoukry A, et al. Structural brain alterations can be detected early in HIV infection. Neurology. 2012;79(24):2328–34.

46. Chang L, Shukla DK. Chapter 18: Imaging studies of the HIV-infected brain. Handb Clin Neurol. 2018;152:229–64.
47. Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. Semin Neurol. 2013;33(4):386–416.
48. Ernst T, Chang L, Jovicich J, Ames N, Arnold S. Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. Neurology. 2002;59(9):1343–9.
49. Thomas JB, Brier MR, Snyder AZ, Vaida FF, Ances BM. Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. Neurology. 2013;80(13):1186–93.
50. Davison JM, Subramaniam RM, Surasi DS, Cooley T, Mercier G, Peller PJ. FDG PET/CT in patients with HIV. AJR Am J Roentgenol. 2011;197(2):284–94.
51. Valcour VG, Shiramizu BT, Sithinamsuwan P, Nidhinandana S, Ratto-Kim S, Ananworanich J, et al. HIV DNA and cognition in a Thai longitudinal HAART initiation cohort: the SEARCH 001 Cohort Study. Neurology. 2009;72(11):992–8.
52. Lyons JL, Uno H, Ancuta P, Kamat A, Moore DJ, Singer EJ, et al. Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. J Acquir Immune Defic Syndr. 2011;57(5):371–9.
53. Price RW, Epstein LG, Becker JT, Cinque P, Gisslen M, Pulliam L, et al. Biomarkers of HIV-1 CNS infection and injury. Neurology. 2007;69(18):1781–8.
54. Peluso MJ, Ferretti F, Peterson J, Lee E, Fuchs D, Boschini A, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. AIDS. 2012;26(14):1765–74.
55. Grant I, Franklin DR Jr, Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014;82(23):2055–62.
56. Crum-Cianflone NF, Moore DJ, Letendre S, Poehlman Roediger M, Eberly L, Weintrob A, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. Neurology. 2013;80(4):371–9.
57. Cole MA, Margolick JB, Cox C, Li X, Selnes OA, Martin EM, et al. Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology. 2007;69(24):2213–20.
58. Cysique LA, Vaida F, Letendre S, Gibson S, Cherner M, Woods SP, et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. Neurology. 2009;73(5):342–8.
59. Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE. Influence of HAART on HIV-related CNS disease and neuroinflammation. J Neuropathol Exp Neurol. 2005;64(6):529–36.
60. Kumar AM, Borodowsky I, Fernandez B, Gonzalez L, Kumar M. Human immunodeficiency virus type 1 RNA levels in different regions of human brain: quantification using real-time reverse transcriptase-polymerase chain reaction. J Neurovirol. 2007;13(3):210–24.
61. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol. 2008;65(1):65–70.
62. Smurzynski M, Wu K, Letendre S, Robertson K, Bosch RJ, Clifford DB, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. AIDS. 2011;25(3):357–65.
63. Caniglia EC, Cain LE, Justice A, Tate J, Logan R, Sabin C, et al. Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. Neurology. 2014;83(2):134–41.
64. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. Lancet Neurol. 2005;4(9):543–55.
65. Sacktor N, Miyahara S, Deng L, Evans S, Schifitto G, Cohen BA, et al. Minocycline treatment for HIV-associated cognitive impairment: results from a randomized trial. Neurology. 2011;77(12):1135–42.

66. Simioni S, Cavassini M, Annoni JM, Metral M, Iglesias K, Rimbault Abraham A, et al. Rivastigmine for HIV-associated neurocognitive disorders: a randomized crossover pilot study. Neurology. 2013;80(6):553–60.
67. Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, et al. Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. AIDS. 2007;21(14):1877–86.
68. Schifitto G, Yiannoutsos CT, Simpson DM, Marra CM, Singer EJ, Kolson DL, et al. A placebo-controlled study of memantine for the treatment of human immunodeficiency virus-associated sensory neuropathy. J Neurovirol. 2006;12(4):328–31.
69. Schifitto G, Zhang J, Evans SR, Sacktor N, Simpson D, Millar LL, et al. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. Neurology. 2007;69(13):1314–21.
70. Lescure FX, Moulignier A, Savatovsky J, Amiel C, Carcelain G, Molina JM, et al. CD8 encephalitis in HIV-infected patients receiving cART: a treatable entity. Clin Infect Dis. 2013;57(1):101–8.
71. Salam S, Mihalova T, Ustianowski A, et al. Relapsing CD8+ encephalitis—looking for a solution Case Reports 2016;2016:bcr2016214961. pp 1–5.
72. Zarkali A, Gorgoraptis N, Miller R, John L, Merve A, Thust S, et al. CD8+ encephalitis: a severe but treatable HIV-related acute encephalopathy. Pract Neurol. 2017;17(1):42–6.
73. Levin SN, Lyons JL. HIV and spinal cord disease. Handb Clin Neurol. 2018;152:213–27.
74. Hamada Y, Watanabe K, Aoki T, Arai N, Honda M, Kikuchi Y, et al. Primary HIV infection with acute transverse myelitis. Intern Med. 2011;50(15):1615–7.
75. Andrade P, Figueiredo C, Carvalho C, Santos L, Sarmento A. Transverse myelitis and acute HIV infection: a case report. BMC Infect Dis. 2014;14:149.
76. Goh C, Desmond PM, Phal PM. MRI in transverse myelitis. J Magn Reson Imaging. 2014;40(6):1267–79.
77. Dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV-1-associated vacuolar myelopathy: an autopsy-based case-control study. Neurology. 1994;44(11):2159–64.
78. Ernst F, Klausner F, Kleindienst W, Bartsch H, Taylor N, Trinka E. Diagnostic challenges in vacuolar myelopathy: a didactic case report. Spinal Cord Ser Cases. 2016;2:16020.
79. Anneken K, Fischera M, Evers S, Kloska S, Husstedt IW. Recurrent vacuolar myelopathy in HIV infection. J Infect. 2006;52(6):e181–3.
80. Bizaare M, Dawood H, Moodley A. Vacuolar myelopathy: a case report of functional, clinical, and radiological improvement after highly active antiretroviral therapy. Int J Infect Dis. 2008;12(4):442–4.
81. Fernández-Fernández FJ, de la Fuente-Aguado J, Ocampo-Hermida A, Iglesias-Castañón A. Remission of HIV-associated myelopathy after highly active antiretroviral therapy. J Postgrad Med. 2004;50(3):195–6.
82. Di Rocco A. HIV myelopathy. In: Handbook of clinical neurology. HIV/AIDS and the nervous system, vol. 85. Amsterdam: Elsevier; 2007.
83. McCombe JA, Auer RN, Maingat FG, Houston S, Gill MJ, Power C. Neurologic immune reconstitution inflammatory syndrome in HIV/AIDS: outcome and epidemiology. Neurology. 2009;72(9):835–41.
84. Johnson T, Nath A. Neurological complications of immune reconstitution in HIV-infected populations. Ann N Y Acad Sci. 2010;1184:106–20.
85. Pérez Valero I, González-Baeza A, Montes Ramírez ML. Central nervous system penetration and effectiveness of darunavir/ritonavir monotherapy. AIDS Rev. 2014;16(2):101–8.
86. Bhatia NS, Chow FC. Neurologic complications in treated HIV-1 infection. Curr Neurol Neurosci Rep. 2016;16(7):62.
87. Kugathasan R, Collier DA, Haddow LJ, El Bouzidi K, Edwards SG, Cartledge JD, et al. Diffuse white matter signal abnormalities on magnetic resonance imaging are associated with human immunodeficiency virus type 1 viral escape in the central nervous system among patients with neurological symptoms. Clin Infect Dis. 2017;64(8):1059–65.

88. Sekiya H, Kawamoto M, Togo M, Yoshimura H, Imai Y, Kohara N. Response regarding "HIV encephalopathy due to drug resistance despite 2-year suppression of HIV viremia by cART". Rinsho Shinkeigaku. 2015;55(6):437.
89. Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. Nat Rev Neurol. 2016;12(11):662–74.
90. Ayoade F, Joel Chandransean AS. HIV-1 associated opportunistic infections, toxoplasmosis. StatPearls [Internet]. 2019.
91. Berger JR. Mass lesions of the brain in AIDS: the dilemmas of distinguishing toxoplasmosis from primary CNS lymphoma. AJNR Am J Neuroradiol. 2003;24(4):554–5.
92. Pierce MA, Johnson MD, Maciunas RJ, Murray MJ, Allen GS, Harbison MA, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. Ann Intern Med. 1995;123(8):594–8.
93. Hussain FS, Hussain NS. Clinical utility of Thallium-201 single photon emission computed tomography and cerebrospinal fluid Epstein-Barr Virus detection using polymerase chain reaction in the diagnosis of AIDS-related primary central nervous system lymphoma. Cureus. 2016;8(5):e606.
94. Jones CJ, Naina HV, Shen Y-MP. Treatment of primary central nervous system lymphoma in the HIV-positive patient: should we be doing more? Blood. 2013;122(21):1.
95. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005;23(22):5034–43.
96. Sierra del Rio M, Rousseau A, Soussain C, Ricard D, Hoang-Xuan K. Primary CNS lymphoma in immunocompetent patients. Oncologist. 2009;14(5):526–39.
97. Grommes C, DeAngelis LM. Primary CNS lymphoma. J Clin Oncol. 2017;35(21):2410–8.
98. Scott BJ, Douglas VC, Tihan T, Rubenstein JL, Josephson SA. A systematic approach to the diagnosis of suspected central nervous system lymphoma. JAMA Neurol. 2013;70(3):311–9.
99. De Luca A, Antinori A, Cingolani A, Larocca LM, Linzalone A, Ammassari A, et al. Evaluation of cerebrospinal fluid EBV-DNA and IL-10 as markers for in vivo diagnosis of AIDS-related primary central nervous system lymphoma. Br J Haematol. 1995;90(4):844–9.
100. Moulignier A, Lamirel C, Picard H, Lebrette MG, Amiel C, Hamidi M, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. Neurology. 2017;89(8):796–804.
101. Offiah CE, Turnbull IW. The imaging appearances of intracranial CNS infections in adult HIV and AIDS patients. Clin Radiol. 2006;61(5):393–401.
102. Maschke M, Kastrup O, Diener HC. CNS manifestations of cytomegalovirus infections: diagnosis and treatment. CNS Drugs. 2002;16(5):303–15.
103. Silva CA, Oliveira AC, Vilas-Boas L, Fink MC, Pannuti CS, Vidal JE. Neurologic cytomegalovirus complications in patients with AIDS: retrospective review of 13 cases and review of the literature. Rev Inst Med Trop Sao Paulo. 2010;52(6):305–10.
104. Dodt KK, Jacobsen PH, Hofmann B, Meyer C, Kolmos HJ, Skinhøj P, et al. Development of cytomegalovirus (CMV) disease may be predicted in HIV-infected patients by CMV polymerase chain reaction and the antigenemia test. AIDS. 1997;11(3):F21–8.
105. Griffiths P. Cytomegalovirus infection of the central nervous system. Herpes. 2004;11(Suppl 2):95A–104A.
106. Nagel MA, Gilden D. Developments in varicella zoster virus vasculopathy. Curr Neurol Neurosci Rep. 2016;16(2):12.
107. De Broucker T, Mailles A, Chabrier S, Morand P, Stahl J-P, group scai. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. Eur J Clin Microbiol Infect Dis. 2012;18(8):12.
108. Picard O, Brunereau L, Pelosse B, Kerob D, Cabane J, Imbert JC. Cerebral infarction associated with vasculitis due to varicella zoster virus in patients infected with the human immunodeficiency virus. Biomed Pharmacother. 1997;51(10):449–54.

109. Gray F, Mohr M, Rozenberg F, Belec L, Lescs MC, Dournon E, et al. Varicella-zoster virus encephalitis in acquired immunodeficiency syndrome: report of four cases. Neuropathol Appl Neurobiol. 1992;18(5):502–14.
110. Chrétien F, Gray F, Lescs MC, Geny C, Dubreuil-Lemaire ML, Ricolfi F, et al. Acute varicella-zoster virus ventriculitis and meningo-myelo-radiculitis in acquired immunodeficiency syndrome. Acta Neuropathol. 1993;86(6):659–65.
111. Brown M, Scarborough M, Brink N, Manji H, Miller R. Varicella zoster virus-associated neurological disease in HIV-infected patients. Int J STD AIDS. 2001;12(2):79–83.
112. Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system – prognosis, diagnostics and treatment. J Infect. 2015;71(3):281–93.
113. Kaewpoowat Q, Salazar L, Aguilera E, Wootton SH, Hasbun R. Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes. Infection. 2016;44(3):337–45.
114. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis. 2009;9(10):625–36.
115. Augusto L, Neves N, Reis C, Abreu C, Sarmento A. Clinical and radiological characterization of progressive multifocal leukoencephalopathy in HIV-infected patients: a retrospective analysis and review of the literature. Acta Medica Port. 2015;28(3):286–96.
116. Loignon M, Toma E. Treatment options for progressive multifocal leukoencephalopathy in HIV-infected persons: current status and future directions. Expert Rev Anti-Infect Ther. 2016;14(2):177–91.
117. White MK, Sariyer IK, Gordon J, Delbue S, Pietropaolo V, Berger JR, et al. Diagnostic assays for polyomavirus JC and progressive multifocal leukoencephalopathy. Rev Med Virol. 2016;26(2):102–14.
118. Alstadhaug KB, Fykse Halstensen R, Odeh F. Progressive multifocal leukoencephalopathy in a patient with systemic mastocytosis treated with cladribine. J Clin Virol. 2017;88:17–20.
119. Shahani L, Shah M, Tavakoli-Tabasi S. Immune reconstitution inflammatory syndrome in a patient with progressive multifocal leukoencephalopathy. BMJ Case Rep. 2015;2015: pp 1–3.
120. Srichatrapimuk S, Sungkanuparph S. Integrated therapy for HIV and cryptococcosis. AIDS Res Ther. 2016;13(1):42.
121. Taramasso L, Tatarelli P, Di Biagio A. Bloodstream infections in HIV-infected patients. Virulence. 2016;7(3):320–8.
122. Warkentien T, Crum-Cianflone NF. An update on cryptococcus among HIV-infected patients. Int J STD AIDS. 2010;21(10):679–84.
123. Wang RJ, Miller RF, Huang L. Approach to fungal infections in human immunodeficiency virus-infected individuals: pneumocystis and beyond. Clin Chest Med. 2017;38(3):465–77.
124. Mourad A, Perfect JR. Present and future therapy of cryptococcus infections. J Fungi (Basel). 2018;4(3):79.
125. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50(3):291–322.
126. Antinori S. New insights into HIV/AIDS-associated cryptococcosis. ISRN AIDS. 2013;2013:471363.
127. Centner CM, Bateman KJ, Heckmann JM. Manifestations of HIV infection in the peripheral nervous system. Lancet Neurol. 2013;12(3):295–309.
128. Evans SR, Ellis RJ, Chen H, Yeh TM, Lee AJ, Schifitto G, et al. Peripheral neuropathy in HIV: prevalence and risk factors. AIDS. 2011;25(7):919–28.
129. Benevides MLAC, Filho SB, Debona R, Bergamaschi ENC, Nunes JC. Prevalence of peripheral neuropathy and associated factors in HIV-infected patients. J Neurol Sci. 2017;375:316–20.
130. Ellis RJ, Rosario D, Clifford DB, McArthur JC, Simpson D, Alexander T, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated

sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER study. Arch Neurol. 2010;67(5):552–8.
131. Schleicher GK, Black A, Mochan A, Richards GA. Effect of human immunodeficiency virus on intensive care unit outcome of patients with Guillain-Barré syndrome. Crit Care Med. 2003;31(6):1848–50.
132. Moulignier A, Authier FJ, Baudrimont M, Pialoux G, Belec L, Polivka M, et al. Peripheral neuropathy in human immunodeficiency virus-infected patients with the diffuse infiltrative lymphocytosis syndrome. Ann Neurol. 1997;41(4):438–45.
133. Brew BJ. The peripheral nerve complications of human immunodeficiency virus (HIV) infection. Muscle Nerve. 2003;28(5):542–52.

Part IV
Fungal and Mycobacterial Infections

Chapter 10
Fungal Infections of the Brain

Maria Fernanda Gonzalez-Lara and Luis Ostrosky-Zeichner

Fungi are ubiquitous organisms living on soil, water, plant debris and sites of vegetable decay. Some, like *Candida,* are commensals on human mucous membranes. Each year, over 150 million people suffer from serious fungal infections and over 1.6 million die, a rate comparable with tuberculosis. High morbidity and elevated cost contribute to the burden of serious fungal diseases. The incidence of Invasive fungal infections (IFI) has increased with the expansion of at-risk population: the HIV epidemic, the improvement of immunosuppressive and cancer chemotherapy, patients undergoing transplant, major surgery, increasingly older populations and premature neonates. Improved diagnostic methods and increased awareness also contribute [1–4]. An estimated 1.5–5 million species of fungi are found worldwide, approximately 300 cause human disease and 15% can cause central nervous system (CNS) infection. The most common fungal CNS infection is cryptococcal meningoencephalitis. The frequency of CNS involvement in common mycoses is described in Table 10.1.

Penetration of fungi to the CNS may occur endogenously via hematogenous seeding of a distant infection, by contiguous spread of orbital and paranasal sinus infection, or by exogenous inoculation through trauma or invasive procedures [5]. Fungi access the CNS directly crossing the blood brain barrier (BBB). Yeasts are

M. F. Gonzalez-Lara (✉)
Department of Infectious Diseases, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Mexico City, Mexico
e-mail: fernanda.gonzalezl@incmnsz.mx

L. Ostrosky-Zeichner
Department of Infectious Diseases, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Mexico City, Mexico

McGovern Medical School, Division of Infectious Diseases, University of Texas, Houston Health Science Center, Memorial Hermann Hospital, Texas Medical Center, Houston, TX, USA
e-mail: luis.ostrosky-zeichner@uth.tmc.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_10

Table 10.1 Prevalence of CNS involvement in invasive fungal infections

Mycosis	CNS involvement (%)
Disseminated cryptococcosis	67–84
Invasive candidiasis	3–64
Blastomycosis	40
Disseminated coccidioidomycosis	25
Disseminated histoplasmosis	5–20
Mucormycosis	12
Invasive aspergillosis	4–6

Data from Goralska et al. [5]

mechanically trapped in the vasculature, bind endothelial cells through specific proteins and transmigrate through trans or paracellular mechanisms. Yeasts can also enter indirectly after infecting phagocytes in the periphery and directing them to the CNS. After CNS infection, the microglia, astrocytes and endothelial cells act as antigen presenting cells, express complement receptors and produce cytokines, chemokines and nitric oxide. Unregulated inflammation can lead to severe tissue damage. Mold infections (*Aspergillus* and the Mucorales) spread from contiguous sites such as the cribriform plate, periorbital and paranasal sinuses. Due to their angioinvasive nature, they cause brain abscesses, encephalitis and vasculitis resulting in neurological deficits, seizures and altered mental status. Any situation that enhances the BBB permeability promotes fungal CNS invasion, such as reduced immunity (reduced circulating T lymphocytes), trauma, surgery, activation of the microglia, and cytokine production [5–8]. Fungal CNS infections present as distinct syndromes: space occupying lesions (abscess or granulomas), hydrocephalus, meningoencephalitis, stroke and spinal infection [2]. Each syndrome and the most frequent etiologic agents are described in Table 10.2.

Yeast Infection

Cryptococcal Meningoencephalitis

One million cases of cryptococcosis are diagnosed each year, of which 650,000 die. Classical taxonomy recognized more than 30 species of *Cryptococcus,* of which the *C. neoformans/ C. gattii complex* is the most commonly known to cause human disease. *C. neoformans variety grubii* and variety *neoformans* typically causing disease in immunocompromised patients and *C. gattii*, in immunocompetent patients [9]. To date, it is known that *C. gattii* causes infection in patients with underlying lung disease, steroid use, smokers and subclinical immune defects (Anti-granulocyte-macrophage colony stimulating factor autoantibodies and subclinical antibody deficiencies) [10–11] *C. neoformans* var. *grubii* is found worldwide*, C. neoformans* var. *neoformans* is primarily found in Europe and C. *gattii* historically restricted to tropical and subtropical regions has been increasingly identified in North America

Table 10.2 CNS fungal infection syndromes

Syndrome	Clinical manifestations	Fungi
Meningitis, meningoencephalitis	Headache, nausea, stiff neck, fever, personality changes, seizures, cranial nerve palsies, hydrocephalus	*Cryptococcus, Coccidioides, Blastomyces, Paracoccidioides, Sporotrix, Histoplasma, Candida*
Space occupying lesions	Granulomas, abscesses, cysts	*Candida, Aspergillus, Cryptococcus, Cladosporium*, Mucormycosis
Rhino-orbito-cerebral syndromes	Nasal discharge or blockage, periorbital pain, recurrent headache, proptosis, impaired ocular movements, visual loss	Mucormycosis, *Aspergillus, Cladosporium*
Acute cerebrovascular events	Ischemic or hemorrhagic Paranasal sinusitis leads to angioinvasion and thrombosis Cardioembolism	*Aspergillus*, Mucorales, *Candida* (cardioembolism), *Coccidioides, Histoplasma, Cryptococcus*
Spinal infection	Destructive lesions of vertebrae upper thoracic level most common Intradural affection as part of leptomeningitis Myelopathy	Common: Coccidioidomycosis, blastomycosis, aspergillosis by proximity of lung infection Uncommon: *Candida, Aspergillus* by hematogenous seeding

(Pacific Northwest, British Columbia and Vancouver Island) and Australia [10–11]. A new classification based on phylogenetic and genotyping studies has been proposed. As a result, the *C. neoformans / C. gatti species complex* was divided into three varieties, five serotypes and eight molecular subtypes: *C. neoformans* var. *grubii* with three genotypes: VNI, VNII and VNB, *C. neoformans* var. *neoformans* (genotype VNIV) and five cryptic species: *C. gattii, C. deuterogattii, C. tetragattii,* C. *decagattii and C. bacillisporus* (genotypes VGI to IV) [9].

The most common risk factor for cryptococcosis is advanced HIV infection (CD4 cell counts < 100 cells/μL), followed by solid organ transplant (SOT) related immunosuppression [12]. Patients who receive steroids, cytotoxic chemotherapy, TNF-α antagonists are also susceptible. In some centers 17–22% of cases occur among otherwise immunocompetent individuals [13].

Symptoms develop over several weeks, although an abrupt onset of headache can occur. Fever, cranial palsies, altered mental status, lethargy and memory loss are common. Obstructive hydrocephalus due to elevated yeast burden obstructing CSF outflow, leads to intracranial hypertension (ICH) [12]. Non-HIV non-transplant patients have a similar presentation, but diagnosis is usually delayed [13]. Other manifestations accompanying disseminated disease are pulmonary infiltrates, cryptococcemia, cutaneous, prostatic and osteolytic lesions.

The occurrence of an immune reconstitution inflammatory syndrome (IRIS) is common in the setting of cryptococcal meningitis (CM). It is defined as the onset of new or worsening signs and symptoms (including neuroimaging findings) of cryptococcosis after a rapid reversal of immune deficiency [14]. In HIV positive patients without a previous diagnosis of CM, unmasking IRIS occurs in a median time of

9 weeks after ART in 33% of patients with subclinical cryptococcosis and 0.2–1.2% of those with latent infection. Paradoxical IRIS occurs in 8–49% with known cryptococcal disease, with a median of 1–10 months onset after ART. IRIS is more frequent when baseline CD4 cell counts <50 cells/μL increase substantially along with a decrease in viral load of >1 $\log_{10}$ copies/mL. IRIS occurs in 5–15% of SOT patients, typically after 4–6 weeks. It is associated with the reduction of immunosuppression and can lead to renal graft loss [14–17]. The pathogenesis involves calcineurin inhibitors suppressing Th1 and Th17 cells, while increasing a Th2 response and Treg lymphocytes function to promote graft tolerance. Antifungal treatment upregulates the Th1 responses and the transcription of inflammatory chemokines. The reversal of anti-inflammatory to proinflammatory response occurs [16]. Immunocompetent hosts can also experience IRIS. Antifungal therapy reverses the Th2 to a Th1 response, leading to an exuberant host response against residual sites of disease [17].

Definitive diagnosis is made by isolating *Cryptococcus* from the CSF or direct yeast detection. India ink staining has a sensitivity of 30–50% in non-AIDS patients, and 80% in AIDS related disease. CSF culture is positive in 90% of patients with CM after 48–72 h incubation, appearing as white to cream colonies. Capsular antigen detection (CrAg) by latex agglutination provides sensitivity and specificity of 93% and 100%, respectively. A lateral flow assay is also available with sensitivity and specificity greater than 98% in CSF. CrAg does not distinguish between *C. neoformans* and *C. gattii*, the use of Canavanine-glycine-bromthymol blue agar can differentiate *C. gatti*, but it's not routinely used [18].

Computed tomography (CT) and magnetic resonance imaging (MRI) are nonspecific, ranging from normal findings to hydrocephalus, cerebral edema, leptomeningeal enhancement, infarction, intraventricular or intraparenchymal cryptococcomas. Dilated perivascular spaces can dilate to form a mucoid collection called gelatinous pseudocyst. These lesions are commonly found in the basal ganglia and thalamus and can be visualized as hypodensities on CT. MRI shows diffusion restriction, hypodensity on T1 and hyperintensity on T2. Contrast enhancement may be absent. Larger lesions, cryptococcomas, are hyperintense on T2-FLAIR and have a ring-like or solid enhancement (Fig. 10.1) [19].

Treatment consists of an induction phase followed by consolidation and maintenance. The favored regimen for induction is a combination of amphotericin B (AmB) with 5-flucytosine (5-FC) for 2 weeks. Lipid formulations of AmB are preferred because of reduced nephrotoxicity despite similar outcomes, especially in patients at risk for acute kidney injury. Combination therapy is associated with faster CSF yeast clearance, fewer relapses and less mortality. Recommended doses are: Liposomal AmB (LAmB): 3–6 mg/Kg/d, lipid complex AmB (ABLC): 5 mg/kg/d or AmB deoxycholate (AmB-d): 0.7–1 mg/kg/d and 5-FC: 100 mg/kg/d in divided doses. In areas where 5-FC is not available, combination therapy of AmB with fluconazole (800 mg/d) is a better alternative than monotherapy [20]. A longer induction phase (4–6 weeks) is reasonable in patients with positive CSF cultures after 2 weeks, non-HIV non-transplant, *C. gattii* meningitis or multiple cryptococcomas. Newer alternatives have been described in recent studies for resource

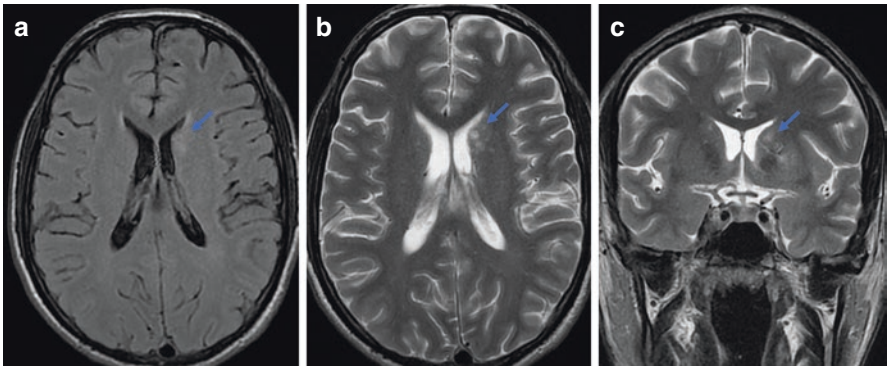


Fig. 10.1 Brain MRI in a patient with cryptococcal meningitis. A 31-year-old HIV positive male who presented with headache, vomit, diplopia and malaise. On examination he had bilateral papilledema. He had a CD4 count of 47 cell/ml. CSF analysis showed 2 leucocytes, glucose 44 mg/dL, proteins 46 mg/dL, opening pressure 35 cm^2H_2O, positive CSF cryptococcal antigen and CSF culture grew C. neoformans. Head MRI showed multiple bilateral nodular lesions with hyperintense rims, predominantly in the head of the left caudate nucleus (arrows). (**a**) Axial FLAIR, (**b**) Axial T2 FSE (**c**) Coronal T2 FSE. (Courtesy of Dr. Griselda Teresa Romero-Sanchez. Department of Radiology and Imaging, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán)

limited settings: The ACTA trial showed 1 week of AmB-d plus 5-FC was non-inferior to 2 weeks of AmB based therapy, and had a lower 10-week mortality [21]. The AMBITION-cm trial showed that a single 10 mg/Kg/d of LAmB was non-inferior to daily 3 mg/Kg/d for 14 days to reduce CSF cryptococcal burden. Phase 3 trial results are pending [22]. Following induction, a consolidation phase with fluconazole 400–800 mg/d for 8 weeks is recommended. Finally, a long-term maintenance with fluconazole 200–400 mg for 6–12 months in non-HIV patients and a minimum of 1 year (until reaching >100 CD4 cells/μL and undetectable viral load >3 months) in patients living with HIV is recommended [20].

The management of ICH should be aggressive. A basal CSF opening pressure > 25 cmH_2O requires daily therapeutic lumbar punctures, until pressure and symptoms are stable for >2 days. A ventriculoperitoneal shunt or ventriculostomy may be considered if refractory ICH occurs. The use of mannitol, corticosteroids or acetazolamide is not recommended [20].

In ART naïve patients, initiation is usually delayed for 2–4 weeks, because of increased mortality attributted to IRIS, seen in the COAT trial [23]. Reduction of immunosuppression should be done with caution in solid organ recipients. The recommended approach is to reduce immunosuppression with a gradual taper of steroids after beginning antifungal therapy. Drug interactions between fluconazole and calcineurin inhibitors should be anticipated [12, 15, 16]. Minor signs of IRIS usually resolve spontaneously. Serial therapeutic LPs should be done in patients with ICH. Corticosteroids do not reduce mortality, they have been associated with adverse effects and are not recommended routinely. However, they may be considered as a life-saving intervention in selected cases with a dose taper over 2–6 weeks [16, 24].

In the case of relapse or persistent disease (Positive CSF cultures after 1 month of therapy) resumption or a longer duration of induction therapy are suggested. Increasing doses may be considered. Salvage therapy with posaconazole, voriconazole and isavuconazole showed favorable results in 48–50% of patients with cryptococcal meningitis who were refractory or intolerant to conventional antifungal treatment. Antifungal susceptibility testing should be pursued since elevated MICs have been found in relapsed cases [25–27].

Cryptococcal meningoencephalitis is fatal without treatment. Despite optimal care 3-month mortality approaches 20% in HIV patients and 20–30% in non-HIV non-transplant patients. Poor prognostic factors in HIV patients are: a baseline CSF cryptococcal antigen > 1:1024, abnormal mental status, a CSF leucocyte count < 20/ μL and a positive culture after 2 weeks of treatment [28, 29]. Cryptococcemia, increased opening pressure and altered mental status are associated with increased mortality in non-HIV non-transplant patients [13]. The presence of IRIS can increase mortality in the HIV population up to 83% and 50% among patients with SOT (1,2) [16, 29].

Candida

Invasive candidiasis (IC) includes candidemia and deep-seated candidiasis (presence of yeasts in sterile sites such as peritoneum, pleural cavity, etc). Candidemia is among the four most common nosocomial bloodstream infections, with most national surveys showing an incidence of 3–5 per 100,000 people in the general populations and 1–2% of all ICU admissions. There are more than 30 species, but >95% of infections are caused by *Candida albicans, C. glabrata, C. tropicalis, C. parapsilosis* and *C. krusei*. Despite regional variations and the epidemiological shift towards non-albicans species in the last decades, *C. albicans* is the most common pathogen. *Candida auris* is a novel multidrug organism causing outbreaks worldwide [30].

Candida is a commensal of the gastrointestinal and genitourinary tract. Invasive disease is a consequence of increased fungal burden and disruption of skin and mucous membranes. Colonization of prosthetic devices or indwelling catheters is common due to biofilm formation. Common risk factors for IC are prematurity, prolonged ICU stay, mechanical ventilation, neutropenia, intravascular catheters, total parenteral nutrition, malignancy, immunosuppression, broad spectrum antibiotics, necrotizing pancreatitis, major surgery and hemodialysis [30].

CNS infection is underestimated and unsuspected. Acute meningitis with micro abscesses or chronic meningitis with a dense exudate at the base of the skull can occur. Autopsy studies report parenchymal involvement in 50% patients with candidemia [31] and up to 66% of candidemic neonates, possibly due to an immature BBB. An LP is recommended routinely in candidemic newborns. Bone and joint involvement are frequent in this age group [32]. Fundoscopy showing retinal infiltrates should raise suspicion of CNS involvement. Micro abscesses are usually

found at the joint between the gray and white matter, the basal ganglia and cerebellum. Concomitant renal and myocardial involvement was found in 80–90% autopsies [33].

Signs and symptoms of candida meningitis are subacute onset of fever, headache, neck stiffness and mental status impairment [31]. Large abscesses have been described in children and adults with chronic granulomatous diseases or CARD9 deficiency causing focal neurological deficits and increased intracranial pressure [34]. Less frequently, *Candida* presents as vasculitis, thrombosis, subarachnoid hemorrhage from rupture of mycotic aneurisms, cranial neuropathy, spinal granulomas and myelitis [5, 31, 35]. Exogenous *Candida* infection occurs as a complication of neurosurgery in the form of surgical site infection, ventriculostomy or hardware infection. These infections usually manifest months after the surgical procedure. Meningitis, intraventricular fungal balls or hydrocephalus can occur. Shunt dysfunction may be the only manifestation [35].

The reference standard for diagnosis is the growth of *Candida* from sterile sites (blood, peritoneal, pleural fluid or CSF). Cultures are insensitive so a large volume of CSF (30 ml) is recommended to maximize positivity. *Candida* meningitis causes neutrophilic or monocytic infiltrate with elevated proteins and low glucose (in 60% if cases), Gram staining is usually negative. In patients with neurosurgical infections, pleocytosis may be absent [35]. β-D glucan is a fungal cell wall constituent (except for *Zygomycetes*), usually measured in the serum for IC diagnosis. Elevated CSF levels may aid the diagnosis of fungal meningitis [36].

Cranial CT may be normal or show hydrocephalus in shunt infections. Microabscesses appear as multiple nodular or ring enhancing nodules on contrast CT but are better visualized on MRI. Macroabscesses on CT appear as iso, hypo or hyperdense lesions with nodular or ring enhancement. Meningeal enhancement and calcifications may be seen. Histopathological study shows necrosis and non-caseating granulomas containing yeasts and pseudohyphae [35, 37].

Treatment should be based on antifungal susceptibility testing. Although there are no randomized trials, the first line of treatment is LAmB (3–5 mg/Kg/day) with or without 5-FC (25 mg/Kg/day) for several weeks, based on *in vitro* synergism and the excellent CSF concentrations achieved with 5-FC. Fluconazole (6–12 mg/Kg/day) is the stepdown agent for maintenance therapy if susceptibility confirmed, and should continue until all signs, symptoms and radiological abnormalities resolve. The combination of fluconazole and 5-FC has been successful in some cases. Voriconazole may be considered when *C. glabrata* or *C. krusei* are isolated. The echinocandins (anidulafungin, micafungin or caspofungin) are not recommended for CNS candidiasis, but there are case reports of success with elevated doses [33].

Removal of infected devices is necessary, since biofilms are difficult to eradicate. Intraventricular administration of antifungals is not routinely recommended but reserved for patients refractory to systemic treatment or when device removal is not possible [38]. The dose of intraventricular AmB-d varies from 0.01 to 1 mg in 2 mL of 5% dextrose. Chemical ventriculitis, headache, nausea and vomiting are frequent side effects [33]. Adjunctive treatment with granulocyte-macrophage

colony-stimulating factor in a patient with CARD9 deficiency and recurrent *Candida* meningoencephalitis contributed to eradication in a case report [39].

Mortality ranges from 10% to 30%. Intracranial hypertension, hypoglycorrhachia less than 35 mg/dL, focal neurologic deficits and onset >2 weeks have been related to a worse prognosis [31].

Dimorphic Fungi

Dimorphic fungi exist as tissue-invasive yeast forms at human body temperature and as molds in the environment. They are geographically restricted so a careful travel history must be taken to anticipate diagnosis.

Histoplasmosis

Histoplasma capsulatum is found around the Ohio and Mississippi rivers, Central America, the north of South America, Southeast Asia, India and in China. Approximately 500,000 infections occur each year after the inhalation of microconidia from soil contaminated with avian droppings or bat guano. One in 2000 acute infections present as progressive disseminated histoplasmosis (PDH) in hosts with impaired cellular immunity such as AIDS, lupus, SOT, CD4 lymphopenia, common variable immunodeficiency, hyper-IgE syndrome and defects in the IL-12 / IFNγ pathways. A third of cases occur in immunocompetent patients. PDH presents as fever, fatigue, weight loss and respiratory symptoms. Common sites of involvement are the liver, spleen, gastrointestinal tract and bone marrow [40]. CNS histoplasmosis occurs in 5–25% PDH. It may present as acute, subacute or chronic meningoencephalitis, focal brain or spinal lesions, stroke syndromes (due to emboli or vasculitis) and hydrocephalus. Infrequent presentations are: Seizures, focal lesion, cognitive dysfunction, hemichorea and ventriculoperitoneal shunt infection [41–44].

CNS histoplasmosis is confirmed by the detection of *H. capsulatum* in CSF or CNS biopsy cultures. CSF analysis may show low glucose, elevated proteins and myeloid pleocytosis. At least 10 ml of CSF should be sent because of reduced sensitivity of cultures. The most sensitive method for diagnosis includes the combination of antibody and antigen detection in the CSF. An elevated antigen may be found in the CSF of 75% cases, with titers higher compared to serum levels, reflecting production in the CSF [40, 45]. Serologic tests for anti-histoplasma antibodies (complement fixation and immunodiffusion) show positive results in 50–90% of cases [42, 46]. Brain biopsy may be needed if non-invasive testing fails to provide a diagnosis. Testing non-CNS specimens in patients with PDH is useful. Biopsies of involved sites may show ovoid budding yeasts with a narrow base, often within macrophages. The highest yield may be achieved in respiratory and bone marrow samples. Cultures are positive in >75% in PDH but take 4–6 weeks to isolate the

organism. Antigen testing of both serum and urine achieves the highest yield. Cross reactivity with blastomycosis, paracoccidioidomycosis and *Penicillum marneffei* infection occurs.

Brain MRI reveals meningeal enhancement, hydrocephalus, brain abscess, granuloma formation or multiple lesions with a ring-enhancing pattern. Lesions are T1 hypointense and T2 variable, with reduced diffusion [46].

The first line of treatment for CNS histoplasmosis is a 4–6-week induction with LAmB or AmBd followed by itraconazole for at least 1 year or until CSF abnormalities or antigen positivity resolve [47, 48]. Lifelong maintenance treatment may be needed in immunocompromised patients. Measurement of itraconazole levels throughout the treatment is recommended. Case reports showed success with voriconazole or posaconazole treatment [48]. Interferon-γ may be a useful adjunct therapy in patients with defects in the IFN/Il-12 pathway. Surgery is rarely needed [3]. The mortality of CNS histoplasmosis is 39%. A recent study showed a relapse rate of 6% in three cases of advanced HIV infection, compared to 50% in previous studies. The mean survival rate at 12 months in patients treated amphotericin B was 8–10.6 months in a recent study [41].

Coccidioidomycosis

Coccidioides immitis and *C. posadasii* are found in the desert soil of southwestern United States, northern Mexico and parts of Central and South America. Following inhalation, arthrocondia turn into spherules that easily rupture leading to the spread of endospores via hematogenous and lymphatic seeding. Vulnerable people are construction and farm workers, military personnel, excavators, archaeologists and persons in correctional facilities. Sixty percent develop asymptomatic infection, or a mild auto-limited respiratory illness known as Valley Fever. Disseminated disease occurs in 1–3%, the most commonly involved sites include the skin, lymph nodes, bones and CNS. Individuals at risk for dissemination include HIV positive, recipients of TNF-α inhibitors, chemotherapy, high-dose corticosteroids, SOT, diabetes mellitus, women in the third trimester of pregnancy, defects in the IFN-γ/IL-12 or STAT3 pathways, African Americans and Filipino ethnicity [49, 50]. Meningitis occurs in nearly half of those with disseminated disease [51]. Coccidioidal meningitis presents within weeks to months after primary infection with headache, blurry vision, photophobia, meningismus, altered mental status, hearing loss and focal neurological deficits. Hydrocephalus is the most frequent complication, it can occur early or late in the course of infection as a result of suppurative inflammation and fibrosis of the subarachnoid space. Vasculitic stroke, cranial neuropathy, arachnoiditis and cerebral abscess are other complications.

The diagnosis is based on positive CSF serology or culture [51]. Sampling other sites of disseminated disease may be useful, since CSF cultures are insensitive. Histopathological examination shows endosporulating spherules. Neuroimaging studies will reveal hydrocephalus in 30–50% of patients throughout the course of

disease. Common findings are diffuse meningeal enhancement, focal or nodular enhancement of basal cisterns, parenchymal or parameningeal abscesses and white matter abnormalities. Contrast MRI reveals basilar cisternal enhancement or vasculitic stroke in 15–20%. Subarachnoid hemorrhage can occur from aneurysmal rupture or dural venous sinus thrombosis [20].

IDSA guidelines recommend initial treatment with fluconazole, 400–1200 mg per day. Higher doses (800–1200 mg) are preferred due to high clinical failure rates with 400 mg [49]. The estimated time for symptom resolution is 4–8 months. Because of the elevated rates of relapse, lifelong treatment with azoles is recommended [52]. Patients with refractory symptoms or CSF abnormalities require higher doses or changing to a different azole [53]. Oral itraconazole 400–600 mg daily with close monitoring of drug levels to assure adequate absorption is an alternative [49]. Voriconazole and posaconazole have been used successfully in refractory cases [54]. Azole therapy should be avoided in the first trimester of pregnancy. Intrathecal (IT) AmB-d was the mainstay of treatment before the advent of fluconazole. The technical difficulties associated with IT administration and the high rate of chemical arachnoiditis, limit its use to refractory cases and pregnant patients during the first trimester [49]. A detailed guide to prepare and administer IT AmB-d, has been published [55]. Intravenous AmB-d is not recommended due to poor CSF penetration and toxicity. The safety and efficacy of intravenous lipid formulations of AmB have been described in animal models only, their use is reserved for refractory cases [49].

Intracranial pressure must be assessed, values >25 cm H_2O require CSF removal as described for cryptococcal meningitis. The presence of ICH or hydrocephalus requires neurosurgical consultation to evaluate ventriculoperitoneal shunting. The use of corticosteroids for vasculitic stroke is controversial and not routinely recommended [49]. Coccidioidal meningitis is universally fatal without treatment, fluconazole reduces mortality to 40% [51].

Blastomycosis

Blastomyces dermatitidis is found in the Mississippi and Ohio River valleys, US Midwest and southeastern states, and the Canadian provinces that border the Great Lakes. After inhalation, *B. dermatitidis* conidia escape phagocytosis and convert to the yeast form. They are characterized by thick, retractile cell walls and broad-based budding that spread by hematogenous dissemination. Blastomycosis ranges from asymptomatic to disseminated infection that most commonly involves the lungs, skin, bones and genitourinary tract. CNS infection occurs in 5–10% of patients with disseminated disease. Common risk factors are HIV, transplant, TNF-α inhibitors and pregnancy [54]. Forty percent of patients with advanced HIV in the preHAART era presented CNS involvement. Manifestations include acute meningitis, isolated chronic meningitis and intracranial abscesses. Other organs are affected in 77% of CNS cases [56]. Recognition of skin lesions may be a clue for diagnosis: Verrucous lesions with raised irregular borders, ulcerative with sharp borders and exudate or crusted appearance, violaceous nodules or pustules. Facial lesions are common [54].

Isolation of *B. dermatitidis* from the CSF is unlikely, cell wall antigen testing by enzyme immunoassay (Mira Vista Diagnostics, Indianapolis, IN) is helpful. Detection of the antigen in urine has 93% sensitivity but low specificity because of cross reactivity with histoplasmosis. Serum samples have a lower sensitivity (60%) [54, 57].

The initial treatment of CNS blastomycosis is a lipid formulation of AmB (3–5 mg/Kg daily) for 4–6 weeks. After an initial response, step down therapy to oral itraconazole (200 mg TID for 3 days and then 200 mg BID), voriconazole (400 mg BID for 2 doses and then 200–300 mg BID) or fluconazole (800 mg QD) is recommended. Treatment for at least 1 year or until resolution of CSF abnormalities is required. Lifelong suppressive therapy may be needed in immunocompromised hosts [57]. CNS blastomycosis mortality can reach 18%.

Other

Paracoccidioidomycosis is caused by *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii* [58]. CNS infections are typically reported in disseminated chronic paracoccidioidomycosis, which is caused by a reactivation of a primary infection in men aged 30–60 years. The most frequent symptoms are paresis and seizures. Imaging usually shows brain or spinal cord lesions that correspond to granulomas. Large yeasts with daughter yeasts in a pilot-wheel configuration can be seen in histopathology. Serological tests are available, with variable sensitivities and specificities. Those who target the gp43 antigen will identify *P. brasiliensis* but not *P. lutzii* [50] *Talaromyces marneffei* infections occur in southeast Asia in patients with advanced HIV infections. Disseminated infections with CNS disease manifest as fever, altered mental status and erythematous nodules or verrucous lesions. Imaging usually show multiple brain abscesses. Galactomannan essays will show positive results. Prognosis is poor [59]. CNS involvement in sporotrichosis is infrequent and usually seen among patients with advanced HIV or immunosuppression. CNS involvement manifests as meningoencephalitis and hydrocephalus, with fever and headache, skin lesions. Other sites of dissemination are the lungs, sinuses, liver, kidneys, eyes and heart (endocarditis) [60, 61].

Mold Infection

Aspergillosis

Aspergillus causes a spectrum of disease that ranges from colonization, allergic responses, chronic aspergillosis and invasive disease. Pulmonary and sinonasal infection may result in angioinvasion and disseminated disease. A mean of 27 cases of invasive aspergillosis (IA) per 100,000 patients occur per year [62]. *Aspergillus fumigatus* is the most frequent species followed by *A. flavus, A. niger, A. terreus, A. nidulans* and *A. versicolor.* The population at the highest risk are hematologic

stem cell transplant (HSCT) recipipents during two specific phases: The prolonged neutropenia of preengraftment and after 100 days when graft versus host disease is usually treated with steroids and immunosuppression. Lung transplant receptors with *Aspergillus* colonization, liver and small intestine transplantation with concomitant CMV infection, acute myeloid leukemia during induction chemotherapy, chronic granulomatous disease and steroid users are other risk factors. Clinical manifestations include fever, respiratory symptoms, nodular and cavitated lung infiltrates. Fungal sinusitis is characterized by pain, facial swelling, purulent rhinorrhea with bone erosion on CT imaging [63].

Between 10% and 20% patients with IA demonstrate CNS involvement, which can be higher (14–60%) in patients with acute leukemia and HSCT [64]. Up to 24% of cases occur among otherwise immunocompetent patients with sinonasal and lung infection. Isolated intracranial infection is seen in 23% [65, 66]. The pathogenesis in concomitant sinus or ear infection is determined by direct invasion and hematogenous dissemination from pulmonary aspergillosis. The clinical presentation includes focal neurologic deficits, seizures, mental status changes, fever and headache. Stroke-like syndromes with infarction, hemorrhage and mycotic aneurisms are more frequent than in *Candida* or *Cryptococcus* infection. *Aspergillus* causes thrombosis of the small perforating arteries, affecting the thalamus, basal ganglia and the corpus callous. It may cause acute stroke due to cerebral anterior and middle artery obstruction (Fig. 10.2) [65]. The occurrence of cavernous sinus thrombosis with periorbital pain, ophtalmoplegia, proptosis, or orbital apex syndrome with visual loss is a neurosurgical emergency. Multiple cranial nerve palsies may occur when there is involvement

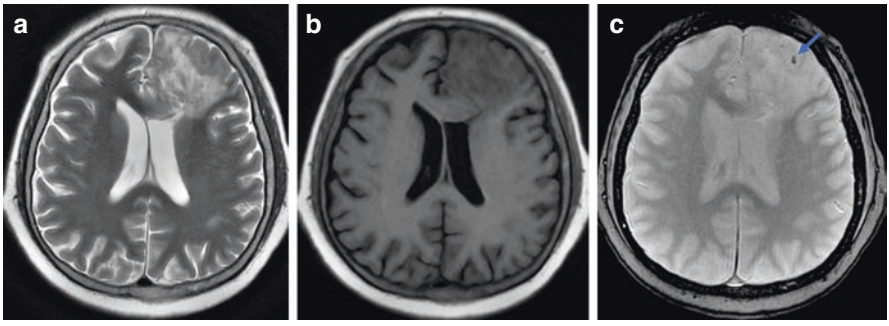


Fig. 10.2 Brain MRI in a patient with disseminated invasive aspergillosis. A 33-year-old male who had liver transplant and retrasplant within 16 days. He presented with multiple nodular lung opacities, positive serum galactomannan, tracheal aspirate grew A. fumigatus. He developed fever, personality changes, inattention and aggressiveness. CSF analysis showed glucose 55 mg/dL, protein 61 mg/dL, 2 leukocytes and a positive CSF galactomannan with an optical density index of 13. HEAD MRI showed a heterogenous mainly hyperintense left frontal lesion. (**a**) Axial T2 FSE (**b**) Axial T1 the lesion is iso to hypointense. (**c**) Axial GRE with blooming foci in keeping with fungal elements (arrow). (Courtesy of Dr. Griselda Teresa Romero-Sanchez, Department of Radiology and Imaging, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán)

of the base of the skull. Meningitis is infrequent. In a review of 93 cases of *Aspergillus* meningitis, 69% occurred among immunocompetent hosts, of which 25% were due to iatrogenic inoculation during epidural anesthesia, 25% related to neurosurgery, 11.5% in intravenous drug abusers, 11.5% due to direct extension of ear, paranasal or orbital disease. No predisposing factor was identified in 25% [67].

Definitive diagnosis of IA requires *Aspergillus* isolation from sterile sites or histopathological observation of septate hyphae with acute angles (45*) and concomitant tissue necrosis or angioinvasion. Antigen detection of galactomannan in the serum or bronchoalveolar lavage detects pulmonary IA with a variable sensitivity depending on the host (44–90%) Coupled with PCR testing, sensitivity may achieve 98% and specificity 93% [67]. Galactomannan, PCR and β-d glucan measurement in the CSF are helpful to support CNS aspergillosis, with a high negative predictive value. Galactomannan showed an overall sensitivity of 86.7% in *Aspergillus* meningitis cases with a median optical density index of 6.58 (range 2.2–578), while PCR has shown 100% sensitivity [67–68].

CSF fluid analysis is not typically useful in the case of focal lesions. In the case of meningitis, pleocytosis is present in 95% of patients with a neutrophil predominance. A positive CSF culture is found in 31% [69, 70]. Imaging frequently shows a mass lesion. Brain MRI can show multiple abscesses and ring enhancing lesions. Lesions are hypointense or isointense in T1 with bright and dim enhancement in T1 and T2 respectively [71]. Blood vessel infiltration with ischemic lesions near the orbit or paranasal sinus using diffusion-weighted imaging can be seen. The differential diagnosis includes brain tumors such as gliomas, lymphoma, metastasis and infectious etiologies such as tuberculomas, toxoplasmosis and pyogenic abscesses [69].

The first line treatment of CNS aspergillosis is voriconazole [70]. Open label studies suggest a benefit over amphotericin B, with complete and partial responses of 35% and 31%, respectively. Historic reports showed complete and partial response of 6 and 3% among patients treated with amphotericin B or itraconazole [71–73]. A systematic review of 120 cases of CNS aspergillosis showed a median survival of 159 days and 47% success with voriconazole. A targeted through voriconazole concentration of 2–5.5 mg/L was suggested [74, 75]. Lipid formulations of amphotericin are reserved for those refractory or intolerant to voriconazole. Case reports have described efficacy of the echinocandins [70]. Treatment length is variable, with a median duration of 48 days (range 1–1128) in a systematic review [73]. Patients with *Aspergillus* meningitis in the literature received voriconazole with different lengths from 8–14 weeks to 5–12 months. Drug interactions between voriconazole and antiepileptic agents such as phenytoin and phenobarbital result in diminished voriconazole levels. Surgical management is encouraged, since it was associated with improved survival in a retrospective study of 81 patients. The reversal of immunosuppression is essential to improve outcome.

CNS aspergillosis is a devastating infection with 50–100% mortality. Patients with HSCT have a worse prognosis. Concomitant surgical resection might reduce mortality to 25–28% [4–7].

Mucormycosis

Mucormycosis (MM) includes a spectrum of subacute, acute and sometimes rapidly progressive infections caused by the aseptate hyphae of the order Mucorales. The most frequent agents are *Rhizopus sp, Mucor sp, Rhizomucor and Leichtimia.* Other genera are *Cunninghamella, Saksenae and Apophysomyces* [74]. Traditional risk factors are poorly controlled diabetes mellitus (DM), especially in the setting of ketoacidosis, high dose steroids and chelation therapy with deferoxamine. MM among patients with hematological malignancies and HSCT has increased in recent years. High suspicion must be maintained in prolonged neutropenia, high risk HSCT (unrelated haploidentical, cord blood or T-cell depleted) and exposure to voriconazole. Intravenous drug users may present with septic emboli [75].

The Mucorales have tropism for angioinvasion, resulting in infarction and necrosis. The most common sites of involvement are the sinuses (39%), lungs (24%) and skin (19%). Disseminated disease (>2 non-contigous sites) develops in 23% of the cases [74]. The clinical presentation of disseminated disease includes pulmonary, cutaneous or gastrointestinal infection. CNS infection can occur as rhino-orbital cerebral mucormycosis (ROCM) in 69% of cases or as hematogenous dissemination of pulmonary infection in 15%. ROCM occurs more frequently in patients with DM. Sinusitis produces necrotic eschars in the nasal mucosa or palate. After sinonasal infection, these molds cab reach the sphenoid and cavernous sinus, the orbits and the brain via the orbital apex or cribiform plate. ROCM causes facial numbness and pain, orbital cellulitis, orbital abscesses, ptosis and proptosis. Cavernous sinus thrombosis is characterized by involvement of the third and fifth cranial nerves with diplopia, ophtalmoplegia, acute loss of vision or blurred vision. Contralateral hemiparesis warrants internal carotid artery thrombosis. Intracranial complications include epidural and subdural abscess, cavernous and less frequently sagittal sinus thrombosis (Fig. 10.3) [74]. Hematogenous dissemination can lead to mycotic aneurisms. Meningitis is rarely observed. Isolated brain involvement without ROCM occurs in 16% of all MM cases and typically affects the basal ganglia in intravenous drug users [75, 76].

The hallmark of mucormycosis is the finding a black necrotic eschar with broad, thin walled, aseptate hyphae with irregular branches at right angles. The absence of a necrotic eschar does not exclude MM, so all immunocompromised patients with paranasal sinus symptoms must undergo rapid ENT exploration and biopsy of suspicious lesions. Perineural invasion is frequent. Cultures lead to recovery in 40–50% of biopsy proven cases. CSF offers a poor yield [75]. Sinus CT may show fluid filled sinuses, edematous mucosa, with bony destruction as a late finding. MRI can identify cavernous sinus thrombosis, thrombosis of cavernous portions of the internal carotid artery and perineural spread [77].

The management of MM is based on multiple simultaneous interventions that include intravenous AmB, immediate surgical consultation for debridement, immunosuppression reduction and controlling predisposing factors (taper steroids, control hyperglycemia and acidosis, increase neutrophil counts) [78, 79]. The first line

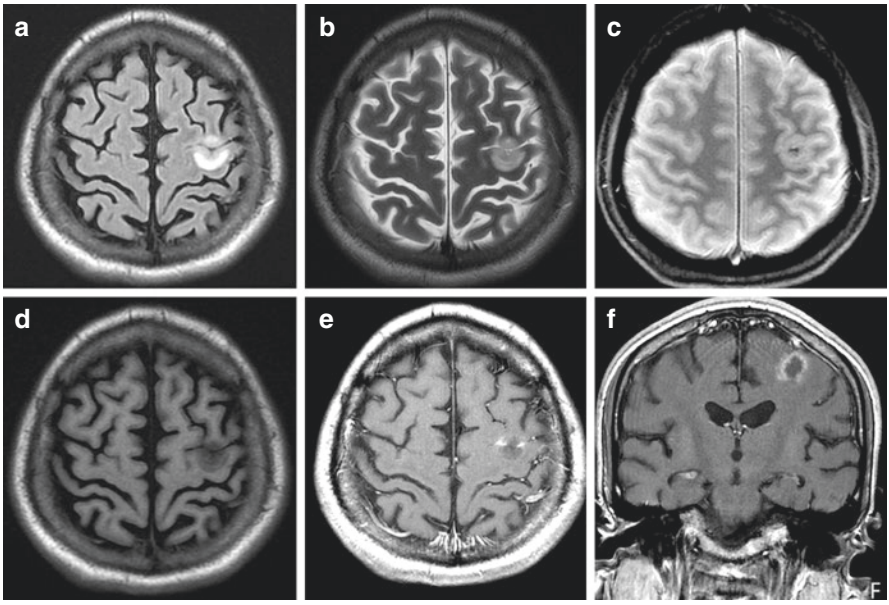


Fig. 10.3 Brain MRI in a patient with Disseminated Mucormycosis. A 19-year-old male with acute lymphoblastic leukemia who underwent remission induction chemotherapy, had prolonged severe neutropenia and presented with fever and multiple bilateral pulmonary cavitated nodules, splenic and renal infarcts. Pulmonary biopsy showed aseptate hyphae. He developed paraparesia. Head MRI showed a hyperintense cortical-subcortical lesion in the left precentral region. (**a**) Axial FLAIR and (**b**) Axial T2 FSE (**c**) Axial GRE with blooming foci in keeping with fungal elements. (**d**) T1, (**e**) and (**d**) axial and (**f**) coronal gadolinium images with peripheral enhancement. (Courtesy of Dr. Griselda Teresa Romero-Sanchez, Department of Radiology and Imaging, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán)

of treatment is AmB, with the preference of lipid formulations. (5 mg/Kg/day of LAMB or 1.2–1.5 mg/Kg/day amphotericin B deoxycholate). The European guidelines suggest a high dose (10 mg/Kg/day) in the setting of CNS involvement can be considered on an individual basis. Increased nephrotoxicity and electrolyte imbalances are cause for concern [80]. There are no data comparing the outcomes of CNS mucormycosis with different AmB doses. A multicenter non-randomized pilot trial in patients without CNS involvement found 45% response at 12 weeks and creatinine level doubling in 40% of patients receiving 10 mg/Kg/day [80]. The DEFEAT Mucor study showed patients receiving a median dose of LAmB of 7.5–8 mg/Kg/day had a global success 56% at 90 days [81]. The combination of lipid-based AmB and caspofungin has been successful in a limited number of diabetic patients with ROCM [82]. Posaconazole and isavuconazole are the only azoles with activity against the Mucorales [83]. Posaconazole can be used as step down or salvage therapy in refractory cases or intolerance to treatment, with complete response rates of 73–80%. The recommended dose is 800 mg divided in 2–4 doses [78]. Isavuconazole was approved for the treatment of mucormycosis, based on the VITAL study, a

phase 3, single arm, open-label noncomparative trial. However, increasing reports of breakthrough IFI infections on isavuconazole, including mucormycosis, is of concern [84].

Surgical resection of necrotic tissue is essential, it improves survival in patients with pulmonary and ROCM [78, 84]. An endoscopic approach is preferred in patients with limited disease, while open surgery is preferred for extensive disease. A survival benefit in radical surgeries (maxillectomy, orbital exenteration or craniofacial resection) in patients with limited life expectancy is uncertain [82]. Antifungal treatment duration is not established, it is defined on an individual basis. It should continue until resolution of all clinical, imaging signs and symptoms resolve. In general, patients that respond to AmB can be switched to oral posaconazole after at least 3 weeks [85].

Overall mortality remains at 25–40% with localized infection but may reach 70–90% in disseminated disease. Isolated cerebral infection has a mortality of 62% while disseminated disease with CNS involvement may reach 98% [74]. Poor survival has been found in ROCM patients with delayed diagnosis, hemiparesis, lid gangrene, bilateral sinus involvement and facial necrosis [86]. In patients with hematological malignancies or HSCT relapsed malignancy or protracted neutropenia are often related to a worse prognosis.

Emergent Fungi

Dematiaceous Molds

Dematiaceous molds are a group of fungi that contain melanin-like pigment in their cell walls and produce brown hyphae. They belong to distantly related orders of Ascomycota that cause a variety of infections collectively known as phaeohyphomycosis (from the Greek "phaeo" for dark) They range from mild cutaneous infections (such as *Exophiala dermatitidis* and *Hortaea wernecki*), subcutaneous infections like chromoblastomycosis and systemic mycosis including brain abscesses [87]. These fungi are found commonly in tropical and subtropical regions. Some species are endemic to the Middle East, East Asia or India. Inhalation with hematogenous dissemination, traumatic introduction or local extension from adjacent sinusitis are involved in their pathogenesis. The most common neurotropic fungi are*: Rhinocladiella mackenziei, Cladophialophora bantiana, Exophiala dermatitidis* and *Fonsecae monophora*. Other species like *Exserohilum, Bipolaris, Chaetomium, Alternaria* are related adjacent chronic sinusitis.

Most cases of CNS infection occur among immunocompetent patients. Several cases among solid organ transplant recipients, malignancy, HIV and intravenous drug use have been reported [8–10, 88, 89]. *C. bantiana* and *R. mackenziei* were the most frequent etiologic agents in a large series, mainly identified in India and the

Middle East, respectively. The most frequent presentation are brain abscesses (single or multiple) causing focal neurologic deficits and seizures. Meningitis caused by *Aureobasidium*, *Bipolaris* and *Cladophialophora* has been described [88, 90]. *Exserohilum rostratum,* another dematiaceous mold, was involved in a multistate outbreak that resulted in 63 deaths in the USA during 2012. More than 750 patients developed fungal infections after receiving steroid injections contaminated with *E. rostratum* and other fungi. Fungal meningitis was detected in 384 patients, some of which developed stroke-like syndromes including basilar stroke and paraspinal infections with septic arthritis. The contaminated products were produced and distributed by a single compounding pharmacy. All products were recalled, and *E. rostratum* was recovered from unopened vials [91].

Diagnosis of phaeohyphomycosis can be made by culture or histopathologic exam of abscess aspiration or biopsy, that show branching, septate hyphae with brown pigment in haematoxylin and eosin or a KOH preparation. Fontana-Masson staining helps to identify the melanized nature of the fungi. Cultures show growth of black molds on Sabouraud or potato dextrose agar, species identification may require ITS sequencing [87]. Determination of CSF β-D-glucan and PCR were useful to confirm suspected cases during the *E. rostratum* outbreak [91].

The treatment of cerebral phaeohyphomycosis includes surgical resection or abscess aspiration and antifungal therapy. Most dematiaceous molds are susceptible to triazoles and AmB. Susceptibility testing is encouraged although not standardized, treatment options are based on *in vitro* data and published case reports. Occasionally, *Lomentosopora prolificans, Curvularia spp, Exophiala spp* and *R. mackenziei* are resistant to AmB, while *L. prolificans* is resistant to all azoles. The outcome is usually poor, even with antifungal therapy. Mortality reaches 50–70%. Voriconazole and posaconazole may provide clinical improvement. In practice, voriconazole is preferred. Initial combination therapy with amphotericin B, an echinocandin or flucytosine until clinical response and continued therapy with an azole is an option [87, 92, 93]. The length of treatment must be individualized, most patients need several months.

Blastomyces helicus

Recently, *B. helicus* (formerly called *Emmonsia*) was recognized as a species. It was first isolated in 1970 from the brain and lungs in a patient in Alberta, Canada. It is found in regions of Western Canada and the USA not considered endemic for *B. dermatitidis*. It causes fatal disseminated (including CNS) disease in immunocompromised patients and companion animals. Histopathological findings include small yeast-like cells with single or multiple budding, sometimes proliferating to form hyphal like elements. The mycelial phase is characterized by the absence of conidia an occasional formation of coiled helices [94].

Antifungal Agents and the CNS

The BBB and blood-cerebrospinal fluid barrier (BCSF) create an obstacle for free diffusion of compounds into the CNS [95, 96]. Systemic infection alters cerebral blood flow, blood and tissue pH and intra / extracellular fluid volumes, all of which influence on systemic pharmacodynamics and drug penetration into the CNS. Meningeal inflammation may increase the concentrations of some antimicrobial agents in the CSF. When the BBB is disrupted, unrestricted drug passage may reach to the pathogen. Many drug characteristics influence drug penetration: lipophilicity (a greater lipophilicity translates into better CNS penetration), protein binding (reduced protein binding increases CNS penetration) and efflux bombs like P-glycoprotein present in the BBB and BCSF that remove compounds from the CNS. Some antifungals exhibit non-linear or highly variable pharmacokinetics (PK), which require therapeutic drug monitoring. This variability is critical when CNS penetration is considered, making plasma concentrations an unreliable surrogate marker. Studies of antifungal drug CNS penetration in humans are limited, information is derived from preclinical animal models [95, 96].

Fluconazole is able to traverse the BBB and achieves a high concentration in the CSF which is dose dependent. This drug achieves a CSF/plasma concentration of 0.6–0.8 and is readily detectable in the brain parenchyma. It has plasma protein binding of 10% and is not a substrate of P-glycoprotein. Itraconazole levels in the CSF are very low, with CSF /plasma concentration ratios of <0.002–0.12, even in the setting of infection. This has been attributed to rapid binding to red blood cells and 98% binding to plasma proteins. Murine experiments show this drug penetrates the brain rapidly, maintaining a lower than plasma concentration and rapidly declining due to efflux through P-glycoprotein (P-gp). The concentration achieved by itraconazole makes this drug a second line therapy for CNS infections. Voriconazole has a lipophilicity that is intermediate between fluconazole and itraconazole, a low molecular weight and is a weak substrate for Pgp. It penetrates human brain tissue and abscess material, exceeding the concentrations seen in plasma. CSF/plasma concentrations vary from 0.22 to 1, which is consistent with a plasma protein binding of 58% and extensive PK variability. Posaconazole penetrates the CNS poorly, with CSF/plasma concentrations of 0.009. Diffusion is increased by meningeal inflammation and it is an inhibitor of Pgp. Brain tissue concentrations are dose dependent and may achieve 70–80% of the plasma concentration at supratherapeutic doses (40 mg/Kg), being able penetrate into fungal abscesses. Although tablet and intravenous administration have less variation in bioavailability and PK, it is not a first line treatment for CNS infections. Isavuconazole has a higher molecular weight than voriconazole and fluconazole and 99% plasma protein binding. It is not a substrate of Pgp and the brain/plasma concentration ratio is 1.8. There is no extensive experience treating CNS infections with this agent [95, 96].

AmB has a large molecular weight that impairs CNS penetration. L-AmB is the formulation that achieves the highest CNS concentration. Despite low concentrations, efficacy for most CNS mycosis including cryptococcal meningitis, is well established. A likely explanation are high meningeal concentrations [95, 96].

5- FC achieves a high CNS penetration due to low molecular weight, low protein binding and polarity. The CSF and brain concentrations are similar to the plasma with a ratio of 0.74–0.8. It is not recommended as monotherapy because of the rapid development of resistance [95, 96].

Caspofungin, micafungin and anidulafungin are inhibitors of β-D- glucan synthesis. They have large molecular weight and high level of protein binding that achieve brain/plasma concentration ratios <0.01. CNS penetration has been observed only with supratherapeutic doses (>2 mg/Kg). Case reports of human data show consistently low CSF and brain/plasma ratios. At this point echinocandins have no role in the treatment of CNS infections [95, 96].

Conclusions

CNS fungal infection presents as meningoencephalitis, brain abscesses, stroke syndromes or spinal infections due to hematogenous dissemination, local extension of paranasal sinus infection or iatrogenous inoculation. CNS involvement is possible in the setting of healthcare associated IFI or endemic mycosis. The most frequent entity is cryptococcal meningitis. Immunocompromised hosts are most affected but disease can occur in healthy individuals. Antifungal treatment is a challenge due to reduced CNS penetration of most antifungals, the need for prolonged treatments and neurosurgical consultation. Morbidity and mortality remain elevated.

References

1. Ko JR, Casadevall A, Perfect J. The spectrum of fungi that infects humans. 2015:1–22. https://doi.org/10.1101/cshperspect.a019273.
2. Raman SR. Fungal infections of the nervous system: current perspective and controversies in management. Int J Surg. 2010;8(8):591–601. https://doi.org/10.1016/j.ijsu.2010.07.293.
3. Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America, vol. 36; 2010. https://doi.org/10.3109/10408410903241444.
4. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012;4(165). https://doi.org/10.1126/scitranslmed.3004404.
5. Góralska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. Infection. 2018;46(4):443–59. https://doi.org/10.1007/s15010-018-1152-2.
6. Liu Y, Mittal R, Solis NV, Prasadarao NV, Filler SG. Mechanisms of candida albicans trafficking to the brain. PLoS Pathog. 2011;7(10). https://doi.org/10.1371/journal.ppat.1002305.
7. Jong A, Wu CH, Prasadarao NV, et al. Invasion of Cryptococcus neoformans into human brain microvascular endothelial cells requires protein kinase C-α activation. Cell Microbiol. 2008;10(9):1854–65. https://doi.org/10.1111/j.1462-5822.2008.01172.x.
8. Santiago-Tirado FH, Doering TL. False friends: phagocytes as Trojan horses in microbial brain infections. PLoS Pathog. 2017;13(12):1–7. https://doi.org/10.1371/journal.ppat.1006680.
9. Hagen F, Khayhan K, Theelen B, et al. Recognition of seven species in the Cryptococcus gattii/Cryptococcus neoformans species complex. Fungal Genet Biol. 2015;78:16–48. https://doi.org/10.1016/j.fgb.2015.02.009.

10. MacDougall L, Fyfe M, Romney M, Starr M, Galanis E. Risk factors for Cryptococcus gattii infection, British Columbia, Canada. Emerg Infect Dis. 2011;17(2):193–9. https://doi.org/10.3201/eid1702.101020.
11. Saijo T, Chen J, Chen SC, et al. Autoantibodies are a risk factor for central nervous system infection by Cryptococcus gattii in otherwise immunocompetent patients. MBio. 2014;5(2):1–8. https://doi.org/10.1128/mBio.00912-14.Editor.
12. Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin N Am. 2016;30(1):179–206. https://doi.org/10.1016/j.idc.2015.10.006.
13. Pappas P. Cryptococcal infections in non-HIV-infected patients. Trans Am Clin Climatol Assoc. 2013;124:61–79.
14. Sun HY, Singh N. Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. Clin Infect Dis. 2011;53(2):168–76. https://doi.org/10.1093/cid/cir276.
15. Singh N, Lortholary O, Alexander BD, et al. Allograft loss in renal transplant recipients with Cryptococcus neoformans associated immune reconstitution syndrome. Transplantation. 2005;80(8):1131–3. https://doi.org/10.1097/01.tp.0000180530.17683.02.
16. Sun HY, Alexander BD, Huprikar S, et al. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. Clin Infect Dis. 2015;60(1):36–44. https://doi.org/10.1093/cid/ciu711.
17. Ecevit IZ, Clancy CJ, Schmalfuss IM, Nguyen H. The poor prognosis of central nervous system cryptococcosis among nonimmunosuppressed patients: a call for better disease recognition and evaluation of adjuncts to antifungal therapy. Clin Infect Dis. 2006;42(in 2):1443–50.
18. Nalintya E, Kiggundu R, Meya D. Evolution of cryptococcal antigen testing: what is new? Curr Fungal Infect Rep. 2016;10(2):62–7. https://doi.org/10.1007/s12281-016-0256-3.
19. Neagu MR, Raibagkar P, Lyons JL, Klein JP. Imaging in neurologic infections II: fungal and viral diseases. Curr Infect Dis Rep. 2015;17(4). https://doi.org/10.1007/s11908-015-0474-9.
20. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291–322. https://doi.org/10.1086/649858.
21. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med. 2018;378(11):1004–17. https://doi.org/10.1056/NEJMoa1710922.
22. Jarvis JN, Leeme TB, Molefi M, et al. Short-course high-dose liposomal amphotericin B for human immunodeficiency virus–associated cryptococcal meningitis: a phase 2 randomized controlled trial. Clin Infect Dis. 2018:1–9. https://doi.org/10.1093/cid/ciy515.
23. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370(26):2487–98. https://doi.org/10.1056/NEJMoa1312884.
24. World Health Organization. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children, March 2018: supplement to the 2016 consolidated guidelines of the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization. 2018. https://apps.who.int/iris/handle/10665/260399.
25. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. J Antimicrob Chemother. 2005;56(4):745–55. https://doi.org/10.1093/jac/dki288.
26. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis. 2003;36(9):1122–31. https://doi.org/10.1086/374557.
27. Thompson GR, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. Clin Infect Dis. 2016;63(3):356–62. https://doi.org/10.1093/cid/ciw305.

28. Anekthananon T, Manosuthi W, Chetchotisakd P, et al. Predictors of poor clinical outcome of cryptococcal meningitis in HIV-infected patients. Int J STD AIDS. 2011;22(11):665–70. https://doi.org/10.1258/ijsa.2011.010538.
29. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 2010;10(11):791–802. https://doi.org/10.1016/S1473-3099(10)70170-5.
30. McCarty TP, Pappas PG. Invasive Candidiasis. Infect Dis Clin N Am. 2016;30(1):103–24. https://doi.org/10.1016/j.idc.2015.10.013.
31. Sánchez-Portocarrero J, Pérez-Cecilia E, Corral O, Romero-Vivas J, Picazo JJ. The central nervous system and infection by Candida species. Diagn Microbiol Infect Dis. 2000;37(3):169–79. https://doi.org/10.1016/S0732-8893(00)00140-1.
32. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2015;62(4):e1–e50. https://doi.org/10.1093/cid/civ933.
33. Parker JC, McCloskey JJ, Lee RS. Human cerebral candidosis – a postmortem evaluation of 19 patients. Hum Pathol. 1981;12(1):23–8. https://doi.org/10.1016/S0046-8177(81)80238-9.
34. Lanternier F, Mahdaviani SA, Barbati E, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species–induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol. 2015;135(6):1558–1568.e2. https://doi.org/10.1016/j.jaci.2014.12.1930.
35. Aristizabal N, Vagner B. Infections of the central nervous system by Candida. J Infect Dis Immun. 2011;3(5):79–84. https://doi.org/10.1097/00006123-199306000-00035.
36. Lyons JL, Thakur KT, Lee R, et al. Utility of measuring (1,3)-β-D-Glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection. J Clin Microbiol. 2015;53(1):319–22. https://doi.org/10.1128/JCM.02301-14.
37. Nakayama H, Shibuya K, Kimura M, Ueda M, Iwabuchi S. Histopathological study of candidal infection in the central nervous system. Jpn J Med Mycol. 2010;51(1):31–45. https://doi.org/10.3314/jjmm.51.31.
38. O'Brien D, Stevens NT, Lim CH, et al. Candida infection of the central nervous system following neurosurgery: a 12-year review. Acta Neurochir. 2011;153(6):1347–50. https://doi.org/10.1007/s00701-011-0990-9.
39. Gavino C, Cotter A, Lichtenstein D, et al. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. Clin Infect Dis. 2014;59(1):81–4. https://doi.org/10.1093/cid/ciu215.
40. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin N Am. 2016;30(1):207–27. https://doi.org/10.1016/j.idc.2015.10.009.
41. Wheat J, Myint T, Guo Y, et al. Central nervous system histoplasmosis. Medicine (Baltimore). 2018;97(13):e0245. https://doi.org/10.1097/MD.0000000000010245.
42. Schestatsky P, Chedid MF, Amaral OB, Unis G, Oliveira FM, Severo LC. Isolated central nervous system histoplasmosis in immunocompetent hosts: a series of 11 cases. Scand J Infect Dis. 2006;38(1):43–8. https://doi.org/10.1080/00365540500372895.
43. Estrada-Bellmann I, Camara-Lemarroy CR, Flores-Cantu H, Calderon-Hernandez HJ, Villareal-Velazquez HJ. Hemichorea in a patient with HIV-associated central nervous system histoplasmosis. Int J STD AIDS. 2016;27(1):75–7. https://doi.org/10.1177/0956462414564608.
44. Veeravagu A, Ludwig C, Camara-Quintana JQ, Jiang B, Lad N, Shuer L. Fungal infection of a ventriculoperitoneal shunt: Histoplasmosis diagnosis and treatment. World Neurosurg. 2013;80(1–2):222.e5–222.e13. https://doi.org/10.1016/j.wneu.2012.12.01.
45. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Infect Dis. 2005;40(6):844–52. https://doi.org/10.1086/427880.
46. Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol. 2014;24(3):217–30. https://doi.org/10.1007/s00062-014-0305-7.

47. Trofa D, Nosanchuk JD. Histoplasmosis of the central nervous system. J Neuro-Oncol. 2012;3(7):1–7. https://doi.org/10.4303/jnp/235594.
48. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25. https://doi.org/10.1086/521259.
49. Stockamp NW, Thompson GR. Coccidioidomycosis. Infect Dis Clin N Am. 2016;30(1):229–46. https://doi.org/10.1016/j.idc.2015.10.008.
50. Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. Emerg Infect Dis. 2017;23(2):308–11. https://doi.org/10.3201/eid2302.160505.
51. Goldstein EJC, Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006;42(1):103–7. https://doi.org/10.1086/497596.
52. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? Ann Intern Med. 1996;124(3):305–10. https://doi.org/10.7326/0003-4819-124-3-199602010-00004.
53. Kim MM, Vikram HR, Kusne S, Seville MT, Blair JE. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. Clin Infect Dis. 2011;53(11):1060–6. https://doi.org/10.1093/cid/cir642.
54. Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. Infect Dis Clin N Am. 2016;30(1):247–64. https://doi.org/10.1016/j.idc.2015.10.002.
55. Ho J, Fowler P, Heidari A, Johnson RH. Intrathecal amphotericin B: a 60-year experience in treating coccidioidal meningitis. Clin Infect Dis. 2017;64(4):519–24. https://doi.org/10.1093/cid/ciw794.
56. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(12):1801–12. https://doi.org/10.1086/588300.
57. Bariola JR, Perry P, Pappas PG, et al. Blastomycosis of the central nervous system: a multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis. 2010;50(6):797–804. https://doi.org/10.1086/650579.
58. Monteiro De Almeida S. Central nervous system paracoccidioidomycosis: an overview. Braz J Infect Dis. 2005;9(2):126–33. https://doi.org/10.1590/S1413-86702005000200002.
59. Le T, Huu Chi N, Kim Cuc NT, et al. AIDS-associated Penicillium marneffei infection of the central nervous system. Clin Infect Dis. 2010;51(12):1458–62. https://doi.org/10.1086/657400.
60. Bonifaz A, Tirado-Sánchez A. Cutaneous disseminated and extracutaneous sporotrichosis: current status of a complex disease. J Fungi. 2017;3(1):6. https://doi.org/10.3390/jof3010006.
61. Freitas DFS, Lima MA, De Almeida-Paes R, et al. Sporotrichosis in the central nervous system caused by Sporothrix brasiliensis. Clin Infect Dis. 2015;61(4):663–4. https://doi.org/10.1093/cid/civ361.
62. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and clinical features of invasive fungal infection in a US Health Care Network. Open Forum Infect Dis. 2018;5(8):2–9. https://doi.org/10.1093/ofid/ofy187.
63. Cadena J, Thompson GR, Patterson TF. Invasive aspergillosis: current strategies for diagnosis and management. Infect Dis Clin N Am. 2016;30(1):125–42. https://doi.org/10.1016/j.idc.2015.10.015.
64. Jantunen E, Volin L, Salonen O, et al. Central nervous system aspergillosis in allogeneic stem cell transplant recipients. Bone Marrow Transplant. 2003;31(3):191–6. https://doi.org/10.1038/sj.bmt.1703812.
65. Kourkoumpetis TK, Desalermos A, Muhammed M, Mylonakis E. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. Med (United States). 2012;91(6):328–36. https://doi.org/10.1097/MD.0b013e318274cd77.

66. Panda PK, Mavidi SK, Wig N, Garg A, Nalwa A, Sharma MC. Intracranial aspergillosis in an immunocompetent young woman. Mycopathologia. 2017;182(5–6):527–38. https://doi.org/10.1007/s11046-016-0106-4.
67. Antinori S, Corbellino M, Meroni L, et al. Aspergillus meningitis: a rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases. J Infect. 2013;66(3):218–38. https://doi.org/10.1016/j.jinf.2012.11.003.
68. Reinwald M, Buchheidt D, Hummel M, et al. Diagnostic performance of an aspergillus-specific nested PCR assay in cerebrospinal fluid samples of immunocompromised patients for detection of central nervous system aspergillosis. PLoS ONE. 2013;8(2):1–6. https://doi.org/10.1371/journal.pone.0056706.
69. Panackal AA, Williamson PR. Fungal infections of the central nervous system. Contin Lifelong Learn Neurol. 2015;21(3):1662–78. https://doi.org/10.1212/CON.0000000000000241.
70. Patterson TF, Thompson GR, Denning DW, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;63(4):433–42. https://doi.org/10.1093/cid/ciw444.
71. Schwartz S. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood. 2005;106(8):2641–5. https://doi.org/10.1182/blood-2005-02-0733.
72. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. Aspergillus Study Group. Medicine (Baltimore). 2000;79(4):250–60.
73. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection. 2011;39(3):201–10. https://doi.org/10.1007/s15010-011-0108-6.
74. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54(suppl 1):23–34. https://doi.org/10.1093/cid/cir866.
75. Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin N Am. 2016;30(1):143–63. https://doi.org/10.1016/j.idc.2015.10.011.
76. Malik AN, Bi WL, McCray B, Abedalthagafi M, Vaitkevicius H, Dunn IF. Isolated cerebral mucormycosis of the basal ganglia. Clin Neurol Neurosurg. 2014;124(9):102–5. https://doi.org/10.1016/j.clineuro.2014.06.022.
77. Palacios E, Rojas R, Rodulfa J, González-Toledo E. Magnetic resonance imaging in fungal infections of the brain. Top Magn Reson Imaging. 2014;23(3):199–212. https://doi.org/10.1097/RMR.0000000000000252014.
78. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20(S3):5–26. https://doi.org/10.1111/1469-0691.12371.
79. Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70(11):3116–23. https://doi.org/10.1093/jac/dkv236.
80. Spellberg B, Ibrahim AS, Chin-Hong PV, et al. The Deferasirox–AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012;67(3):715–22. https://doi.org/10.1093/jac/dkr375.
81. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47(3):364–71. https://doi.org/10.1086/589857.
82. Zuniga MG, Turner JH. Treatment outcomes in acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2014;22(3):242–8. https://doi.org/10.1097/MOO.0000000000000048.
83. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP. Breakthrough fungal infections in patients with leukemia receiving isavuconazole. Clin Infect Dis. 2018:1–10. https://doi.org/10.1093/cid/ciy406.

84. Vironneau P, Kania R, Morizot G, et al. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect. 2014;20(5):O336–9. https://doi.org/10.1111/1469-0691.12408.
85. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118(5):1216–24. https://doi.org/10.1182/blood-2011-03-316430.
86. Bhansali A, Bhadada S, Sharma A, et al. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. Postgrad Med J. 2004;80(949):670–4. https://doi.org/10.1136/pgmj.2003.016030.
87. Chowdhary A, Meis JF, Guarro J, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect. 2014;20(S3):47–75. https://doi.org/10.1111/1469-0691.12515.
88. Revankar SG, Sutton DA, Rinaldi MG. Primary central nervous system phaeohyphomycosis: a review of 101 cases. Clin Infect Dis. 2004;38(2):206–16. https://doi.org/10.1086/380635.
89. Kantarcioglu AS, Guarro J, De Hoog S, Apaydin H, Kiraz N. An updated comprehensive systematic review of Cladophialophora bantiana and analysis of epidemiology, clinical characteristics, and outcome of cerebral cases. Med Mycol. 2017;55(6):579–604. https://doi.org/10.1093/mmy/myw124.
90. Filizzola MJ, Martinez F, Rauf SJ. Phaeohyphomycosis of the central nervous system in immunocompetent hosts: report of a case and review of the literature. Int J Infect Dis. 2003;7(4):282–6. https://doi.org/10.1016/S1201-9712(03)90108-1.
91. Larone DH, Walsh TJ. Exserohilum rostratum: anatomy of a national outbreak of fungal meningitis. Clin Microbiol Newsl. 2013;35(23):185–93. https://doi.org/10.1016/j.clinmicnews.2013.11.001.
92. Revankar SG, Sutton DA. Melanized fungi in human disease. Clin Microbiol Rev. 2010;23(4):884–928. https://doi.org/10.1128/CMR.00019-10.
93. Katragkou A, Pana ZD, Perlin DS, Kontoyiannis DP, Walsh TJ, Roilides E. Exserohilum infections: review of 48 cases before the 2012 United States outbreak. Med Mycol. 2014;52(4):376–86. https://doi.org/10.1093/mmy/myt030.
94. Schwartz IS, Wiederhold NP, Hanson KE, Patterson TF, Sigler L. Blastomyces helicus, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in Western Canada and the United States. Clin Infect Dis. 2018:1–8. https://doi.org/10.1093/cid/ciy483.
95. Stott KE, Hope W. Pharmacokinetics–pharmacodynamics of antifungal agents in the central nervous system. Expert Opin Drug Metab Toxicol. 2018;14(8):803–15. https://doi.org/10.1080/17425255.2018.1492551.
96. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014;27(1):68–88. https://doi.org/10.1128/CMR.00046-13.

Chapter 11
Neurocysticercosis and Other CNS Helminthic Infections

M. B. Tanabe, M. Schilling, and A. C. White Jr.

The term helminth refers to multicellular organisms that are members of the animal kingdom. These include roundworms (phylum Nematoda), and flatworms (phylum Platyhelminthes). The latter includes the tapeworms (subphylum Cestoda) and the flukes (subphylum Trematoda). A wide range of helminths can cause central nervous system (CNS) infections. Globally, human helminth infections are extremely common, though less so in wealthy countries. However, even in non-endemic countries, helminths can cause serious infections, especially among immigrants and travelers. Table 11.1 summarizes the clinical presentation, diagnosis and treatment of all the helminthic CNS infections covered in this chapter.

M. B. Tanabe (✉)
Department of Medicine, Division of Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA
e-mail: MBTANABE@UMTB.EDU

M. Schilling
Department of Medicine, University of Texas Medical Branch, Galveston, TX, USA
e-mail: mtschill@UTMB.EDU

A. C. WhiteJr.
Department of Internal Medicine, Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA
e-mail: acwhite@UTMB.EDU

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_11

Table 11.1 Summary of helminthic CNS infection

	Organism	Clinical neurological presentation	Diagnostic methods	Treatment
Cestodes	Parenchymal NCC	Seizures, headaches	Single lesion: cystic or nodular enhancing lesion <2 cm in size Viable cysts: vesicular lesions with evidence of associated contrast enhancement and/or surrounding edema Calcified cysts: nodular calcifications <20 mm in diameter or with or without surrounding edema and/or contrast enhancement	Single: albendazole + steroids × 1 week + AEDs Viable cysts: 1–2 cysts: albendazole + steroids × 10–14 days + AEDs >2 cysts: albendazole + praziquantel + corticosteroids × 10–14 days + AEDs Calcified: no anti-parasitic therapy Only symptomatic with AEDs
	Ventricular NCC	Obstructive hydrocephalus	Cysts within the ventricles, obstructive or loculated hydrocephalus with disproportionate dilation of the ventricles	Non-adherent cysts: minimally invasive neuroendoscopy Adherent cysts: VP shunt followed by albendazole + steroids
	Subarachnoid NCC	Communicating hydrocephalus, meningitis, stroke	Cysts in the Sylvian fissure (giant cysticerci), in the basilar cistern or interhemispheric spaces. Strokes or meningitis without discrete cysts	Difficult to treat VP shunt followed by albendazole + steroids for 1+ years
	Spinal NCC	Radiculomyelopathy	Cysts within spinal subarachnoid space with or without evidence of inflammation/diffuse subarachnoid arachnoiditis	Surgical removal of cysts
	Ocular NCC	Impaired vision, ocular palsies	Cysts in the anterior chamber, vitreous humor, subretinal space, conjunctiva, or extraocular muscles. Subconjunctival cysts can be visible on eye surface	Surgical removal of cysts
	Echinococcus spp.	Mass lesion	Imaging showing complex cysts (single or multiple) with smooth borders. "Hydatid sand" Serology: blood	Surgical removal + albendazole
	Spirometra spp.	Seizures, mass lesion	Gold standard: visualization of the larva Imaging: lesions with irregular, patchy, serpentiginous patterns and surrounding edema Serology: blood or CSF	Surgical removal or sterotactic aspiration + prazinquatel

	Organism	Clinical neurological presentation	Diagnostic methods	Treatment
Nematodes	*Astrongylus cantonensis*	Eosinophilic meningitis	Gold standard: parasites in CSF via PCR Lumbar puncture with eosinophilia	Corticosteroids +/− albendazole
	Gnathostoma spinigerum	Eosinophilic meningitis, cranial neuropathies	Gold standard: parasite in tissues Lumbar puncture with eosinophilia Imaging: MRI with "migrating tracts"	Corticosteroids +/− albendazole
	Trichinella spirallis	Eosinophilic meningitis	Serology: blood Imaging: multiple ring enhancing or nodular lesions with calcifications	Corticosteroids +/− albendazole
	Strongyloides stercolaris	Bacterial meningitis	Gold standard: parasites in stool CSF with findings of GN meningitis Serology: blood	Ivermectin + antibiotics for bacterial CNS infection
	Toxocara spp.	Eosinophilic meningitis	Serology: CSF or blood	Corticosteroids + albendazole
	Baylisascaris procyonis	Eosinophilic meningitis	Serology: blood, vitreous fluid and CSF	Corticosteroids + albendazole
Trematodes	*Schistosoma spp.*	Stroke, seizures, myelopathy	Gold standard: eggs in biopsy from affected tissues Imaging: Acute: cerebral edema or atrophy. Chronic: tree like pattern with central linear enhancement surrounding by enhancing nodules Serology: FAST-ELISA	Praziquantel + corticosteroids
	Paragonimus spp.	Seizures, mass lesion	Gold standard: eggs in sputum, BAL or stool Serology: Blood and CSF	Praziquantel + corticosteroids

ICP increased intracranial pressure, *CSF* cerebrospinal fluid, *NCC* neurocysticercosis, *AMS* altered mental status, *AEDs* anti-epileptic drugs, *GN* gran negative bacteria

CNS Diseases Caused by Cestodes

Neurocysticercosis

Taenia solium is a cestode parasite that has two distinct morphologic forms. The intestinal tapeworm form is only found in humans and the cystic larval form that is found in both humans and pigs. Cysticercosis refers to infection by the larval form of *Taenia solium.* Neurocysticercosis refers to cysticercosis of the central nervous system. Neurocysticercosis is a major cause of seizures and other neurologic morbidity worldwide.

Epidemiology

Cysticercosis is endemic in most regions of Central and South America, Sub-Saharan Africa, and India. It is also endemic in parts of China, Southeast Asia, and Oceania. There are no good data on the global burden of disease, but somewhere between 8 and 50 million people are thought to have symptomatic infections. Cysticercosis is endemic in every region, in which there are pigs with access to human fecal material, and the prevalence is usually higher in rural or periurban areas. NCC has been clearly associated with seizures and epilepsy. In some endemic areas, the rate of epilepsy approaches 3%, with 25–40% of these cases having evidence of cysticercosis [1, 2]. A meta-analysis suggested that 29% of seizures in endemic regions are due to NCC [3]. Cases in non-endemic countries, such as United States, Europe, and the Persian Gulf are seen in the immigrant population. Even these areas occasionally note local transmission from tapeworm carriers. Reviews of the US Nationwide Inpatient Sample found an estimated 2000 hospitalizations per year related to neurocysticercosis [4, 5]. Using inpatient data alone largely underestimates burden of disease. For example, a study using Oregon database from 2010 to 2013 found as many new cases of NCC among outpatients as among inpatients [6]. Neurocysticercosis was documented in 2% of patients presenting to US emergency departments with seizures [7].

Life Cycle/Parasitology

The lifecycle of the *T. solium* includes two hosts. Pigs are the intermediate host. Cysticerci (cystic larvae) are found in the muscle of pigs. Humans develop infestation with tapeworm (termed taeniasis) if they ingest undercooked pork contaminated with *T. solium* cysticerci. Once ingested, the scolex evaginates and attaches to the intestine wall by hooks and suckers. Segments termed proglottids develop from the base of the scolex and form a long ribbon-like chain, which can reach up to a length of up to 30 ft. Mature proglottids are shed from the distal end and are off white in color, 0.5–1 cm wide, 1–2 cm long and 1–3 mm thick. The species can be

identified by noting 9–14 uterine branches in the terminal proglottids. Taeniasis is mostly asymptomatic. Both proglottids and microscopic ova are intermittently shed in stool. The ova are sticky and can be found under the fingernails of tapeworm carriers.

When pigs ingest ova or proglottids, the eggs hatch in the intestine of the pig and release invasive larvae called oncospheres. The oncospheres penetrate the intestinal mucosa using hooklets and proteases and enter the bloodstream. They travel through the blood to tissues, where they form cysticerci. Cysticerci appear in the muscle as thin-walled translucent oblong balloons, approximately 0.5–1 cm in diameter and 1–2 cm long.

Human cysticercosis follows ingestion of ova from a tapeworm carrier. Tapeworm carriers can infect themselves by ingestion of the ova or infect others around them. After ingesting the ova, oncospheres penetrate into the blood stream and travel to tissue such as muscle, brain and eyes. Most data suggest that cysticercosis is acquired by close contact usually within households. Note that cysticercosis is not acquired directly from eating pork. For example, cysticercosis has been noted in orthodox Jewish children in New York city (from domestic servants, who were tapeworm carriers) and among vegetarians in India.

Pathogenesis/Pathology

Tissue cysticerci develop over a period of weeks after ingestion of the ova. Mature cysticerci in the brain appear as translucent balloon-like structures, approximately 1–2 cm in diameter with an invaginated scolex appearing as an off-white opaque nodule attached to the side. The viable phase is usually asymptomatic and usually persists for a few years. Several parasite molecules have been shown to suppress the host inflammatory response. The cysticercus evades complement-mediated destruction by means of parasite paramyosin (which inhibits C1q), taeniastatin (which inhibits both classical and alternate pathways and may interfere with lymphocyte proliferation and macrophage function), and sulfated polysaccharides (which activate complement away from the parasite). Cysticerci also induce production of alternatively activated macrophages and prostaglandin, which downregulate the inflammatory response. Cysts remain viable for years but eventually lose the ability to evade the host response. The cyst is then attacked by a granulomatous inflammatory infiltrate composed of plasma cells, lymphocytes, macrophages and eosinophils. This response is associated with release of Th1 cytokines such as Interleukin-12, Interferon-y and Interleukin-2 [8, 9]. The walls of the cyst degenerates and is invaded by the inflammatory cells. As the host inflammation progresses, the cyst collapses leaving a residual granuloma. At this stage the parasite is no longer viable. Eventually, the granulomatous tissue is replaced by fibrosis and calcifications [10].

Neuroimaging studies using CT and MRI have noted similar findings to above described pathologic stages [11, 12]. Cysticerci appear as round, cystic lesions, typically 1–2 cm in diameter. The cyst fluid is often isodense with cerebral spinal fluid. The early inflammatory response causes the cyst wall to increase in density

and to enhance with contrast. As the cysticercus degenerates, cyst fluid increases in density from inflammatory cells. and eventually becomes fibrotic and collapses. Neuroimaging reveals focal enhancement, suggestive of granuloma formation. The final stage is defined by focal areas of dense calcification, typically several millimeters in diameter. Presence of brain calcifications has been associated with seizures [13–15].

Infection per se does not typically cause symptoms. The main clinical manifestation, seizures, is caused by the host inflammatory response. In most cases with seizures and cystic lesions are associated with signs of inflammation on neuroimaging studies (either edema or contrast enhancement). By contrast, asymptomatic lesions found incidentally at autopsy are not associated with significant inflammation. Among the inflammatory factors, the neuropeptide substance P is a critical mediator of seizures [16]. Seizures can also occur with calcified lesions. Some of the calcified cysticerci are associated with intermittent inflammation, likely due to granuloma break down and release of parasite antigens [17]. In addition, there is some evidence that fibrosis or hippocampal sclerosis associated with calcified lesions also lead to seizures.

Cysticerci in the ventricles do not typically present with seizures, but instead present with obstructive hydrocephalus. In most cases, this is due to mechanical obstruction of cerebrospinal fluid flow by cysticerci lodging in the ventricular outflow tracks (e.g. foramen of Monroe, Aqueduct of Sylvia, or foramena of Luschke and Magendie). The cysticerci are large and cannot pass readily through these narrowings (which are typically 1 mm in diameter).

Cysticerci in the basilar cisterns can also be associated with arachnoiditis. The arachnoiditis may lead to angiitis with small or large vessel strokes. The strokes are usually ischemic, but can be hemorrhagic. Additionally, chronic arachnoiditis may lead to CSF outflow obstruction and communicating hydrocephalus.

Clinical Manifestations and Classifications

NCC is a spectrum of diseases, with variable clinical presentations depending on the location of the lesions, viability of the parasite and the host response. NCC is divided into parenchymal and extraparenchymal NCC. In general, parenchymal NCC is associated with seizures or headache. Extraparenchymal NCC is associated with symptoms of elevated intracranial pressure such as headache, nausea, vomiting, dizziness, and altered mental status. The seizures can be focal, focal with generalization or generalized. Patients can present with a variety of other neurologic manifestations which include headaches, spinal radiculopathies, cerebral vascular accidents (lacunar infarcts, thrombotic or hemorrhagic strokes), visual changes, meningitis or mass lesions. NCC has been associated with neurocognitive deficits and decreased quality of life. One study suggests that learning disabilities are more commonly seen in infected children [18]. It is important to understand how to correctly classify cysticercosis in order to correctly diagnose and manage the disease.

Parenchymal Disease

Parenchymal lesions can be further subdivided into single enhancing lesion, cystic parenchymal lesions and calcified parenchymal lesions. Single enhancing lesion is the most common presentation in hospital-based series from the USA and India [19, 20]. This form is also referred to as solitary cysticercal granuloma. This stage represents the parasite in transition from viable to degenerating in response to host inflammation. Imaging studies may demonstrate a ring or focal area of enhancement, often with surrounding edema Fig. 11.1c. Patients typically present with one or more seizures and/or headaches. Symptoms such as fever, hilar or cervical adenopathy, or weight loss or focal neurologic findings suggest an alternative diagnosis such as tuberculosis, brain abscess or tumor.

Viable parenchymal cysticerci is the most common presentation in hospital-based series from Latin America [21]. In most cases, patients present with seizure and/or headache. On neuroimaging studies, they present with one or more cystic lesions (Fig. 11.1a, b). The cysticerci are typically round, 4–20 mm in diameter and have cyst fluid that is isodense with CSF. The cyst wall is thin (<1 mm) and may not be visible. The scolex when apparent, is a round or tubular mass 1–3 mm long attached to the cyst wall. It may be equal or more dense than brain parenchyma. Symptomatic lesions usually have associated contrast enhancement of the cyst wall or surrounding edema. This definition overlaps with single enhancing lesion.

Calcified parenchymal lesions are the most common radiographic abnormality seen on population-based studies in endemic areas [22, 23]. Figure 11.1f shows imaging finding of multiple calcified parenchymal lesions. Most of these lesions are asymptomatic. Those that are symptomatic are often found to have associated perilesional edema or enhancement. The edema is thought to be due to periodic breakdown of the granuloma leading to intermittent inflammation. Nash et al. prospectively followed a cohort of patients with calcifications and perilesional edema. They found that perilesional edema episodes were common and often associated with symptoms (most commonly seizures) that in some cases symptoms that were disabling [15]. Calcified parenchymal lesions may also be associated with hippocampal atrophy that likely predispose to recurrent seizures [24].

A minority of patients with parenchymal cysts present with numerous cysticerci and diffuse cerebral edema. Termed cysticercal encephalitis, this form of disease is the result of host inflammatory response to a large number of cysts in the brain parenchyma. This form has been more commonly reported in young females [25].

Extraparenchymal Disease

Extraparenchymal disease can be subdivided into ventricular, subarachnoid, spinal and ocular cysticerci. In general, extraparenchymal disease is associated with a worse prognosis than parenchymal disease. In ventricular NCC, cysticerci are found

in the ventricular cavity or attached to the choroid plexus. These comprise about 10–20% of NCC cases in hospital-based series [26]. Typically, symptoms develop when cysticerci block the ventricular outflow tracts, leading to symptoms of obstructive hydrocephalus and increased intracranial pressure, such as chronic headache, nausea, vomiting, altered mental status. Occasionally, patients can present with episodes of sudden loss of consciousness related to head movements, caused by intermittent obstruction of the third or fourth ventricle by mobile cysts. This is termed Brun's syndrome [27].

Subarachnoid neurocysticercosis refers to NCC involving the subarachnoid space of the basilar cisterns and/or Sylvian fissures. This term is typically not applied to those with cystic lesions in the gyri over the brain convexity. The latter group, while technically having subarachnoid neurocysticercosis, are grouped with parenchymal disease due to a similar clinical presentation, pathogenesis, and response to therapy. Basilar subarachnoid neurocysticercosis occurs in about 5% of hospitalized cases. Patients present with headaches, meningeal signs, hydrocephalus, vasculitis or stroke [28]. They also frequently have cysticerci in the brain parenchyma (presenting with seizures) or the ventricles (presenting with obstructive hydrocephalus). Cysticerci in the Sylvian fissures can enlarge up to 10 cm in diameter, termed giant cysticerci, since cyst growth is not limited by pressure from the brain parenchyma. This can present mass effect or midline shift. Cysticerci in the basilar cistern can be difficult to see on imaging studies. The cyst walls are thin and the cyst fluid is often isodense with cerebrospinal fluid. Chronic arachnoiditis may develop as a result of local inflammation, which may be seen as focal or diffuse meningeal enhancement, vasculitis or stroke. Cysticerci in the basilar cisterns are frequently associated with cyst involvement of the spine, which can sometimes be asymptomatic [29].

Spinal cysticerci occurs in approximately 1% of hospitalized cases [30]. It primarily involves the subarachnoid space with inflammatory changes and demyelinating changes in the nerve roots, which leads to radicular pain or myelopathy. Rarely, cysticerci can involve the spinal medulla, resembling a transverse myelitis.

Ocular cysticercosis occurs in approximately 1–3% of hospitalized cases [31, 32]. Involvement may include cysticerci in the anterior chamber, vitreous humor, subretinal space, conjunctiva or extraocular muscles. The latter leads to ocular palsies. Subconjunctival cysts may be visible on the surface of the eye. Symptoms of vitreal or subretinal disease include impaired vision, eye pain and diplopia. Ocular cysticercosis should be excluded by fundoscopic exam in all patients with NCC and direct visualization of the parasite is pathognomonic for diagnosis of cysticercosis [33].

Clinical cases with large number of cysticerci often include more than one of the above forms of NCC. The clinical presentation may reflect each location of the cysticerci.

Diagnosis

Recent guidelines for NCC management were publish that discuss proper diagnosis and management of NCC [33]. Del Brutto et al. recently released revised diagnostic criteria that has been validated with subarachnoid and ventricular cysticercosis [34, 35]. NCC should be suspected in patients with seizures and/or manifestations of elevated intracranial pressure in the setting of exposure. Diagnosis relies heavily on

neuroimaging. All patients with suspected NCC should undergo a thorough history and physical examination, with a focus on exposure history. Exposure history should include residence or prolonged exposure in an endemic area. Queries about access to sanitation throughout life, contact with pork-raising areas (especially among family or neighbors), or known contact with asymptomatic carrier can help calrify exposure. Since tapeworm carriers can infect themselves, patients should be asked about exposure to undercooked pork as well. History should include query about symptoms of disease that can present like NCC (e.g. fever, night sweats, weight loss would suggest TB). Examination should similarly look for evidence of mimics to NCC. For example, regional adenopathy could suggest TB or malignancy. A thorough neurologic examination is also important. Focal findings are unusually in patients with parenchymal or ventricular neurocysticercosis and would suggest other diagnoses. Ophthalmologic examination should be performed on all suspected patients to exclude ocular cysticercosis. As mentioned above, direct visualization of the parasite on fundoscopic exam is pathognomonic for NCC. Evaluation of suspected NCC should include neuroimaging with both non-contrast CT and MRI of the brain. Non-contrast CT is highly sensitive for identifying calcifications and demonstrates most parenchymal cysticerci, as well as cysticerci involvement of the eye and orbits [30, 36]. MRI is more sensitive at detecting small lesions, evaluating for degenerative change such as edema and/or enhancement surrounding calcified lesions, and visualizing the scolex within cysts [37, 38] (Fig. 11.1). MRI is also

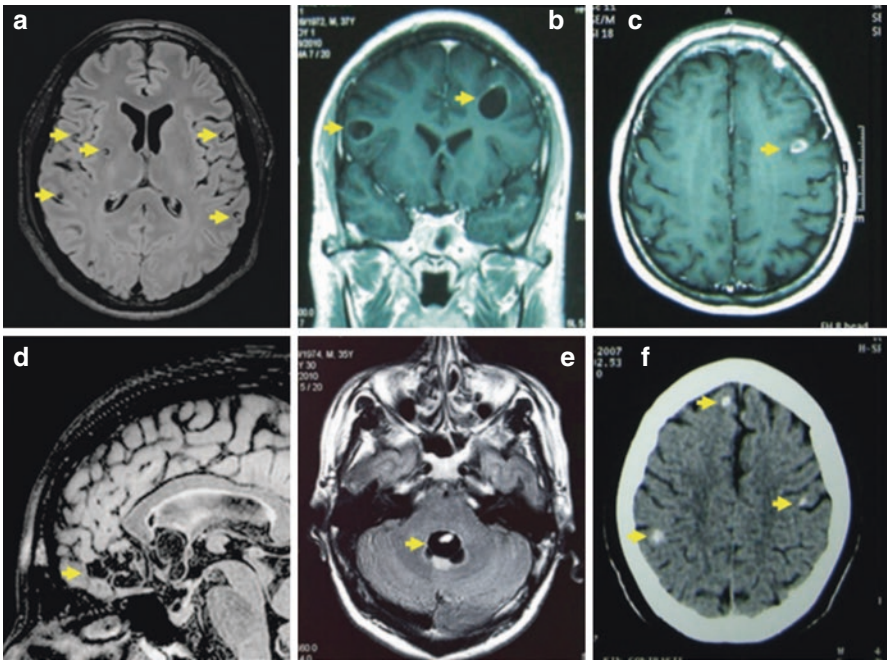


Fig. 11.1 (**a**–**f**) Stages of human neurocysticercosis**.** (**a**) FLAIR MRI sequence T1, showing Parenchymal viable cysts. (**c**) post contrast T1 MRI sequence, single enhancing lesion extensive basal. (**d**), FLAIR MRI sequence with subarachnoid neurocysticercosis in the anterior fossa. (**e**), FLAIR MRI sequence, viable cyst in the IV and intraparenchymal brain calcifications. FLAIR fluid-attenuated inversion recovery. (From White and Garcia [44], with permission)

better at identifying intraventricular and subarachnoid cysticerci, as viable cysticerci are isodense with CSF and difficult to detect on non-contrast CT. New three-dimensional MRI sequences such as Fast Imaging Employing Steady-State Acquisition (FIESTA), 3D constructive interference steady state (CISS) and balance fast field echo (BFFE) have improved the sensitivity and specificity of MRI for detecting cysticerci within the cerebrospinal fluid [39]. Patients found to have basal subarachnoid involvement should also undergo MRI of spine, as spinal involvement is often found in cases of basal subarachnoid cysticercosis [39].

Serologic testing can be important as a confirmatory test in patients with suspected NCC and is especially important in those whose diagnosis is uncertain based on clinical and radiographic findings. Antibody test of choice is the enzyme-linked immunoelectrotransfer blot assay, which detects antibodies to T. solium in serum through lentil lectin purified glycoprotein antigens [35, 40]. This assay is available from the United States Centers for Disease Control and Prevention (CDC) and some reference laboratories. Sensitivity of this immunoblot assay varies with form of NCC. Serum specimen is generally more sensitive that CSF. In those with multiple parenchymal cysticerci, subarachnoid or ventricular lesions, then sensitivity is nearly 100%. However, the sensitivity patients with only one lesion is as low as 50–60% [41]. Thus, a negative serologic test does not exclude NCC in patients with compatible clinical and radiographic findings [42]. There are only rare false positive results. However, positive antibody tests may be seen in individuals from endemic areas with previous infection and/or extraneural cysticercosis Enzyme-linked immunosorbent assays using crude antigen to detect antibody are not recommended given their poor sensitivity and specificity. Assays for parasite antigen in CSF, serum and urine have been developed. They are less sensitive than EITB but may be useful in tracking a response to treatment if available [43]. Brain biopsy is only rarely needed, but may be helpful when the diagnosis is not clear after imaging and serologic testing.

Management

Prior to initiation of therapy for cysticercosis, all patients should have fundoscopic exam performed to exclude intraocular neurocysticercosis and screen for papill-edema [44]. In those patients who are likely to require prolonged steroid course (greater than 1-month course), the Infectious Disease Society of America/American Society for Tropical Medicine and Hygiene guidelines recommend screening for latent tuberculosis infection prior to initiation of steroids. *Strongyloides stercoralis* is coendemic with *T. solium* in many areas. Thus, it is important to consider coinfection of Strongyloides and the risk of hyperinfection with corticosteroid use. There is controversy on whether the best management approach is screening or empiric therapy for *Strongyloides* coinfection. Given that diagnosis of *Strongyloides* infection is often difficult, some experts recommend empiric treatment with ivermectin [33].

Initial approach to treatment should focus on symptomatic treatment of increased intracranial pressure and seizures. Symptoms and signs of elevated intra-cranial

pressure include headache, nausea/vomiting, papilledema, and altered mental status. Management of diffuse cerebral edema consists of corticosteroids. In cases where elevated intra-cranial pressure is due to hydrocephalus, surgical intervention is required. For ventricular disease, the typical approach is removal of the obstructing cyst. Regardless of the cause of elevated intracranial hypertension, antiparasitic therapy is contraindicated and can only be considered after addressing the intracranial hypertension.

Seizures due to NCC generally respond well to monotherapy with first-line anti-epileptic drugs. Choice of anti-epileptic drugs should be guided by local availability, cost, drug interactions and potential side effects. Most cases have used phenytoin, carbamazepine or phenobarbital, however newer agents such as levetiracetam may be preferable to older agents given less drug interactions [33]. Risk factors for seizure recurrence after withdrawal of anti-epileptic drugs include persistent viable parenchymal cysts, abnormal EEG, residual calcifications, breakthrough seizures or frequent seizures, perilesional gliosis or hippocampal sclerosis on MRI. For the patient with a single enhancing lesion and no risk factors for recurrence, AEDs can be safely withdrawn if imaging studies are negative at 6 months Patients with more than one lesion should be seizure free for two or more years prior to considering anti-epileptic drugs are withdrawn, as is the case for idiopathic epilepsy [33, 45]. Patients with single enhancing lesions, with few seizures, no breakthrough seizures, and a negative MRI, can safely be tapered off anti-epileptic drugs after 6 months of treatment [33, 43].

Antiparasitic therapy is warranted for all patients with viable and/or degenerating parenchymal cysts on neuroimaging. Initiation of antiparasitic therapy is never an emergency and should be deferred until patient is stabilized. Increased intracranial pressure is a contra-indication to antiparasitic therapy. Studies have shown that use of antiparasitic medications hastens resolution of cysts and diminishes seizure risk [46]. However, antiparasitic therapy may transiently exacerbate neurologic symptoms due to inflammation caused by host response to the dying parasite. Adjunctive corticosteroids should be started prior to initiation of anti-parasitic therapy. This has been shown to be associated with fewer seizures [33, 47].

Patients with single enhancing lesions usually present with seizures and thus should be treated with anti-epileptic drugs. Recent meta-analyses suggest that albendazole (15 mg/kg/day in two divided doses taken with food) in combination with steroids slightly decreases seizure recurrence [47]. Therefore, the IDSA/ASTMH guidelines recommend a short 1-week course of albendazole and steroids in addition to antiepileptic drugs for these patients [33].

For viable parenchymal cysticercosis, two randomized control trials have shown more rapid radiographic resolution of cysts and fewer seizures when patient are treated with antiparasitic medications and corticosteroids [48, 49]. For patients with 1–2 cysticerci, there is no difference in response to monotherapy using albendazole when compared to combination with both albendazole and praziquantel. However, in those with >2 cystic lesions, significantly higher rates of resolution were seen with the combination of albendazole and praziquantel compared to albendazole alone [50, 51]. Based on this, albendazole alone (15 mg/kg/day in two divided doses

taken with food) is recommended for those with one to two cystic lesions, and combination albendazole with praziquantel (50 mg/kg/day in three divided doses) for those with more than two cystic lesions [33]. Duration of treatment is 10–14 days for viable parenchymal cystic lesions. Even with combination therapy, not all patients resolve their lesions. Thus, if parenchymal lesions persist on MRI 6 months after completion of the initial course of therapy, retreatment is recommended.

Calcified parenchymal lesions do not contain viable parasite. Thus, there is no indication for antiparasitic therapy. Calcified lesions can intermittently develop perilesional edema from host response that can serve as a focus for seizures. Anti-inflammatory medications such as high dose corticosteroids or methotrexate may help to control edema. However, some data suggest that steroid withdrawal may exacerbate perilesional edema [33, 52]. Currently only symptomatic therapy is routinely recommended for isolated calcified lesions.

There are limited data on optimal dosing of adjunctive corticosteroids. Commonly used doses include prednisone 1 mg/kg/day or dexamethasone 0.1 mg/kg/day (usually split into three daily doses) begun 1 day prior to antiparasitic therapy, continued for duration of antiparasitic therapy and followed by a rapid taper. Garcia et al. suggested that a higher, prolonged dose (dexamethasone 8 mg/day for 28 days followed by a taper vs. 6 mg/day for 10 days) had fewer seizure recurrences [53].

Currently, there is no controlled trial data on management of intraventricular NCC. Patients generally present with symptoms and signs of obstructive hydrocephalus. The presentation may vary from a mild chronic headache to severe acute coma. In those with stable hydrocephalus, management depends on whether cysts appear inflamed or adherent to the ventricular wall. In patients with non-adherent intraventricular cysticerci, treatment with minimally invasive neuroendoscopy has been associated with a favorable response, especially with cysticerci in the lateral and third ventricles [54]. Some experts have reported good response with neuroendoscopy for cysts in the fourth ventricle using an anterior approach. This approach is easier if the aqueduct is dilated by hydrocephalus. However, there is a high risk adverse outcomes with this approach given requirement to navigate through the aqueduct with adjacent critical brain structures [55–57]. IDSA/ASTMH guidelines recommend an individualized approach to cysts in the fourth ventricle depending on experience of the neuroendoscopist and the degree of dilation of the aqueduct. If the cysts can be completely removed with endoscopy, there is no indication for subsequent treatment with antiparasitic therapy [33]. Those with adherent cysts should be managed with CSF diversion, given high risk of hemorrhage with attempted removal of the cysts [33]. If patients undergo shunt placement alone, there is a high risk of shunt failure. There are some data that steroids and antiparasitic drugs may decrease the risk of subsequent shunt failure.

Subarachnoid NCC is a particularly severe form of the disease and is difficult to treat. Those patients that present with communicating hydrocephalus often require CSF diversion via VP shunt, followed by antiparasitic therapy and corticosteroids. Endoscopic removal of subarachnoid cysticerci via third ventriculostomy has been described in those without hydrocephalus but is unproven [54]. Subarachnoid cysts do not respond to short courses of antiparasitic therapy used for parenchymal

neurocysticercosis. Current guidelines recommend continuing anti-parasitic therapy until resolution of cysticerci on MRI, often requiring a year or more of treatment. Patients treated with longer than 2 weeks of albendazole require monitoring for hepatotoxicity and leukopenia. It is recommended to check blood counts and liver enzymes weekly for the first month and monthly thereafter. IDSA/ASTMH guidelines suggest that methotrexate can be used as a steroid-sparing agent after initial stabilization in those patients requiring prolonged courses of anti-inflammatory therapy [33, 58]. Nash et al. reported using etanercept as a steroid-sparing agent [59].

There is no evidence that management of NCC should be different in children than in adults. Dosing of therapy should be weight based [33]. Management of NCC during pregnancy presents challenges due to concerns about teratogenicity of the drugs. Those who have elevated intra-cranial pressure should be managed aggressively as is the case for non-pregnant patients. Generally, anti-parasitic therapy can be differed until after delivery.

Prevention

Prevention strategies should target each of the stages of transmission, including human tapeworm, porcine cysticercosis and reducing transmission between humans. Preventing human tapeworm infection can be done by eliminating human consumption of contaminated pork. This can be accomplished by inspection of pork for cysticerci, which can be visible in raw meat. Freezing or adequately cooking the meat also destroys the cysticerci. Transmission of porcine cysticercosis can be stopped by eliminating access of pigs to human feces via improved sanitation and confining pigs. A vaccine for porcine cysticercosis is commercially available in India. Use of the vaccine along with mass chemotherapy of pigs with oxfendazole, and treatment of tapeworm carriers can lead to elimination of transmission [60, 61].

Echinococcosis

Echinococcosis is a zoonosis caused by larval stages of *Echinococcus spp*. The parasites of the *Echinococcus granulosus* complex are responsible for cystic echinococcosis, whereas *Echinococcus multilocularis* causes alveolar echinococcosis [62, 63]. *Echinococcus granulosus*, formerly considered a single species, is now known to comprise a number of species and genotypes. Cystic echinococcus is endemic in South America, the Mediterranean region, Near and Middle East, East Africa and central Asia, including parts of China. Alveolar echinococcus is found in central and eastern Europe, central Asia, Alaska and Canada [62–64].

The definite hosts of *E granulosus* complex parasites are dog and other canines. The intermediate hosts are usually ruminants (sheep, cattle, goats, camels and pigs). The definite hosts of *E. multilocularis* are mainly foxes and wolves. Intermediate

hosts are rodents. Definite hosts acquire infection by ingesting viscera of intermediate hosts contaminated with cysts. The life cycle of both *Echinococcus spp.* are similar with exception of the lack of internal protoscolexes in *E. multilocularis*, spreading via budding of multiple internal vesicles that may spread hematogenously to other organs.

Humans acquire the infection by ingesting ova shed by definite hosts. After ingestion, the oncosphere (invasive larvae) is released. It penetrates the intestine and migrates through the bloodstream to other organs. *E. granulosus* complex has a predilection for the liver (66%) and lungs (25%). CNS involvement is only noted in 1–2% of cases, most frequently in children [65–67]. *E. multilocularis* also is found almost exclusively in the liver but CNS lesions usually present as a consequence of late metastatic disease.

Hepatic disease presents with symptoms resembling a hepatic malignancy with symptoms of mechanical compression. Ruptured cysts may present with eosinophilia, fever, pruritus, urticaria or anaphylaxis. In the CNS, echinococcosis presents as a mass lesion [66, 67]. Symptoms include headaches, visual changes, seizures, focal abnormalities or symptoms of increase intracranial pressure due to compression to adjacent structures. Infection in the spinal cord has predilection for thorax and presents with spinal compression.

CNS echinococcosis diagnosis is made via imaging studies. In the brain, the *E granulosus* complex cysts are well-defined single supratentorial spherical lesions with smooth borders, rare calcifications and minimal edema [66–69]. Most of them are found in the distribution of the middle cerebral artery. In contrast, *E. multilocularis* lesions are multiple, semisolid, multi-loculated with frequent calcification and edema. By MRI, the wall of *E granulosus* complex cysts has low signal intensity on T2 imaging in contrast to the high intensity fluid content. Protoscolices within the cyst ("Hydatid sand") are not as often seen with CNS cysts, but when found, are diagnostic (Fig. 11.2). Less common locations for the hydatid cysts include the pons, ventricles, subarachnoid spaces, cavernous sinus, cerebellum and skull. Serologic diagnostic testing via ELISA or IFA, is directed against Antigen 5 and Antigen B for CE, and Antigen Em2 and Antigen Em18 for AE [70, 71]. Both may cross react with *Taenia solium*. Sensitivity and specificity are not optimal for extrahepatic disease.

For CNS disease, surgical removal and adjunctive antiparasitic treatment with albendazole are the gold standard. Prolonged medical treatment is recommended for unresectable cases and for CNS *E. multilocularis,* as it presents as part of disseminated disease. At present time, there is no serological marker for therapy efficacy, as serology testing remains positive for years after therapy. Long-term follow-up relies on imaging and clinical symptoms.

Sparganosis

Sparganosis is a zoonosis caused by larvae of *Spirometra spp*. Humans are incidental hosts acquiring the disease through contact with intermediate or definite hosts via ingestion of undercooked or raw meat, poultices and larva-infected water [72,

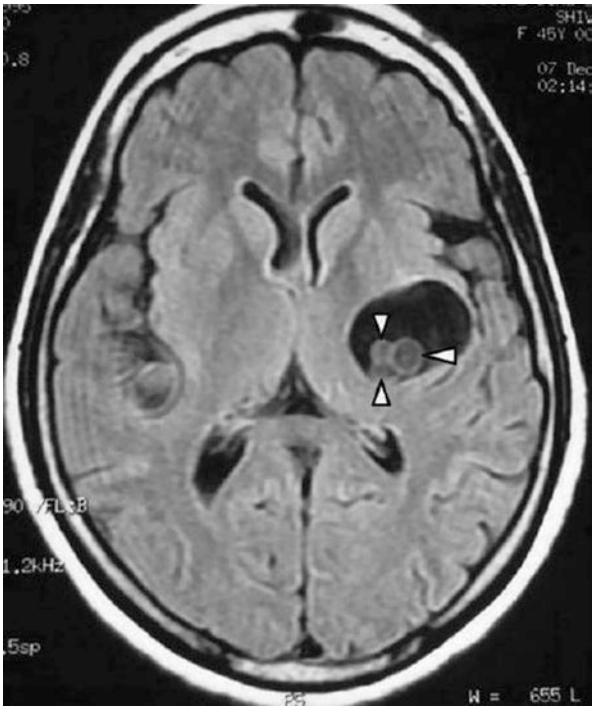


Fig. 11.2 CNS Echinococcosis with daughter cysts. MRI of brain T2 FLAIR sequence demonstrating large cyst in right frontoparietal area with daughter cysts within (arrows). (From Vidhate et al. [71], with permission)

73]. While *Spirometra* species are found worldwide, most human cases are due to *Spirometra erinaceieuropaei*, *Spirometra ranarum* or *Spirometra proliferum*, which are found in Southeast Asia, Japan, China and Korea.

The lifecycle consists of adult tapeworms living in the intestines of definite hosts (domestic and wild carnivores). Copepods are the first intermediate hosts. Frogs, snakes and fish are the second intermediate hosts [73]. After ingestion or contact with the infected hosts, the larvae can invade the human tissues of the eyes, brain, breast, spinal cord and subcutaneous tissues. Incubation period depends on the infection route (6–11 days up to several years). The proliferative form of sparganosis (*S. proliferum*), invades systemically via continuous branching and budding at different organs (lungs, abdomen, brain) which gradually expand over 5–25 years of infection [73].

Sparganosis presents as inflammatory nodules in the subcutaneous tissues and muscles, abdominal cavity, perirenal fat, breast, genitourinary system, lymphatics, lungs, eyes and CNS. Ocular sparganosis causes periorbital edema, proptosis, painful eye movements, ptosis, orbital cellulitis, corneal ulcerations and vision changes. Central nervous system disease, usually presents with seizures, hemiparesis and headache. It can also present as cerebral hemorrhages or obstructive hydrocephalus. When invading the spinal canal, symptoms are similar to tumors [73–76].

On neuroimaging studies, sparganosis presents as mainly supratentorial peripheral lesions with irregular, patchy, serpentigenous patterns and surrounding edema [73–76]. Brain lesions with live parasites may present with “worm-body sign”, “tunnel sign” and “migration signs” [73]. Intracerebral hemorrhage or hematoma can be present, representing capillary lesions along the path of the larvae.

Detection of specific IgG antibodies from peripheral blood or CSF by ELISA have sensitivities of 85.7–90% and specificities 87–97.5% [72]. Cross-reactivity has been noted with clonorchiasis, cysticercosis and paragonimiasis. Gold standard is direct visualization of the larva in lesion or biopsy. PCR provides a sensitive method to distinguish between subspecies.

Surgical removal or stereotactic aspiration of active nodules has been the standard for both diagnosis and treatment. Recent studies note cure with high dose praziquantel therapy (50–75 mg/kg/d for at least 14 days, repeated monthly), especially in patients considered unresectable [73, 74, 77].

CNS Diseases Caused by Nematodes

Angiostrongyliasis

Angiostrongyliasis or neuroangiostrongyliasis is a disease caused by *Astrongylus cantonensis*, the rat lungworm [78, 79]. It is the most common cause of eosinophilic meningitis. The disease was formerly considered to be mild and of low morbidity and mortality, however recent cases reported severe neurological presentations such as paralysis and hemorrhagic encephalitis with sequelae despite appropriate treatment [80, 81].

Neuroangiostrongyliasis is an emerging zoonosis. Although traditionally considered a disease of the Far East (SE Asia and Southern China), it is currently being reported in many subtropical and temperate regions (Pacific Islands including Hawaii, Egypt, Caribbean, South America, and the southern United States) [78, 82]. The definite hosts of *A. cantonensis* are rats. As the name implies, "the rat lungworm" adult form resides and deposits eggs on the pulmonary arteries and right ventricle of the heart of rats. The intermediate hosts (mollusks including freshwater snails, semi-slugs, and slugs) are infected via water contaminated with rat feces. In humans, the most common cause of infection is consumption of undercooked or raw infected mollusks, as well as vegetables and fruit juice contaminated by slime from the mollusk hosts. After ingestion, *A. cantonensis* penetrates the intestines and migrate via blood vessels, and infect the CNS and eyes [79, 83, 84].

Incubation period lasts between 1 and 35 days (mean 2 weeks) after consumption of infected material. Early presentation includes non-specific gastrointestinal symptoms that coincides with migration of parasite. CNS angiostrongyliasis present with severe headaches (95% cases), neck stiffness, nausea, photophobia, paresthesias and limb pain [79, 80, 83, 84]. Identification of migratory focal neurological signs, cranial nerve abnormalities or migratory hyperesthesias that do not follow dermatomal distribution should prompt the clinical suspicion of the disease [83]. Encephalitis and radiculomyelitis are less common presentations. Ocular angiostrongyliasis is rare and presents with diplopia, conjunctivitis, retinal abnormalities, blindness or symptoms compatible with optic neuritis [84].

Presumptive diagnosis is made based on clinical symptoms, lumbar puncture (LP) findings and exposure history. The hallmark of the diagnosis is eosinophilia in

the CSF studies, usually >10% of eosinophils. CSF shows variable leukocytosis (0–160 cells/mm), increase protein and normal glucose concentrations. Diagnosis is confirmed with presence of parasites in CSF. Real time PCR for *A. cantonensis* in the CSF is available for confirmation in endemic areas. Ophthalmologic examination may reveal the parasite in ocular angiostrongyliasis. Serologies are no longer recommended [83]. Peripheral blood eosinophilia can be present but does not aid in the diagnosis. CT and MRI are usually non-specific. They may demonstrate edema and ventricular dilation, leptomeningeal enhancement, subcortical white matter changes [84] (Fig. 11.3).

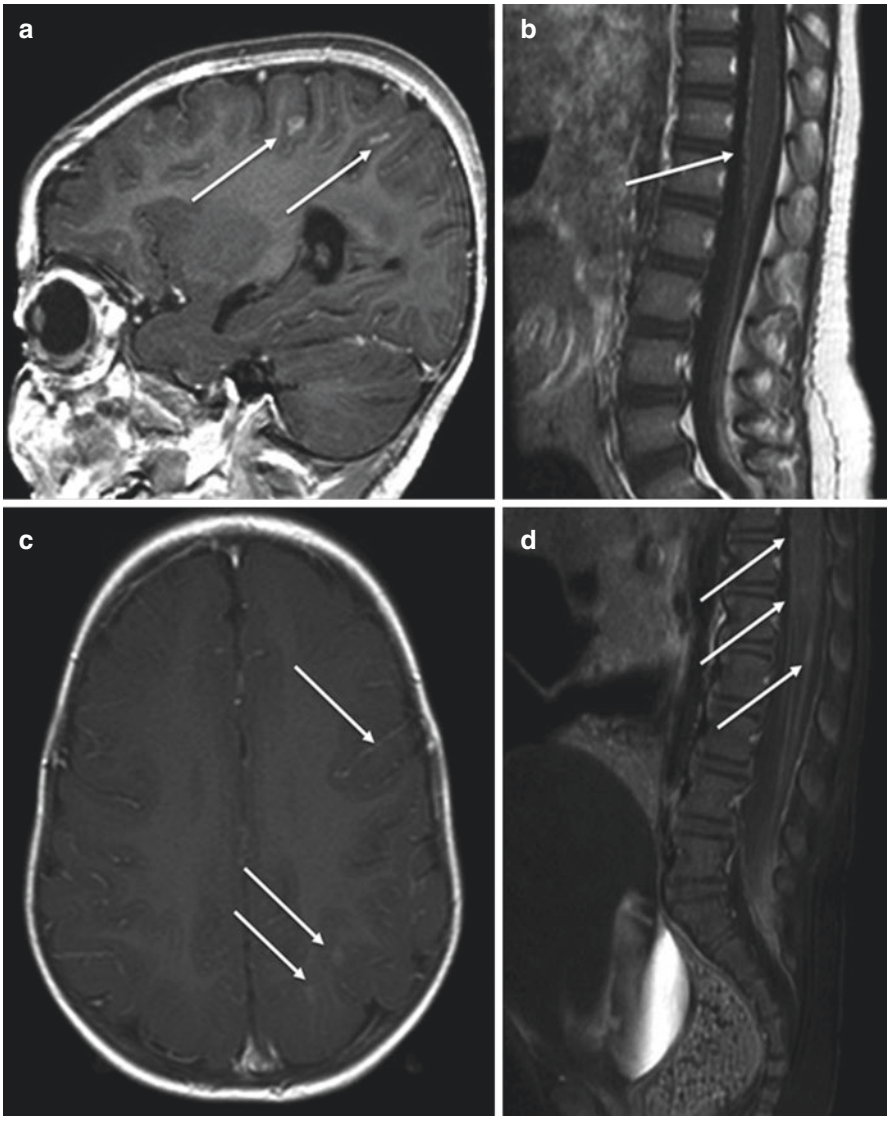


Fig. 11.3 (**a**–**d**) Cerebral and spinal cord Angiostrongylus infection

High dose corticosteroids have been accepted as standard therapy, due to improve outcomes in non-comatose patients [83]. Antihelminthic drug use is controversial. Albendazole may reduce the duration of symptoms when given along with corticosteroids [80, 83, 85]. For ocular angiostrongyliasis, treatment is surgical removal of the parasites via open surgery or laser mediated killing.

MRI scans of the brain with contrast, demonstrating patchy asymmetric liner and nodular enhancement (A-B). MRI of the lumbar spine with contrast, showing cauda equina enhancement (C) and multifocal nodular enhancement (D). Image courtesy of Foster MD et al. [86].

Gnathostomiasis

Gnathostomiasis is a human foodborne zoonotic disease. Of the five species pathogenic to humans, *G. spinigerum* is most common and the sole cause of human CNS symptomatology. The disease can be divided into cutaneous, ocular and visceral (includes neurognathostomiasis).

Gnathostomiasis is distributed in Southeast Asia, Latin America, and sub-Saharan Africa [87–89]. Neurognathostomiasis is confined to Thailand (>90% of cases) and Southeast Asia [87]. Gnathostomiasis can have a long incubation period and present in immigrants living in non-endemic countries.

Definite hosts depend on the species: domestic and wild cats and dogs (*G. spinigerum)*, domestic and wild pigs (*G. hispidum)*, wild boars (*G. doloresi)* and weasles (*G. nippodicum)*. First intermediate hosts are copepods, while second intermediate hosts are fish, frogs, snakes, eels, birds and fowls. In humans after ingestion of parasitized flesh, the larvae pass through the intestines and continue to migrate to different tissues such as subcutaneous tissues, skeletal muscles and CNS. The larva's size causes mechanical injury with subsequent inflammation and hemorrhage along their tract [90].

Nausea, vomiting, pruritus and upper abdominal pain occur 24–48 h after ingestion of the infected material. Afterwards, there is an incubation period of 3 weeks to 5 years. The typical presentation is a self-resolved recurrent migratory edema with eruptions, nodules, or abscesses in the subcutaneous tissues. With CNS involvement, symptoms are often more severe than neuroangiostrongyliasis. The classic presentation involves severe radicular pain with or without headache (from meningitis or subdural hemorrhage) lasting 1–5 days and subsequent paralysis of extremities or cranial nerves (most commonly CN VI) [87, 89]. Spinal cord disease presents in 55% of patients. In decreasing order of frequency, it causes radiculomyelitis, radiculomyeloencephalitis, meningitis, meningoencephalitis, subarachnoid and intraparenchymal hemorrhage. Reported mortality ranges from 7% to 12%, commonly due to involvement of vital areas of the brainstem, hemorrhage or secondary infections. Up to 46% of patients will have permanent neurological sequelae. Ocular gnathostomiasis presents as uveitis, iritis, hemorrhage, glaucoma, retinal disease [89].

Definitive diagnosis is by demonstration of the parasite in tissues from biopsy or removal from subcutaneous tissue. In CNS disease, recovery of larva is usually not possible [87]. Eosinophilia in peripheral blood can be found during the invasive stages. A hallmark finding is eosinophilic pleocytosis in CSF studies with 40–54% of eosinophilia. CSF studies show normal glucose, mildly elevated protein, elevated opening pressure and xanthochromia [87]. MRI may demonstrate tracts of migratory parasites often accompanied by intra-cranial hemorrhage [91]. In the spine, MRI shows hyperintense lesions associated with diffuse swelling of multiple segments of the spine. An immunoblot assay has nearly 100% specificity, but is not available in the Americas [87].

There are no randomized controlled trials of antihelminthic therapy for neurognathostomiasis. Reported cases have used 3–4 week course of albendazole therapy for CNS infection with variable results and frequent relapses [87]. Steroids are given for relief of brain and spinal edema. For ocular involvement, removal of the parasite is recommended.

Trichinellosis

Trichinellosis (or trichinosis) is a foodborne infection caused by *Trichinella* cysts. Infection has been detected worldwide except in Antarctica. Trichinellosis has been traditionally linked to undercooked or raw pork. However, due to improved sanitary controls in pork production, most cases are now associated with game meats (including wild boars in Europe and polar bears in North America) [92].

Most infections are asymptomatic. However, non-specific gastrointestinal symptoms can develop 2–10 days after the ingestion of infected tissue. After a week of infection, larvae begin to migrate to muscle and other tissues causing periorbital and facial edema, fever, myalgias, weakness, rashes and splinter hemorrhages. Fevers can persist for 1–3 weeks. Severe manifestations include myocarditis, pneumonitis and CNS involvement, usually occurring after 3 weeks post infection [93]. CNS involvement occurs in 10–20% of cases with mortality up to 50% of cases [88]. Patients present with delirium, encephalitis, meningitis, cranial neuropathies, paraplegia, cerebellar symptoms and focal symptoms corresponding to affection to different lobes of the brain [94].

Early diagnosis is challenging. Demonstration of *Trichinella* larvae cysts in affected tissue provides a definitive diagnosis. Peripheral eosinophilia is found in 90% of cases and elevated creatinine phosphokinase and lactate dehydrogenase are common. CSF is usually unremarkable. CT and MRI can demonstrate multiple ring enhancing or nodular lesions with calcifications. Detection of anti-Trichinella IgG (ELISA or IFA) using excretory-secretory antigens is the most commonly used serologic method with good sensitivity and specificity (100% and + 80% respectively) [95].

In severe cases, treatment with steroids is recommended to reduce inflammation. Mild disease is usually self-limited but symptoms may persist for 2–6 months. Most

experts recommend antiparasitic therapy with albendazole in severe cases, with longer course of antihelminthics in chronic infections [93]. Post exposure prophylaxis might be beneficial when given within 6 days of possible infection [96].

Strongyloidiasis

Strongyloides stercolaris is a common soil-transmitted helminthiasis worldwide. High burdens of disease are found in warm, humid areas of Central and South America, Sub-Saharan Africa and Southeast Asia [97, 98]. Humans acquire the infection primarily through skin contact with contaminated soil. Infectious filariform larvae penetrate the skin, migrate through the bloodstream to the lungs, penetrate the alveoli, migrate up the airway, and develop into female adult parasites in the wall of the small intestines. Larvae are released in the intestinal wall, penetrate into the lumen and are shed in stool. A portion of the larvae mature into invasive filariform larvae, which can reinvade through the colon or skin, leading to an autoinfectious cycle that can persist for decades. Patients with chronic infection typically have few symptoms. Some note non-specific gastrointestinal symptoms, pruritus, or larva currens (a fleeting, intermittent serpiginous rash below the waist area at the site of larval penetration) or they are noted to have eosinophilia. In a subset of patients, the autoinfection cycle accelerates, which can lead to hyperinfection, in which autoinfection escapes control by the host, causing massive parasite proliferation and symptomatic larval migration [97]. During this severe and even fatal process, mobile larvae can carry enteric bacteria during migration to sterile locations, causing polymicrobial bacteremia, meningitis and other types of infection. The main risk factors for severe disease and hyperinfection are treatment with corticosteroids, HTLV-1 infection, malnutrition, and other diseases that compromise neutrophil and eosinophil function [88, 97, 99, 100].

Hyperinfection can present with localized symptoms from larval migration (e.g. abdominal pain, pulmonary hemorrhage, asthma, or gastrointestinal bleeding) or with symptoms from bacterial superinfections. The latter can present with septic shock, vasculitis, DIC, pneumonia, and neurological complications [97, 99]. In the CNS, the most common presentations are meningitis or meningoencephalitis due to gram negative or other enteric bacteria. Other presentations are cerebritis, cerebral vasculitis, cranial nerve palsies, seizures and focal neurological deficits [99].

Definite diagnosis is made by demonstration of parasites in stool, bronchial aspirate/sputum, or duodenal aspirate [99]. PCR is the most sensitive test, but is not widely available [101]. Eosinophilia is common during chronic infection but unusual in severe cases. CSF studies are concordant with aseptic or bacterial meningitis [97]. Imaging is usually unremarkable but can show brain abscesses, vasculitis, focal hemorrhage and necrosis. Blood cultures can be positive in severe infections, usually due to polymicrobial enteric bacteremia. Serology (IgG) is useful in chronic infections with a sensitivity of 83–89% and specificity 97.2%, but has cross-reactions with filariasis and other helminths. PCR in the blood has shown to be unreliable for screening but may be use in confirmatory testing [102].

The recommended treatment is ivermectin, which is more effective than albendazole and has fewer side effects than thiabendazole [103]. Antibiotics are given if bacterial infections are found. Immunosuppression with corticosteroids should be discontinued or reduced if possible.

Toxocariasis

Toxocariasis is a global zoonotic helminthic disease caused by *Toxocara canis* and *T. cati* transmitted by dogs and cats respectively. Eggs shed by the definite hosts (dogs and cats respectively) and mature in the environment. When humans ingest the eggs, the larvae hatch in the intestines, penetrate the intestinal wall, and migrate through the blood stream to reach tissues including liver, lungs, heart, muscle, eyes and brain.

Most infections are asymptomatic, but clinical presentations can include visceral larva migrans, ocular larva migrans, and neurotoxocariasis [104, 105]. Visceral larval migrans is more common in children and is typically asymptomatic. Heavy infection may cause abdominal pain, anorexia, fever, myalgias, hepatomegaly, cough, and bronchospasm. Ocular larva migrans presents with unilateral vision loss, strabismus or eye pain [104]. CNS involvement (neurotoxocariosis) is rare with slightly over 100 cases reported. Neurologic disease presents as myelitis (60%), encephalitis (47%), eosinophilic meningitis (29%), or a combination of them [106, 107]. Diagnosis should be suspected in patients with history of exposure to animals, geophagia and eosinophilia. Imaging of the brain are usually unremarkable, but can show migratory tracts or focal enhancing lesions [107]. Antibodies against *Toxocara spp*. can be detected in serum or CSF [106]. ELISA for detection of antibodies against secreting-excreting antigens have varied sensitivities and specificities, with better performance when recombinant antigens are used [104, 108]. Serology confirmation is done via western blot.

Anti-inflammatory therapy with corticosteroids is the mainstay of therapy, especially with larvae in the eye or nervous system. In visceral larva migrans, antiparasitic treatment is aimed to avoid the larvae reaching the CNS or the eye [104]. Albendazole for 5 days is the treatment of choice for visceral larva migrants. Prolonged courses of albendazole (e.g. >3 weeks) have been used in neurotoxicariasis [106]. Mortality rate is estimated to be 6%, with frequent relapses.

Baylisascariasis

Baylisascariasis is a zoonosis caused by the raccoon roundworm *Baylisascaris procyonis,* which is endemic in North America, but has also been noted in Europe and Japan. While it can cause visceral and ocular larva migrans, most cases present with neurologic involvement [109, 110].

Raccoon latrines (areas for common defecation) are known to be the major source of infection. Humans are infected by ingesting eggs. Upon ingestion, the larvae penetrate the intestines and migrates to different tissues. The parasites and associated inflammation form necrotic linear tracks in the CNS tissues. Larvae can become stagnant and encapsulate in different tissues and organs causing granulomas.

In contrast to toxocariasis, human bayliscariasis typically presents with severe CNS disease. A prodrome of fever, ataxia, lethargy, somnolence or irritability precedes frank neurologic involvement. Fulminant eosinophilic meningoencephalitis presents with spasticity, hemi/quadriparesis, ocular or cranial nerve involvement, seizures, coma and death. Death was reported in 28% of cases, while survivors often suffer severe neurological sequelae.

Laboratory tests typically include peripheral eosinophilia. CSF shows pleocytosis with eosinophilia. Serology is usually positive in blood, vitreous fluid and CSF. ELISA, Immunoblot or IFA can be used for IgG against excretory-secretory antigens [110–112]. Imaging is non-specific, revealing atrophy and some periventricular and deep matter white changes.

Treatment should be started immediately and not wait for a definitive diagnosis. Treatment consists of high dose corticosteroids and albendazole (25–50 mg/kg/d for 20 days) [109, 110, 112, 113]. However, even with treatment, the prognosis is poor. Systemic steroids have been used in most of the CNS cases. Treatment with antihelminthics is also recommended after possible exposure.

CNS Diseases Caused by Trematodes

Schistosomiasis

Schistosomiasis, also known as blood fluke or bilharzia, is a water-borne disease caused by *Schistosoma spp*.. Intestinal schistosomiasis is caused by *Schistosoma mansoni, S. japonicum, S. S. mekongi* and *S. intercalatum*. Urogenital schistosomiasis is caused by *Schistosoma haematobium*. Neuroschistosomiasis is a severe infection in the CNS that can be caused by all subspecies except *intercalatum*.

Schistosomiasis is endemic in tropical and subtropical areas, in areas with inadequate sanitation and freshwater snail hosts. *Schistosoma spp*. have a distinct geographical distribution. *S. mansoni* (Africa, Middle East, Caribbean, South America), *S. japonicum* (China, Indonesia, the Phillipines), *S. mekongi* (Laos, Cambodia), *S. intercalatum* (central Africa), *S. haematobium* (Africa, Middle East). Humans are the definite hosts. Eggs are shed in the feces or urine of infected people and make their way into water. Miracidia released from the eggs infect freshwater snails, the intermediate hosts, which in turn release the cercariae (invasive larvae) into the water. When humans are exposed to contaminated water, the cercariae penetrate the human skin, transform into schistosomula, which migrate through the bloodstream and settle in veins [114–116]. *S. japonicum* usually localizes to the superior mesenteric veins, while *S. mansoni* is found the inferior mesenteric veins. *S. haematobium* resides in the venous plexus of the bladder as well as the rectal venules. *Schistosoma*

spp. lay eggs in the small venules, and are transported into the intestines and bladder by host granulomas. Patients may present with a popular rash at the time of infection (cercarial dermatitis), an acute illness 2–10 weeks later with fever, cough, rash, and hepatomegaly (Katayama fever), or with chronic disease from granulomas (portal hypertension, intestinal schistosomiasis, hematuria, renal failure).

Neuroschistosomiasis is thought to result from aberrant migration of the adult worms, but some cases may be due to aberrant migration of ova. Neuroschistosomiasis occurs in less than 5% of infected patients. *S. japonicum* and *S. mekongi* are associated with cerebral involvement, whereas *S. mansoni* and *S. haematobium* more often involve the spinal column. Cerebral involvement presents as acute schistosomal encephalopathy with fever, headache, diffuse encephalopathy and seizures [115, 117]. Most patients have peripheral eosinophilia. In the chronic phase, pseudotumor encephalic schistosomiasis presents as a slow growing tumor-like lesion causing headache, nystagmus, focal neurological signs, cranial nerve dysfunction and intracranial hypertension. Spinal cord schistosomiasis presents as a non-specific myelopathy or transverse myelitis, as well as flaccid paraplegia, arreflexia.

Definite diagnosis is made with demonstration of egg in biopsy from affected tissues. CSF may show some pleocytosis (lymphocyte predominant with or without eosinophilia), increased protein, normal glucose and increased intracranial pressures, but does not contain ova. Eosinophilia can be present in blood. Imaging can be compatible with cerebral edema or atrophy in acute schistosomal encephalopathy [115, 116]. In the chronic phase, a tree like pattern with central linear enhancement surrounding by enhancing nodules that correspond to granulomas surrounding ova [118]. Hydrocephalus and intracranial hemorrhages can also be present in chronic neuroschistosomiasis. In spinal cord disease, MRI shows enlargement of the spinal cord and thickening of the conus medullaris and cauda equina. Antibody tests can aid in diagnosis, but stool and urine microscopy is usually negative. FAST-ELISA is available for antibodies against *Schistosoma spp.*. Sensitivity is high for *S. mansoni* (99%) and *S. haematobium* (95%) but low for *S. japonicum* infections (−50%). Immunoblots are available for confirmation, using antigens that are species specific. PCR are available as lab-based testing, but they are not commercially available.

Medical therapy with praziquantel is the standard of care, duration and dosage depends on the species [117]. Treatment may need to be repeated after 2–4 weeks to kill all immature worms, as antihelminthics are only effective against mature forms. Prophylaxis with praziquantel via mass drug administration in endemic areas has proven to aid in elimination of the disease. In neuroschistosomiasis, adjunctive therapy with steroids is indicated.

Paragonimiasis

Paragonimiasis is a disease caused by flukes of the genus *Paragonimus.* The classic form involves the lungs, however extrapulmonary disease including CNS disease and subcutaneous nodules are common manifestations for some species (e.g.

Paragonimus skrjabini). Most of the world's burden of paragonimiasis has been noted in China (mainly *Paragonimus westermani* and *P skrjabini*). However, diseases is also endemic in Southeast and South Asia (mainly due to *Paragonimus heterotremus*), central and west Africa (*Paragonimus africanus*), the pacific coast of Latin America (*Paragonimus mexicana*), and Northern America (*Paragonimus kellicotti*) [119].

The adult parasites reside in the lungs of the definite hosts (dogs, pigs, cats, and wild carnivores); eggs shed into sputum are coughed, swallowed and excreted in the feces. The cycle requires two intermediate hosts, snails and crustaceans respectively. Humans, as accidental hosts, become infected by ingestion of raw or undercooked crustaceans. In humans, parasites penetrate the intestines and invade the pleura and lungs. Aberrant migration of the larvae can lead to infection of other tissues like the brain and subcutaneous tissues. This appears to be more common with some species (e.g. *P. skrjabini*) [120, 121].

Infection can be asymptomatic. Symptomatic patients present with chronic cough, chest pain, and/or hemoptysis which may be confused with pulmonary tuberculosis in endemic areas [122, 123]. Patients with cerebral infection can present with headache, mental confusion, behavioral and visual changes, seizures, focal motor signs due to tumor like lesions. Other presentations are meningitis, myelopathy, hydrocephalus and cerebral hemorrhage [121].

Nearly all cases have peripheral eosinophilia Definite diagnosis is made by demonstration of eggs in sputum, BAL or stool. Antibodies can be positive in blood and CSF by ELISA or immunoblot. Imaging findings are non-specific, presenting as low attenuating lesions or masses with edema and migration tracts.

Recommended treatment is praziquantel, second line is triclabendazole. Steroids are usually added in CNS paragonimiasis to decrease inflammation [121]. Acute disease has better prognosis than chronic cases when fibrosis and mechanical damage has already occurred.

References

1. Rajshekhar V, Raghava MV, Prabhakaran V, Oommen A, Muliyil J. Active epilepsy as an index of burden of neurocysticercosis in Vellore district, India. Neurology. 2006;67(12):2135–9.
2. Moyano LM, Saito M, Montano SM, Gonzalvez G, Olaya S, Ayvar V, et al. Neurocysticercosis as a cause of epilepsy and seizures in two community-based studies in a cysticercosis-endemic region in Peru. PLoS Negl Trop Dis. 2014;8(2):e2692.
3. Debacq G, Moyano LM, Garcia HH, Boumediene F, Marin B, Ngoungou EB, et al. Systematic review and meta-analysis estimating association of cysticercosis and neurocysticercosis with epilepsy. PLoS Negl Trop Dis. 2017;11(3):e0005153.
4. O'Neal SE, Flecker RH. Hospitalization frequency and charges for neurocysticercosis, United States, 2003–2012. Emerg Infect Dis. 2015;21(6):969–76.
5. O'Keefe KA, Eberhard ML, Shafir SC, Wilkins P, Ash LR, Sorvillo FJ. Cysticercosis-related hospitalizations in the United States, 1998–2011. Am J Trop Med Hyg. 2015;92(2):354–9.
6. Flecker RH, O'Neal SE, Townes JM. Evaluating healthcare claims for neurocysticercosis by using all-payer all-claims data, Oregon, 2010–2013. Emerg Infect Dis. 2016;22(12):2168–70.

7. Ong S, Talan DA, Moran GJ, Mower W, Newdow M, Tsang VC, et al. Neurocysticercosis in radiographically imaged seizure patients in U.S. emergency departments. Emerg Infect Dis. 2002;8(6):608–13.
8. Restrepo BI, Llaguno P, Sandoval MA, Enciso JA, Teale JM. Analysis of immune lesions in neurocysticercosis patients: central nervous system response to helminth appears Th1-like instead of Th2. J Neuroimmunol. 1998;89(1–2):64–72.
9. Restrepo BI, Alvarez JI, Castano JA, Arias LF, Restrepo M, Trujillo J, et al. Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. Infect Immun. 2001;69(7):4554–60.
10. Garcia HH, Nash TE, Del Brutto OH. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. Lancet Neurol. 2014;13(12):1202–15.
11. Kramer LD, Locke GE, Byrd SE, Daryabagi J. Cerebral cysticercosis: documentation of natural history with CT. Radiology. 1989;171(2):459–62.
12. Dumas JL, Visy JM, Belin C, Gaston A, Goldlust D, Dumas M. Parenchymal neurocysticercosis: follow-up and staging by MRI. Neuroradiology. 1997;39(1):12–8.
13. Nash TE, Pretell EJ, Lescano AG, Bustos JA, Gilman RH, Gonzalez AE, et al. Perilesional brain oedema and seizure activity in patients with calcified neurocysticercosis: a prospective cohort and nested case-control study. Lancet Neurol. 2008;7(12):1099–105.
14. Gupta RK, Awasthi R, Rathore RK, Verma A, Sahoo P, Paliwal VK, et al. Understanding epileptogenesis in calcified neurocysticercosis with perfusion MRI. Neurology. 2012;78(9):618–25.
15. Nash TE, Ware JM, Mahanty S. Natural history of patients with perilesional edema around Taenia solium calcified granulomas. J Infect Dis. 2017;215(7):1141–7.
16. Robinson P, Garza A, Weinstock J, Serpa JA, Goodman JC, Eckols KT, et al. Substance P causes seizures in neurocysticercosis. PLoS Pathog. 2012;8(2):e1002489.
17. Nash TE, Bartelt LA, Korpe PS, Lopes B, Houpt ER. Calcified neurocysticercus, perilesional edema, and histologic inflammation. Am J Trop Med Hyg. 2014;90(2):318–21.
18. Singhi P, Malhi P, Suthar R, Deo B, Khandelwal NK. Long-term cognitive outcome of children with parenchymal neurocysticercosis: a prospective observation study. J Child Neurol. 2018;33(7):468–73.
19. Garcia HH, Gonzalez AE, Rodriguez S, Tsang VC, Pretell EJ, Gonzales I, et al. Neurocysticercosis: unraveling the nature of the single cysticercal granuloma. Neurology. 2010;75(7):654–8.
20. Serpa JA, Graviss EA, Kass JS, White AC Jr. Neurocysticercosis in Houston, Texas: an update. Medicine (Baltimore). 2011;90(1):81–6.
21. Webb CM, White AC Jr. Update on the diagnosis and management of neurocysticercosis. Curr Infect Dis Rep. 2016;18(12):44.
22. Del Brutto OH, Arroyo G, Del Brutto VJ, Zambrano M, Garcia HH. On the relationship between calcified neurocysticercosis and epilepsy in an endemic village: a large-scale, computed tomography-based population study in rural Ecuador. Epilepsia. 2017;58(11):1955–61.
23. Moyano LM, O'Neal SE, Ayvar V, Gonzalvez G, Gamboa R, Vilchez P, et al. High prevalence of asymptomatic neurocysticercosis in an endemic rural community in Peru. PLoS Negl Trop Dis. 2016;10(12):e0005130.
24. Del Brutto OH, Issa NP, Salgado P, Del Brutto VJ, Zambrano M, Lama J, et al. The association between neurocysticercosis and hippocampal atrophy is related to age. Am J Trop Med Hyg. 2017;96(1):243–8.
25. Qavi A, Garg RK, Malhotra HS, Jain A, Kumar N, Malhotra KP, et al. Disseminated cysticercosis: clinical spectrum, toll-like receptor-4 gene polymorphisms and role of albendazole: a prospective follow-up of 60 cases with a review of 56 published cases. Medicine (Baltimore). 2016;95(39):e4882.
26. Rangel-Castilla L, Serpa JA, Gopinath SP, Graviss EA, Diaz-Marchan P, White AC Jr. Contemporary neurosurgical approaches to neurocysticercosis. Am J Trop Med Hyg. 2009;80(3):373–8.
27. Torres-Corzo J, Rodriguez-della Vecchia R, Rangel-Castilla L. Bruns syndrome caused by intraventricular neurocysticercosis treated using flexible endoscopy. J Neurosurg. 2006;104(5):746–8.

28. Marcin Sierra M, Arroyo M, Cadena Torres M, Ramirez Cruz N, Garcia Hernandez F, Taboada D, et al. Extraparenchymal neurocysticercosis: demographic, clinicoradiological, and inflammatory features. PLoS Negl Trop Dis. 2017;11(6):e0005646.
29. Callacondo D, Garcia HH, Gonzales I, Escalante D, Nash TE. High frequency of spinal involvement in patients with basal subarachnoid neurocysticercosis. Neurology. 2012;78(18):1394–400.
30. Alsina GA, Johnson JP, McBride DQ, Rhoten PR, Mehringer CM, Stokes JK. Spinal neurocysticercosis. Neurosurg Focus. 2002;12(6):e8.
31. Pushker N, Bajaj MS, Chandra M, Neena. Ocular and orbital cysticercosis. Acta Ophthalmol Scand. 2001;79(4):408–13.
32. Rath S, Honavar SG, Naik M, Anand R, Agarwal B, Krishnaiah S, et al. Orbital cysticercosis: clinical manifestations, diagnosis, management, and outcome. Ophthalmology. 2010;117(3):600–5, 5.e1.
33. White AC, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2018;98(4):945–66.
34. Bustos JA, Garcia HH, Del Brutto OH. Reliability of diagnostic criteria for neurocysticercosis for patients with ventricular cystic lesions or granulomas: a systematic review. Am J Trop Med Hyg. 2017;97(3):653–7.
35. Del Brutto OH, Nash TE, White AC Jr, Rajshekhar V, Wilkins PP, Singh G, et al. Revised diagnostic criteria for neurocysticercosis. J Neurol Sci. 2017;372:202–10.
36. Sharma T, Sinha S, Shah N, Gopal L, Shanmugam MP, Bhende P, et al. Intraocular cysticercosis: clinical characteristics and visual outcome after vitreoretinal surgery. Ophthalmology. 2003;110(5):996–1004.
37. Lerner A, Shiroishi MS, Zee CS, Law M, Go JL. Imaging of neurocysticercosis. Neuroimaging Clin N Am. 2012;22(4):659–76.
38. do Amaral LL, Ferreira RM, da Rocha AJ, Ferreira NP. Neurocysticercosis: evaluation with advanced magnetic resonance techniques and atypical forms. Top Magn Reson Imaging. 2005;16(2):127–44.
39. Carrillo Mezo R, Lara Garcia J, Arroyo M, Fleury A. Relevance of 3D magnetic resonance imaging sequences in diagnosing basal subarachnoid neurocysticercosis. Acta Trop. 2015;152:60–5.
40. Tsang VC, Brand JA, Boyer AE. An enzyme-linked immunoelectrotransfer blot assay and glycoprotein antigens for diagnosing human cysticercosis (Taenia solium). J Infect Dis. 1989;159(1):50–9.
41. Wilson M, Bryan RT, Fried JA, Ware DA, Schantz PM, Pilcher JB, et al. Clinical evaluation of the cysticercosis enzyme-linked immunoelectrotransfer blot in patients with neurocysticercosis. J Infect Dis. 1991;164(5):1007–9.
42. Garcia HH, Gilman RH, Catacora M, Verastegui M, Gonzalez AE, Tsang VC. Serologic evolution of neurocysticercosis patients after antiparasitic therapy. Cysticercosis Working Group in Peru. J Infect Dis. 1997;175(2):486–9.
43. Gonzalez AE, Bustos JA, Garcia HH, Rodriguez S, Zimic M, Castillo Y, et al. Successful antiparasitic treatment for cysticercosis is associated with a fast and marked reduction of circulating antigen levels in a naturally infected pig model. Am J Trop Med Hyg. 2015;93(6):1305–10.
44. White AC Jr, Garcia HH. Updates on the management of neurocysticercosis. Curr Opin Infect Dis. 2018;31(5):377–82.
45. Bustos JA, Garcia HH, Del Brutto OH. Antiepileptic drug therapy and recommendations for withdrawal in patients with seizures and epilepsy due to neurocysticercosis. Expert Rev Neurother. 2016;16(9):1079–85.
46. Garcia HH, Evans CA, Nash TE, Takayanagui OM, White AC Jr, Botero D, et al. Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev. 2002;15(4):747–56.
47. Zhao BC, Jiang HY, Ma WY, Jin DD, Li HM, Lu H, et al. Albendazole and corticosteroids for the treatment of solitary cysticercus granuloma: a network meta-analysis. PLoS Negl Trop Dis. 2016;10(2):e0004418.

48. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med. 2004;350(3):249–58.
49. Romo ML, Wyka K, Carpio A, Leslie D, Andrews H, Bagiella E, et al. The effect of albendazole treatment on seizure outcomes in patients with symptomatic neurocysticercosis. Trans R Soc Trop Med Hyg. 2015;109(11):738–46.
50. Garcia HH, Lescano AG, Gonzales I, Bustos JA, Pretell EJ, Horton J, et al. Cysticidal efficacy of combined treatment with praziquantel and albendazole for parenchymal brain cysticercosis. Clin Infect Dis. 2016;62(11):1375–9.
51. Garcia HH, Gonzales I, Lescano AG, Bustos JA, Zimic M, Escalante D, et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. Lancet Infect Dis. 2014;14(8):687–95.
52. Mejia R, Nash TE. Corticosteroid withdrawal precipitates perilesional edema around calcified Taenia solium cysts. Am J Trop Med Hyg. 2013;89(5):919–23.
53. Garcia HH, Gonzales I, Lescano AG, Bustos JA, Pretell EJ, Saavedra H, et al. Enhanced steroid dosing reduces seizures during antiparasitic treatment for cysticercosis and early after. Epilepsia. 2014;55(9):1452–9.
54. Proano JV, Torres-Corzo J, Rodriguez-Della Vecchia R, Guizar-Sahagun G, Rangel-Castilla L. Intraventricular and subarachnoid basal cisterns neurocysticercosis: a comparative study between traditional treatment versus neuroendoscopic surgery. Childs Nerv Syst. 2009;25(11):1467–75.
55. Chen G, Xiao Q, Zheng J, Wu J, Ao Q, Liu Y. Endoscopic transaqueductal removal of fourth ventricular neurocysticercosis: report of three cases. Turk Neurosurg. 2015;25(3):488–92.
56. Kaif M, Husain M, Ojha BK. Endoscopic management of intraventricular neurocysticercosis. Turk Neurosurg. 2019;29(1):59–65.
57. Nash TE, Ware JM, Mahanty S. Intraventricular neurocysticercosis: experience and long-term outcome from a tertiary referral center in the United States. Am J Trop Med Hyg. 2018;98(6):1755–62.
58. White AC. Controlling the host response in neurocysticercosis. Am J Trop Med Hyg. 2019;100(3):483–4.
59. Nash TE, Ware JM, Coyle CM, Mahanty S. Etanercept to control inflammation in the treatment of complicated neurocysticercosis. Am J Trop Med Hyg. 2019;100(3):609–16.
60. Okello AL, Thomas L, Inthavong P, Ash A, Khamlome B, Keokamphet C, et al. Assessing the impact of a joint human-porcine intervention package for Taenia solium control: results of a pilot study from northern Lao PDR. Acta Trop. 2016;159:185–91.
61. Garcia HH, Gonzalez AE, Tsang VC, O'Neal SE, Llanos-Zavalaga F, Gonzalvez G, et al. Elimination of Taenia solium transmission in Northern Peru. N Engl J Med. 2016;374(24):2335–44.
62. Kern P, Menezes da Silva A, Akhan O, Müllhaupt B, Vizcaychipi KA, Budke C, et al. The Echinococcoses: diagnosis, clinical management and burden of disease. Adv Parasitol. 2017;96:259–369.
63. Wen H, Vuitton L, Tuxun T, Li J, Vuitton DA, Zhang W, et al. Echinococcosis: advances in the 21st century. Clin Microbiol Rev. 2019;32(2):e00075–18.
64. Brunetti E, Kern P, Vuitton DA, WHO-IWGE WPft. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16.
65. Luo K, Luo DH, Zhang TR, Wen H. Primary intracranial and spinal hydatidosis: a retrospective study of 21 cases. Pathog Glob Health. 2013;107(2):47–51.
66. Altinörs N, Bavbek M, Caner HH, Erdogan B. Central nervous system hydatidosis in Turkey: a cooperative study and literature survey analysis of 458 cases. J Neurosurg. 2000;93(1):1–8.
67. Stojkovic M, Junghanss T. Cystic and alveolar echinococcosis. Handb Clin Neurol. 2013;114:327–34.
68. Luo X, Jedlicka SS, Jellison KL. Role of wall shear stress in Cryptosporidium parvum Oocyst attachment to environmental biofilms. Appl Environ Microbiol. 2017;83(24):e01533–17.
69. Mohindra S, Savardekar A, Gupta R, Tripathi M, Rane S. Varied types of intracranial hydatid cysts: radiological features and management techniques. Acta Neurochir. 2012;154(1):165–72.

70. Pagnozzi D, Addis MF, Biosa G, Roggio AM, Tedde V, Mariconti M, et al. Diagnostic accuracy of antigen 5-based ELISAs for human cystic echinococcosis. PLoS Negl Trop Dis. 2016;10:e0004585.
71. Vidhate MR, Singh D, Sharma P, Singh MK. Cerebral hydatid cyst showing pathognomonic daughter cysts. Ann Indian Acad Neurol. 2011;14:217–8.
72. Kim JG, Ahn CS, Sohn WM, Nawa Y, Kong Y. Human sparganosis in Korea. J Korean Med Sci. 2018;33(44):e273.
73. Liu Q, Li MW, Wang ZD, Zhao GH, Zhu XQ. Human sparganosis, a neglected food borne zoonosis. Lancet Infect Dis. 2015;15(10):1226–35.
74. Hong D, Xie H, Wan H, An N, Xu C, Zhang J. Efficacy comparison between long-term high-dose praziquantel and surgical therapy for cerebral sparganosis: a multicenter retrospective cohort study. PLoS Negl Trop Dis. 2018;12(10):e0006918.
75. Liao H, Li D, Zhou B, Liu J, Li Y, Liu H, et al. Imaging characteristics of cerebral sparganosis with live worms. J Neuroradiol. 2016;43(6):378–83.
76. Yu Y, Shen J, Yuan Z, Xia Z, Gao F, Jiang L, et al. Cerebral sparganosis in children: epidemiologic and radiologic characteristics and treatment outcomes: a report of 9 cases. World Neurosurg. 2016;89:153–8.
77. Zhang P, Zou Y, Yu FX, Wang Z, Lv H, Liu XH, et al. Follow-up study of high-dose praziquantel therapy for cerebral sparganosis. PLoS Negl Trop Dis. 2019;13(1):e0007018.
78. Barratt J, Chan D, Sandaradura I, Malik R, Spielman D, Lee R, et al. Angiostrongylus cantonensis: a review of its distribution, molecular biology and clinical significance as a human pathogen. Parasitology. 2016;143(9):1087–118.
79. Wang QP, Lai DH, Zhu XQ, Chen XG, Lun ZR. Human angiostrongyliasis. Lancet Infect Dis. 2008;8(10):621–30.
80. Ansdell V, Wattanagoon Y. Angiostrongylus cantonensis in travelers: clinical manifestations, diagnosis, and treatment. Curr Opin Infect Dis. 2018;31(5):399–408.
81. McAuliffe L, Fortin Ensign S, Larson D, Bavaro M, Yetto J, Cathey M, et al. Severe CNS angiostrongyliasis in a young marine: a case report and literature review. Lancet Infect Dis. 2019; 19(4): e132–e142.
82. Liu EW, Schwartz BS, Hysmith ND, DeVincenzo JP, Larson DT, Maves RC, et al. Rat lungworm infection associated with central nervous system disease – eight U.S. states, January 2011–January 2017. MMWR Morb Mortal Wkly Rep. 2018;67(30):825–8.
83. Clinical Subcommittee of the Hawaii Governor's Joint Task Force on Rat Lungworm Disease. Aug 29, 2018.
84. Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Trop. 2015;141(Pt A):46–53.
85. Jitpimolmard S, Sawanyawisuth K, Morakote N, Vejjajiva A, Puntumetakul M, Sanchaisuriya K, et al. Albendazole therapy for eosinophilic meningitis caused by Angiostrongylus cantonensis. Parasitol Res. 2007;100(6):1293–6.
86. Foster CE, Nicholson EG, Chun AC, Gharfeh M, Anvari S, Seeborg FO, et al. Angiostrongylus cantonensis infection: a cause of fever of unknown origin in pediatric patients. Clin Infect Dis. 2016;63(11):1475–8.
87. Katchanov J, Sawanyawisuth K, Chotmongkol V, Nawa Y. Neurognathostomiasis, a neglected parasitosis of the central nervous system. Emerg Infect Dis. 2011;17:1174–80.
88. Dzikowiec M, Goralska K, Blaszkowska J. Neuroinvasions caused by parasites. Ann Parasitol. 2017;63(4):243–53.
89. Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. Clin Microbiol Rev. 2009;22:484–92.
90. Sawanyawisuth K, Chlebicki MP, Pratt E, Kanpittaya J, Intapan PM. Sequential imaging studies of cerebral gnathostomiasis with subdural hemorrhage as its complication. Trans R Soc Trop Med Hyg. 2009;103(1):102–4.
91. Kanpittaya J, Sawanyawisuth K, Intapan PM, Khotsri P, Chotmongkol V, Maleewong W. A comparative study of neuroimaging features between human neuro-gnathostomiasis and angiostrongyliasis. Neurol Sci. 2012;33(4):893–8.

92. Rostami A, Gamble HR, Dupouy-Camet J, Khazan H, Bruschi F. Meat sources of infection for outbreaks of human trichinellosis. Food Microbiol. 2017;64:65–71.
93. Gottstein B, Pozio E, Nöckler K. Epidemiology, diagnosis, treatment, and control of trichinellosis. Clin Microbiol Rev. 2009;22(1):127–45.
94. Neghina R, Neghina AM, Marincu I, Iacobiciu I. Reviews on trichinellosis (II): neurological involvement. Foodborne Pathog Dis. 2011;8(5):579–85.
95. Taher EE, Meabed EMH, El Akkad DMH, Kamel NO, Sabry MA. Modified dot-ELISA for diagnosis of human trichinellosis. Exp Parasitol. 2017;177:40–6.
96. Faber M, Schink S, Mayer-Scholl A, Ziesch C, Schönfelder R, Wichmann-Schauer H, et al. Outbreak of trichinellosis due to wild boar meat and evaluation of the effectiveness of post exposure prophylaxis, Germany, 2013. Clin Infect Dis. 2015;60(12):e98–e104.
97. Krolewiecki A, Nutman TB. Strongyloidiasis: a neglected tropical disease. Infect Dis Clin N Am. 2019;33(1):135–51.
98. Schär F, Trostdorf U, Giardina F, Khieu V, Muth S, Marti H, et al. Strongyloides stercoralis: global distribution and risk factors. PLoS Negl Trop Dis. 2013;7(7):e2288.
99. Woll F, Gotuzzo E, Montes M. Strongyloides stercoralis infection complicating the central nervous system. Handb Clin Neurol. 2013;114:229–34.
100. Montes M, Sawhney C, Barros N. Strongyloides stercoralis: there but not seen. Curr Opin Infect Dis. 2010;23(5):500–4.
101. Formenti F, La Marca G, Perandin F, Pajola B, Romano M, Santucci B, et al. A diagnostic study comparing conventional and real-time PCR for Strongyloides stercoralis on urine and on faecal samples. Acta Trop. 2019;190:284–7.
102. Buonfrate D, Requena-Mendez A, Angheben A, Cinquini M, Cruciani M, Fittipaldo A, et al. Accuracy of molecular biology techniques for the diagnosis of Strongyloides stercoralis infection-a systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(2):e0006229.
103. Henriquez-Camacho C, Gotuzzo E, Echevarria J, White AC Jr, Terashima A, Samalvides F, et al. Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection. Cochrane Database Syst Rev. 2016;18(1):Cd007745.
104. Ma G, Holland CV, Wang T, Hofmann A, Fan CK, Maizels RM, et al. Human toxocariasis. Lancet Infect Dis. 2018;18(1):e14–24.
105. Moreira GM, Telmo Pde L, Mendonca M, Moreira AN, McBride AJ, Scaini CJ, et al. Human toxocariasis: current advances in diagnostics, treatment, and interventions. Trends Parasitol. 2014;30(9):456–64.
106. Deshayes S, Bonhomme J, de La Blanchardiere A. Neurotoxocariasis: a systematic literature review. Infection. 2016;44(5):565–74.
107. Sánchez SS, García HH, Nicoletti A. Clinical and magnetic resonance imaging findings of neurotoxocariasis. Front Neurol. 2018;9:53.
108. LMD S, Magalhaes CG, Telmo PL, Cerqueira MP, Donassolo RA, FPL L, et al. Sensitivity and specificity of recombinant proteins in Toxocara spp. for serodiagnosis in humans: differences in adult and child populations. PLoS ONE. 2018;13(12):e0208991.
109. Kazacos KR, Jelicks LA, Tanowitz HB. Baylisascaris larva migrans. Handb Clin Neurol. 2013;114:251–62.
110. Graeff-Teixeira C, Morassutti AL, Kazacos KR. Update on baylisascariasis, a highly pathogenic zoonotic infection. Clin Microbiol Rev. 2016;29(2):375–99.
111. Rascoe LN, Santamaria C, Handali S, Dangoudoubiyam S, Kazacos KR, Wilkins PP, et al. Interlaboratory optimization and evaluation of a serological assay for diagnosis of human baylisascariasis. Clin Vaccine Immunol. 2013;20(11):1758–63.
112. Sircar AD, Abanyie F, Blumberg D, Chin-Hong P, Coulter KS, Cunningham D, et al. Raccoon roundworm infection associated with central nervous system disease and ocular disease – six states, 2013–2015. MMWR Morb Mortal Wkly Rep. 2016;65(35):930–3.
113. Peters JM, Madhavan VL, Kazacos KR, Husson RN, Dangoudoubiyam S, Soul JS. Good outcome with early empiric treatment of neural larva migrans due to baylisascaris procyonis. Pediatrics. 2012;129(3):e806–11.

114. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the diagnosis of human schistosomiasis. Clin Microbiol Rev. 2015;28(4):939–67.
115. Ross AG, McManus DP, Farrar J, Hunstman RJ, Gray DJ, Li YS. Neuroschistosomiasis. J Neurol. 2012;259(1):22–32.
116. Ferrari TC, Moreira PR. Neuroschistosomiasis: clinical symptoms and pathogenesis. Lancet Neurol. 2011;10(9):853–64.
117. Coyle CM. Schistosomiasis of the nervous system. Handb Clin Neurol. 2013;114:271–81.
118. Liu H, Lim CC, Feng X, Yao Z, Chen Y, Sun H, et al. MRI in cerebral schistosomiasis: characteristic nodular enhancement in 33 patients. AJR Am J Roentgenol. 2008;191(2):582–8.
119. Furst T, Keiser J, Utzinger J. Global burden of human food-borne trematodiasis: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(3):210–21.
120. Zhang XL, Wang Y, Wang GX, Chen WB, He X, Niu H, et al. Distribution and clinical features of paragonimiasis skrjabini in three gorges reservoir region. Parasitol Int. 2012;61(4):645–9.
121. Chen J, Chen Z, Lin J, Zhu G, Meng H, Cui G, et al. Cerebral paragonimiasis: a retrospective analysis of 89 cases. Clin Neurol Neurosurg. 2013;115(5):546–51.
122. Calvopina M, Romero-Alvarez D, Macias R, Sugiyama H. Severe pleuropulmonary paragonimiasis caused by paragonimus mexicanus treated as tuberculosis in Ecuador. Am J Trop Med Hyg. 2017;96(1):97–9.
123. Lane MA, Marcos LA, Onen NF, Demertzis LM, Hayes EV, Davila SZ, et al. Paragonimus kellicotti Flukes in Missouri, USA. Emerg Infect Dis. 2012;18(8):1263–7.

Chapter 12
Free-Living Ameba

Jennifer R. Cope, Ibne Karim M. Ali, and Ourania Georgacopoulos

Free-living amebae (FLA) are eukaryotic protozoa that exist freely in nature and only invade hosts as opportunistic pathogens. Their name is representative of the crawling locomotion they use to move about their environment, with characteristic formation of pseudopodia protruding from the cytoplasm. FLA are distributed globally and are found in natural sources including soil and water, but can also be found on contaminated surfaces such as contact lens cases [1]. FLA exist in nature in several life stages, the most common being the trophozoite and cyst. The trophozoite stage is a vegetative stage during which the ameba is metabolically active, feeding on bacteria, yeast and detritus found in its environment. During times of environmental adversity, the trophozoite will morph into a protective and dormant cyst, capable of withstanding environmental conditions and shielding itself from stress until favorable conditions are restored. The transformation from trophozoite to cyst is known as encystation.

Many genera of FLA exist that are benign, however, three genera are known human pathogens that cause highly fatal central nervous system (CNS) infections in humans. These are *Acanthamoeba* spp. , *Balamuthia mandrillaris*, and *Naegleria fowleri*. Additionally, two other genera of FLA, *Sappinia pedata* and *Paravahlkampfia francinae*, have caused two types of CNS infections in humans. *Acanthamoeba* spp. and *Balamuthia mandrillaris* both cause the highly fatal granulomatous amebic encephalitis (GAE). *Naegleria fowleri*, also commonly referred to as the brain-eating ameba, causes primary amebic meningoencephalitis (PAM), which can infect

J. R. Cope (✉) · I. K. M. Ali
Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
e-mail: bjt9@cdc.gov

O. Georgacopoulos
National Center for Emerging and Zoonotic Diseases, Waterborne Disease Prevention Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_12

any individual whether immunocompromised or not. *Acanthamoeba* spp. mostly infect immunocompromised patients, while cases of *Balamuthia mandrillaris* can infect any individual. Cases of PAM usually occur in children and young adults and have a high fatality rate. Only one case of *Sappinia pedata* has been recorded, having caused encephalitis in an otherwise healthy person. *Paravahlkampfia francinae* caused headache, fever, and nausea in an otherwise healthy 18-year old male, and was detected in the patient's cerebrospinal fluid (CSF) [1] A commonality between all CNS infections from FLA are their propensity to cause fulminant, highly fatal disease that often go undiagnosed or are only identified post-mortem.

Primary Amebic Meningoencephalitis (PAM) Caused by *Naegleria fowleri*

Microbiology/Pathogenesis

Naegleria fowleri is an ameboflagellate, protist pathogen that causes the highly fatal PAM. It is the only species out of 40 identified *Naegleria* species that is a human pathogen. Eight distinct genotypes of *Naegleria fowleri* have been identified, and are found distributed across the globe except in Antarctica [2].

Naegleria fowleri is thermophilic, growing best at temperatures 40–46 °C but can survive for a short amount of time at higher temperatures. It has been isolated from soil and freshwater pools, puddles, lakes, rivers, swimming pools, hot springs, thermally polluted effluents from power plants, hydrotherapy pools, aquaria, sewage canals, irrigation canals and humans' throat and nasal canals. However, *Naegleria fowleri* cannot survive in salt water, and colder temperatures render it inactive [1]. Like other FLA, *Naegleria fowleri* can also serve as a host for bacteria such as *Legionella pneumophila* [1, 3].

The ameba exists in three stages: cyst, flagellate and trophozoite. *Naegleria fowleri* is only pathogenic in the trophozoite stage when it is metabolically active, feeding and reproducing. The trophozoite measures about 10–25 μM and can have eruptive locomotion. Trophozoites move with the use of pseudopodia. Trophozoites contain a single nucleus, and a characteristic, centrally located, large nucleolus. In its natural habitats trophozoites feed on Gram negative bacteria such as *Escherichia coli*. During adverse environmental conditions, trophozoites transiently convert into pear-shaped flagellate form containing typically two flagella that propel it. The exact trigger of this conversion is largely unknown, but is believed to be linked to change in osmolarity of the environment. They are non-feeding temporary forms which usually revert back to the trophozoite stage in favorable conditions. During harsh environmental conditions, the trophozoite may encyst to protect itself, such as during times of low nutrient resources or adverse temperatures. Cysts are usually round shaped, and measure 7–15 μM with a smooth cyst wall containing one or more pores. The *Naegleria fowleri* cyst is metabolically inactive. Neither flagellate nor cyst forms have ever been detected in CSF or brain tissue.

Humans become infected with *Naegleria fowleri* when water containing the ameba enters the nose and travels through the olfactory neuroepithelia to the central

nervous system [3]. The amebae attach to the nasal mucosa and travel via the olfactory nerve through the cribriform plate where they reach the final destination in the olfactory bulbs. Once infected, the amebae can provoke a chemotactic response on nerve cells. Additionally, the amebae use food cups on the surface of the trophozoite to ingest bacteria, yeast and brain tissue, causing necrosis of brain matter [4].

Epidemiology

Analysis of PAM cases reported in the United States has shown that it is an acute and fulminant infection with high mortality (97%). From 1962–2018, there have been 145 PAM cases reported in the United States with 0–8 cases reported annually. Cases primarily occur in the warm summer months of July and August with the most common type of water exposure being lakes, rivers, and ponds followed by rivers and streams. Exposures have also occurred in natural hot springs. PAM usually occurs in children and young adults with a median age of 12 years but can affect all ages. Nearly three-quarters of cases are male which is hypothesized to be related to the types of activities that males might be more likely to do in water rather than an innate susceptibility to infection among males. Generally, in the United States, cases have occurred after exposure to warm freshwater in southern tier states, where the climate is generally warmer [5].

In the last decade in the United States, some notable changes have been observed in the epidemiology of PAM cases. First, beginning in 2010, the first PAM case was reported from the state of Minnesota, 600 miles farther north than any previously reported case [6]. A second case was reported from Minnesota in 2012 and was associated with the same lake as the first. Both cases occurred during unusually warm summers. Second, several cases were reported from Louisiana that were associated with use of water from treated public drinking water systems, including two cases associated with neti pot use and one case who was exposed to tap water used on a backyard waterslide [7, 8]. Additional novel exposures have occurred recently, including a case occurring after exposure to an artificial whitewater river and a surf park venue [9].

Outside of the United States, less is known about the epidemiology of PAM but from published case reports, it seems similar in that cases tend to occur in young healthy people with exposure to warm, freshwater. A male predominance is also noted among international cases.

Clinical Presentation

The incubation period for PAM (time from exposure to symptom onset) ranges from 1 to 9 days with a median of 5 days. Early symptoms are nonspecific and include headache, fever, nausea, and vomiting. As the illness progresses, the signs and symptoms are generally indistinguishable from other types of meningitis, and include nuchal rigidity, altered mental status, seizures, and coma. The time from

symptom onset to death is 1–18 days with a median of 5 days [10]. Death occurs as a result of cerebral edema and intractable intracranial hypertension resulting in brain herniation. The collection of cerebrospinal fluid (CSF) from PAM patients typically shows an elevated opening pressure. Routine studies show an elevated white blood cell (WBC) count with a polymorphonuclear cell predominance, elevated total protein, and low glucose. A wet mount of the CSF might show motile trophozoites of *Naegleria fowleri* when handled by an expert microscopist. Additionally, CSF prepared with Wright-Giemsa stain (as is often done for a manual WBC count) might reveal trophozoites. Brain imaging is usually not helpful in the diagnosis of PAM. Initial imaging, which is often a computed tomography (CT) scan of the brain, is usually normal. Later on in the course, imaging of the brain usually shows findings of cerebral edema.

Diagnosis

Microscopy and H&E staining: Direct microscopic observation of *N. fowleri* trophozoites in freshly collected CSF is the fastest way to make a preliminary PAM diagnosis although a subsequent molecular-based confirmation is still recommended. A wet mount of the CSF might show motile trophozoites of *N. fowleri* when handled by an expert pathologist or microbiologist. Sometimes a low-speed centrifugation (at 500 X g for 5 min at room temperature) can help to concentrate amebae at the bottom of the tube especially when the ameba burden is low. The sedimented CSF containing visible amebae may also be subject to an enflagellation experiment [11]. Only *N. fowleri* trophozoites (30–50% of them) convert into a flagellate form as opposed to *Acanthamoeba* or *B. mandrillaris* trophozoites. If unidirectional, motile trophozoites are not seen in the wet mount, but structures resembling trophozoites are seen, CSF should be subject to Wright-Giemsa or Trichrome staining to reveal the nuclear morphology of suspected trophozoites [12]. CSF or brain tissue may also be subject to hematoxylin and eosin (H&E) staining, which may identify trophozoites containing characteristic nuclear morphology – a single nucleus with a prominent, centrally-placed large nucleolus. However, identifying trophozoites can be challenging due to intense infiltration of macrophages, or presence of necrotic debris [13]. Gram staining is usually not very helpful as it will also stain host cells, and is prone to giving false-positive results. An evaluation of microscopic images through telediagnosis is available via CDC's DPDx - Laboratory Identification of Parasites of Public Health Concern (https://www.cdc.gov/dpdx/).

Immunohistochemistry (IHC) and indirect immunofluorescence (IIF) assays: IHC and IIF assays may be performed with tissue sections obtained from brain or other tissue. However, because patients rapidly deteriorate and die within a few days of the onset of symptoms, IHC and IIF assays are usually performed on post-mortem specimens. Additionally, these assays are time-consuming (requiring 1–2 days to complete), and are not suitable for diagnosing critically ill PAM patients. In these assays, antisera developed against *N. fowleri* are used that are not commercially

available, further limiting their use in PAM diagnoses. At the Centers for Disease Control and Prevention (CDC), an *N. fowleri*-specific rabbit polyclonal antisera is routinely used for these assays at 1:100 dilution.

Indirect immunofluorescence antibody (IFA) assay: An IFA assay is available at CDC to detect antibody response in the serum using the *N. fowleri*-specific rabbit polyclonal antisera. However, this assay has very little diagnostic value, because the antibody response has rarely been seen in the serum of PAM patients likely because of rapid progression of disease and death within a few days giving no time to mount an antibody response. A serum titer of 1:128 or above is considered positive for *N. fowleri* by IFA assay. A positive *N. fowleri*- antibody response was detected in a U.S. PAM survivor in which the antibody titer was 1:4096 after 10 days of hospitalization [14].

PCR and real-time PCR: Several conventional PCRs and real-time PCRs are available for the detection of *N. fowleri* DNA although the majority of these have not been tested for clinical diagnosis [15–21]. PCR is the preferred diagnostic tool for *N. fowleri* because they are: (a) rapid (take only 2–5 hours), (b) highly sensitive (DNA from a single ameba can be amplified) and (c) species-specific (i.e., selectively amplifies *N. fowleri* DNA, and does not amplify DNA from *B. mandrillaris* or *Acanthamoeba* species). Success of PCR largely depends on the copy number of the target being amplified. PCRs with multi-copy targets have higher sensitivity than those with single copies. A rapid, and highly sensitive real-time PCR to detect *N. fowleri* DNA is available at CDC [21]. It targets the 18S small subunit ribosomal RNA genes of *N. fowleri*, which have a few thousand copies in the extrachromosomal circular plasmids per genome. Currently, this is the gold-standard test for *N. fowleri* detection and is routinely used at CDC. However, one caveat is that real-time PCR is not readily available in resource-poor settings as it requires expensive instruments and expertise to run.

A genotyping method is available that is based on the *N. fowleri* internal transcribed spacers 1 and 2 (ITS1 and ITS2) sequences, and mitochondrial small subunit rDNA [22, 23]. Eight distinct genotypes have been detected across samples of *N. fowleri* from the environment and clinical cases worldwide. Three genotypes have been detected in the United States including one that appears to be significantly less prevalent. Different authors have used different genotype assignment for the same genotype, making it difficult to understand the actual prevalence of a particular genotype. For example, what Zhou et al. [23] described as genotype 2 (or more accurately "genotype II" in their article), is genotype 1 in the article by De Jonckheere [22].

Treatment

In the United States, there have been only four confirmed survivors of PAM, with another two well-described, confirmed survivors internationally [14, 24–26]. As a rare infection, clinical trial data for the treatment of PAM is nonexistent. The

recommended treatment protocol is based on *in vitro* drug susceptibility testing against *N. fowleri* and reports of successfully treated survivor cases. The currently recommended treatment protocol is outlined in Table 12.1. Amphotericin B has been a mainstay of PAM treatment. It has been used to treat all PAM survivors. While liposomal and lipid-complex amphotericin B formulations are commonly used in hospitals, conventional amphotericin B is preferred for PAM treatment given its lower minimum inhibitory concentration (MIC) against *N. fowleri* and improved effectiveness in a mouse model [27]. Miltefosine is a more recent addition to the PAM treatment regimen. It is currently approved in the United States for the treatment of leishmaniasis. Its limited availability in hospitals has made it difficult to administer to patients in a timely manner. It can be obtained by contacting Profounda, Inc. (http://www.impavido.com/order-page) Recent *in vitro* and *in vivo* work suggests posaconazole might have better activity against *N. fowleri* than fluconazole [28].

This combination of drugs has been used successfully in three recent U.S. survivors including a 12-year-old girl and an 8-year-old boy in 2013 and a 16-year-old boy in 2016 [24, 25]. The 12-year-old girl was treated within 36 hours of symptom onset and her cerebral edema was aggressively managed with CSF drainage, hyperosmolar therapy with mannitol and 3% saline, moderate hyperventilation, and induced hypothermia. She made a full neurologic recovery. The 16-year-old boy who survived in 2016 was treated similarly and made a full recovery, returning to school. The 8-year-old boy in 2013 received the same drug regimen but it was started several days after symptom onset. Although the patient survived, he suffered permanent neurologic disability. Early diagnosis and treatment as well as aggressive management of cerebral edema were thought to have contributed to the survival of

Table 12.1 Currently recommended treatment protocol for primary amebic meningoencephalitis

Drug	Dose	Route	Maximum dose	Duration	Comments
Amphotericin B	1.5 mg/kg/day in two divided doses	IV	1.5 mg/kg/day	3 days	
then	1 mg/kg/day once daily	IV		11 days	14-day course
Amphotericin B	1.5 mg once daily	Intrathecal	1.5 mg/day	2 days	
then	1 mg/day every other day	Intrathecal		8 days	10-day course
Azithromycin	10 mg/kg/day once daily	IV/PO	500 mg/day	28 days	
Fluconazole	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Rifampin	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days	
Miltefosine	Weight <45 kg 50 mg BID Weight >45 kg 50 mg TID	PO	2.5 mg/kg/day	28 days	50 mg tablets
Dexamethasone	0.6 mg/kg/day in four divided doses	IV	0.6 mg/kg/day	4 days	

these patients. Despite these notable successes, many patients have received similar if not the exact same drugs and therapies, but have not survived. The ideal PAM treatment regimen remains unknown and PAM remains an illness with very high mortality, despite treatment, making prevention measures very important.

Prevention

Similar to treatment, there are no rigorous studies to support prevention measure for PAM. However, given what is known about the transmission of *N. fowleri* through nasal entry, the following are recommended as prevention measures to minimize the risk of acquiring PAM. When it comes to recreational water activities in untreated freshwater bodies such as lakes, rivers, ponds, and hot springs, the only certain way to prevent PAM is to avoid these activities. However, this is not often practical or desired; therefore, actions should be taken to limit the amount of water going up the nose during these activities such as holding the nose shut, using nose clips, or keeping the head above water when taking part in recreational water activities in warm freshwater. When performing nasal or sinus rinsing (whether for religious or therapeutic purposes), use water that has been boiled and left to cool, purchased as sterile or distilled, or filtered using a filter labeled as "absolute pore size of 1 μM or smaller".

Amebic Encephalitis Caused by *Balamuthia mandrillaris*

Microbiology/Pathogenesis

Balamuthia mandrillaris was first isolated from a mandrill and correctly identified in 1986. Prior to this isolation, *Balamuthia mandrillaris* was mistaken for *Acanthamoeba*, as the two amebae are difficult to distinguish when using light microscopy. *Balamuthia mandrillaris* is the only species in the genus. Although its environmental niche appears to be soil, its main source of food remains unknown [29]. *Balamuthia mandrillaris* has two life stages, the trophozoite (12–60 μM) and the cyst (6–30 μM). The trophozoite can be uninucleate or binucleate which is a unique characteristics for this species and can be helpful in distinguishing it from *Acanthamoeba* species. Unlike *N. fowleri* or *Acanthamoeba* trophozoites, they do not show any visible locomotion, or feed on bacteria under laboratory growth conditions. In contrast, they grow on mammalian cell cultures such as human lung fibroblast, monkey kidney cells, or microvascular endothelial cells from human brains. In mammalian cells, *B. mandrillaris* trophozoites have a very sluggish spider-like walking movement. The cyst is a round shape, usually containing a single nucleus and have an irregular and wavy outer wall and a round inner wall. In the mature cysts, a third layer of refractive granules are often seen below the inner cyst wall [1, 30].

Similar to *Acanthamoeba* spp., *Balamuthia mandrillaris* causes granulomatous amebic encephalitis (GAE) leading to hemorrhagic necrosis of the midbrain, thalamus, brainstem and cerebellum. Humans can become infected via several routes, the most common being ingestion or introduction of the amebae through a cut in the skin, and spread through the blood to the CNS.

Epidemiology

Of the three known pathogenic free-living ameba genuses, the least is known about *Balamuthia* epidemiology. There are an estimated 200 cases reported in the literature, with the most reported from the United States and Peru. A recent review of *Balamuthia* cases reported in the United States from 1974 to 2016 identified 109 cases, 90% of which were fatal [31]. The patients described in this case series ranged in age from 4 months to 91 years with a median age of 36 years. The majority of cases were male (68%) and Hispanic (55%). Geographically, cases tended to be reported in residents from states in the south and southwest and soil exposure was commonly reported. Soil exposures were reported to have occurred as a result of gardening, landscaping, and yard work or play as well as farming, ranching, or other agricultural activities. However, because of what is likely a prolonged incubation period, the exact exposures leading to *Balamuthia* disease are usually unknown. *Balamuthia* cases occur at any time of year with no apparent seasonality. In the U.S. case series, alcohol misuse and illegal drug use were reported in nearly one-quarter of cases. Over one-third of cases had an immunocompromised condition.

In addition to environmental exposures, *Balamuthia* disease has also been documented to occur as a result of solid organ transplantation. To date, this has occurred on three occasions in the United States, in which a donor unknown to be infected with *Balamuthia* had organs transplanted into recipients who subsequently developed encephalitis [32, 33]. The median incubation period for these cases (day of transplantation to symptom onset) was 21 days. However, this incubation period is thought to be shorter than would be expected for a *Balamuthia* infection acquired from the environment since organ transplantation is a direct inoculation into an immunocompromised host.

Clinical Presentation

The incubation period for *Balamuthia* disease is unknown (outside of the organ transplantation cases noted above) but is generally thought to be weeks, months or even years. *Balamuthia* disease primarily presents as encephalitis (99% in the U.S. case series) but can also cause cutaneous disease and a combination of cutaneous and central nervous system disease in which a cutaneous lesion precedes the onset of encephalitis. In cases for which postmortem exams were performed,

evidence of *Balamuthia* organisms have been found in the lungs, kidneys, pancreas, and adrenal glands. Signs and symptoms at initial presentation with *Balamuthia* disease include fever, headache, vomiting, lethargy, altered mental status, seizures, and weakness. In the U.S. case series, the median length of time from symptom onset to death was 24 days with range from just a few days to over a year [31]. CSF studies from patients with *Balamuthia* encephalitis generally show a mildly elevated WBC (<500 cells/μL) with a lymphocytic predominance, elevated protein, and low to normal glucose. Amebae are only rarely visualized in the CSF. Brain imaging (such as CT or magnetic resonance imaging [MRI]) is always abnormal in *Balamuthia* encephalitis patients and findings are generally reported as enhancing lesions, multifocal lesions, and edema. Lesions can be found in all regions of the brain.

Skin manifestations are only rarely reported in the U.S. case series (6% of cases); however, skin lesions are commonly seen in Peruvian cases. The lesions are described as a painless plaque ranging from 1 to several centimeters in diameter commonly located on the central face, especially the nose and extremities [34]. Ulceration generally only occurs with larger lesions. Systemic symptoms are usually absent and skin lesions may precede onset of CNS symptoms by weeks or months. Skins lesions, when present, represent an opportunity for early treatment to prevent the development of encephalitis.

Diagnosis

Microscopy and H&E staining Direct microscopic observation of *B. mandrillaris* trophozoites in freshly collected CSF is rarely seen. Trophozoites and/or cysts of *B. mandrillaris* can be detected in brain biopsy tissues by microscopy, but a subsequent molecular-based confirmation is still needed to distinguish them from *Acanthamoeba* species. Trophozoites and cysts of *B. mandrillaris* may be seen in brain or other affected tissue by H&E staining, which may identify trophozoites containing a single nucleus with a prominent, centrally placed large nucleolus. Occasionally, two opposing nucleolus may be seen inside the nucleus, which is not seen in the nucleus of *N. fowleri* or *Acanthamoeba* species, and is a reliable morphologic feature of this species. Gram staining is usually not very helpful and may be prone to giving false-positive results as it will also stain host cells. An evaluation of microscopic images is available through the telediagnosis support of CDC's DPDx.

IHC and IIF assays These may be performed with tissue sections obtained from patient's brain or other affected tissue (e.g., skin). In the IHC or IIF assays, antisera developed against *B. mandrillaris* are used. However, these specific antisera are not commercially available, limiting their general use in *B. mandrillaris* diagnosis. At CDC, a *B. mandrillaris*-specific rabbit polyclonal antisera is routinely used at a 1:100 dilution for these assays.

IFA serology assay An IFA assay is available at CDC to detect an antibody response in the patient's serum using the *B. mandrillaris*-specific rabbit polyclonal antisera at 1:100 dilution. A serum titer of 1:64 or above is considered positive for *B. mandrillaris* by IFA assay. A positive *B. mandrillaris*- antibody response is usually detected in immunocompetent GAE patients [29]. However, a positive antibody titer might be detected in some healthy individuals likely due to a past exposure to this ameba [35]. Because of this, confirming an acute infection solely based on the antibody titer is unreliable, and at CDC, the IFA assay is used with other tests, and in conjunction with patient's clinical signs and symptoms. The IFA assay has limited diagnostic value when used as a standalone method.

PCR and real-time PCR Several conventional PCRs and real-time PCRs are available for the detection of *B. mandrillaris* DNA [21, 36–38]. PCR is the preferred diagnostic tool for *B. mandrillaris* because it is fast, highly sensitive, and species-specific. The preferred specimen types for *B. mandrillaris* detection by PCR are fresh and frozen tissues that have not been treated with formalin, which degrades the quality of DNA resulting in false-negative PCR results. However, one group has developed a *B. mandrillaris* mitochondrial 16S rDNA-based PCR that works with the formalin-fixed archived clinical specimens [39]. Success of PCR also largely depends on the copy number of the target DNA being amplified. PCRs with multi-copy targets have higher sensitivity over those that target single copy DNA. A real-time PCR to detect *B. mandrillaris* DNA is available at CDC targeting 18S small subunit ribosomal RNA genes of *B. mandrillaris*, which are contained as few thousand copies per genome. Because *B. mandrillaris* are rarely detected in CSF, a negative PCR result on CSF does not completely rule out a *B. mandrillaris* infection. However, a positive test with the CSF has the potential to eliminate the need for obtaining a brain biopsy tissue, which is a highly invasive procedure.

Although *B. mandrillaris* isolates have been recovered from humans and a range of animal GAE cases including non-human primates, there is no reliable genotyping tool to answer some of the outstanding questions – (a) Can humans and animals be infected with the same isolate/genotype of *B. mandrillaris*?; (b) Are certain isolates/genotypes of *B. mandrillaris* more virulent than the others?; (c) Do they show organ tropisms, and certain isolates/genotypes selectively prefer brain tissues as oppose to the skin tissues?; and (d) Do multiple species exist within the genera *Balamuthia*?

Treatment

An evidence-based approach to the treatment of *Balamuthia* disease is lacking and treatment recommendations are based on *in vitro* drug susceptibility testing against *Balamuthia* and reports of successfully treated survivor cases. Drugs that have been used successfully in combination to treat *Balamuthia* disease include pentamidine,

sulfadiazine, flucytosine, fluconazole, azithromycin/clarithromycin, and miltefosine. Although pentamidine has good amebacidal activity *in vitro* and has been used successfully in the past in combination with the drugs listed below, pentamidine is toxic and does not cross the normal, intact blood-brain barrier well so its use must be a clinical decision.

Prevention

Because little is known about the exact environmental exposures that lead to *Balamuthia* infection, there are currently no known ways to prevent it. Organ donors should be carefully evaluated and donors who die of unknown neurological causes should be evaluated for infections, including *Balamuthia*, that might be transmitted via organ transplantation.

Amebic Encephalitis Caused by *Acanthamoeba* spp.

Microbiology/Pathogenesis

Several *Acanthamoeba* spp. cause granulomatous amebic encephalitis including *A. culbertsoni*, *A. castellanni*, *A. polyphaga*, *A. astronyxis*, *A. healyi* and *A. divionensis*. A defining characteristic of this ameba are its acanthopodia radiating from the surface of the body. These acanthopodia may help the ameba with cell adhesion when infecting the host. *Acanthamoeba* can be found in natural and man-made environments such as soil, fresh and brackish waters, bottled water, cooling towers, air conditioning units, humidifiers, hot tubs, hydrotherapy tubs, dental irrigation units, dialysis machines, dust, cell cultures, contact lens cases and more. They have also been isolated from bodily orifices such as ear discharge, stool samples, and brain, lungs, and skin of healthy individuals. *Acanthamoeba* has two life-cycle stages: a trophozoite and a cyst. Trophozoites measure 15–45 μM in length. They are the feeding form, and they actively show movement in laboratory growth conditions with the help of pseudopodia known as acanthapodia. Trophozoite usually contain a single nucleus, with a large, centrally-located nucleolus. Trophozoites feed on Gram negative bacteria such as *E. coli* in the environment. In adverse conditions, trophozoites convert into more resistant double-walled cysts that measure 10–25 μM. *Acanthamoeba* cysts usually have a wrinkled outer wall, known as the ectocyst, and an inner wall, known as the endocyst, which is stellate, polygonal, or round-shaped. Cysts with a polygonal endocyst are often used as a unique morphologic feature that distinguishes it from *N. fowleri* or *B. mandrillaris* cysts.

Brain autopsies of patients infected with *Acanthamoeba* show cerebral edema, areas of cortical and basal ganglia softening and necrotic and hemorrhagic CNS

tissue. Amebic trophozoites and cysts are present throughout the CNS tissue. They are thought to enter through cuts and breaks in the skin and spread hematogenously to the lungs and brain or may be inhaled. Additionally, the presence of the ameba in nasal mucosa may suggest a nasopharyngeal route of entry. Damage to the host tissue is cause by phagocytosis of the host cell. Some species have food cups on the surface called amoebastome, which help ingest tissue [1].

Epidemiology

Acanthamoeba spp. cause disease primarily in immunocompromised patients although there are some reports of otherwise healthy individuals being diagnosed with *Acanthamoeba* disease. The types of immunocompromised conditions that are reported in *Acanthamoeba* patients include HIV/AIDS, solid organ transplantation, hematologic malignancies, bone marrow transplantation, other cancers, and diabetes. In the United States, there have been 0–12 cases of *Acanthamoeba* disease reported annually since 1955 with a median age of 42 years and a majority male (72%) (CDC unpublished data). The exact exposures leading to *Acanthamoeba* disease are generally unknown but are thought to be soil or water exposures. Recently, five immunocompromised patients with *Acanthamoeba* disease were reported to have performed nasal rinsing with tap water prior to becoming ill [40]. There is no apparent seasonality for infection and cases are reported from across the United States and around the world.

Clinical Presentation

The incubation period for *Acanthamoeba* disease is unknown but is generally thought to be weeks, months, or even years. *Acanthamoeba* disease has a wide range of clinical presentations. *Acanthamoeba* disease can present as encephalitis alone or in combination with manifestations in other organ systems. *Acanthamoeba* spp. can also cause skin lesions, rhinosinusitis, osteomyelitis, and pneumonia.

In *Acanthamoeba* encephalitis, CSF studies generally show elevated protein, low or normal glucose, and a mildly elevated WBC (<500 cells/μL) with a lymphocytic predominance. Amebae are only rarely visualized in the CSF. Brain imaging in encephalitis cases is usually abnormal and might show single or multiple hypodense, ring-enhancing, and/or space-occupying lesions. There might also be hemorrhage within the lesions and surrounding edema.

Diagnosis

Direct microscopic observation of *Acanthamoeba* trophozoites or cysts in freshly collected CSF is rare. Trophozoites and cysts of *Acanthamoeba* can be detected in brain biopsy tissue, but a subsequent molecular-based confirmation is still needed.

When structures resembling trophozoites or cysts of *Acanthamoeba* are seen in biopsy tissue or CSF, they should be subject to Wright-Giemsa or Trichrome staining to reveal the nuclear morphology [12]. Brain tissue may also be subject to H&E staining, which may identify cysts containing characteristic polygonal endocysts. Again, Gram staining is usually not very helpful. An evaluation of microscopic images is available through the telediagnosis support of CDC's DPDx.

Immunohistochemistry (IHC) and indirect immunofluorescence (IIF) assays IHC and IIF assays may be performed with tissue sections obtained from patient's brain or other affected tissue (e.g., skin). In the IHC or IIF assays, antisera developed against *Acanthamoeba* are used. However, these specific antisera are not commercially available, limiting their general use in *Acanthamoeba* diagnosis. At CDC, an *Acanthamoeba*-specific rabbit polyclonal antisera at 1:100 dilution is routinely used for these assays.

IFA assay Some studies detected antibodies against *Acanthamoeba* in healthy individuals, and patients who are acutely suffering from illnesses unrelated to *Acanthamoeba* infection [41]. Patients with *Acanthamoeba* GAE usually show a positive antibody titer by IFA assay [12, 41] although immunocompromised GAE patients may show a lower antibody titer. An IFA assay is available at the CDC to detect antibody response in the serum using the *Acanthamoeba*-specific rabbit polyclonal antisera. A serum titer of 1:128 or above is considered positive for *Acanthamoeba* by IFA assay. However, because a positive antibody titer might be detected in some healthy individuals or patients with unrelated complications likely due to a past exposure, confirming an acute infection solely based on the antibody titer is unreliable. At CDC, the IFA assay is used with other tests, and in conjunction with patient's clinical signs and symptoms. Thus, the IFA assay has limited diagnostic value.

PCR and real-time PCR Several conventional PCRs and real-time PCRs are available for the detection of *Acanthamoeba* DNA [21, 39, 42, 43]. PCR is the preferred diagnostic tool as it is rapid, highly sensitive and species-specific (i.e., selectively amplifies *Acanthamoeba* species). Success of PCR detection largely depends on the copy number of the target DNA being amplified. PCRs with multi-copy targets have higher sensitivity over those that target single copy DNA. A real-time PCR to detect *Aanthamoeba* species DNA is available at CDC. It targets 18S small subunit ribosomal RNA genes of this ameba, which are contained about few thousand copies per genome. One caveat, PCR is not readily available in resource-poor settings.

A PCR based on the 18S rDNA sequences followed by Sanger sequencing has been described for genotyping of *Acanthamoeba* species [44]. At least 18 different genotypes (T1-T18) of *Acanthamoeba* species have been detected. At least nine of these are associated with human infections. Genotypes T1, T12, and T18 are almost exclusively associated with GAE; T3, T6, and T11 with *Acanthamoeba* keratitis; and T4, T5, and T10 with both GAE and keratitis. T4 is the predominant genotype detected in GAE cases. It is common that more than one species of *Acanthamoeba* share the same genotype. A molecular-based *Acanthamoeba* speciation (i.e., species-specific identification) is currently non-existent.

Treatment

There are no definitive treatment recommendations for *Acanthamoeba* disease and several different combination regimens have been reported in cases of successful treatment. Drugs that have been used successfully in varying combinations to treat survivors of *Acanthamoeba* GAE and systemic infections include pentamidine, sulfadiazine, trimethoprim-sulfamethoxazole, flucytosine, fluconazole, and miltefosine. Cutaneous infections have also be treated with topical formulations of chlorhexidine, ketoconazole, and miltefosine. For transplant patients taking immunosuppressive drugs, there may be a role for decreasing their level of immunosuppression but this decision must be carefully weighed against the risk of possible organ rejection.

Prevention

Given the likely ubiquitous nature of *Acanthamoeba* spp. in the environment in both soil and water, exposure to *Acanthamoeba* spp. is difficult to avoid. However, given the possible evidence for transmission via tap water used for nasal rinsing, nasal rinsing should either be completely avoided among immunocompromised patients or the water used should be boiled and cooled, filtered, or purchased as distilled or sterile.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

References

1. Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: Acanthamoeba spp., Balamuthia mandrillaris, Naegleria fowleri, and Sappinia diploidea. FEMS Immunol Med Microbiol. 2007;50(1):1–26.
2. De Jonckheere JF. What do we know by now about the genus Naegleria? Exp Parasitol. 2014;145(Suppl):S2–9.
3. Siddiqui R, Ali IKM, Cope JR, Khan NA. Biology and pathogenesis of Naegleria fowleri. Acta Trop. 2016;164:375–94.
4. Marciano-Cabral F, Cabral GA. The immune response to Naegleria fowleri amebae and pathogenesis of infection. FEMS Immunol Med Microbiol. 2007;51(2):243–59.
5. Yoder JS, Eddy BA, Visvesvara GS, Capewell L, Beach MJ. The epidemiology of primary amoebic meningoencephalitis in the USA, 1962–2008. Epidemiol Infect. 2010;138(7):968–75.
6. Kemble SK, Lynfield R, DeVries AS, Drehner DM, Pomputius WF 3rd, Beach MJ, et al. Fatal Naegleria fowleri infection acquired in Minnesota: possible expanded range of a deadly thermophilic organism. Clin Infect Dis. 2012;54(6):805–9.
7. Yoder JS, Straif-Bourgeois S, Roy SL, Moore TA, Visvesvara GS, Ratard RC, et al. Primary amebic meningoencephalitis deaths associated with sinus irrigation using contaminated tap water. Clin Infect Dis. 2012;55(9):e79–85.

8. Cope JR, Ratard RC, Hill VR, Sokol T, Causey JJ, Yoder JS, et al. The first association of a primary amebic meningoencephalitis death with culturable Naegleria fowleri in tap water from a US treated public drinking water system. Clin Infect Dis. 2015;60(8):e36–42.
9. Cope JR, Murphy J, Kahler A, Gorbett DG, Ali I, Taylor B, et al. Primary amebic meningoencephalitis associated with rafting on an artificial whitewater river: case report and environmental investigation. Clin Infect Dis. 2018;66(4):548–53.
10. Capewell LG, Harris AM, Yoder JS, Cope JR, Eddy BA, Roy SL, et al. Diagnosis, clinical course, and treatment of primary amoebic meningoencephalitis in the United States, 1937–2013. J Pediatric Infect Dis Soc. 2015;4(4):e68–75.
11. Cope JRAI, Visvesvara GS. Pathogenic and opportunistic free-living amebae. In: Carroll KCPM, Landry ML, McAdam AJ, Patel R, Richter SS, Warnock DW, editors. Manual of clinical microbiology 2. 12th ed. Washington, DC: ASM Press; 2019. p. 2486–96.
12. Martinez AJ, Janitschke K. Acanthamoeba, an opportunistic microorganism: a review. Infection. 1985;13(6):251–6.
13. Guarner J, Bartlett J, Shieh WJ, Paddock CD, Visvesvara GS, Zaki SR. Histopathologic spectrum and immunohistochemical diagnosis of amebic meningoencephalitis. Mod Pathol. 2007;20(12):1230–7.
14. Seidel JS, Harmatz P, Visvesvara GS, Cohen A, Edwards J, Turner J. Successful treatment of primary amebic meningoencephalitis. N Engl J Med. 1982;306(6):346–8.
15. Streby A, Mull BJ, Levy K, Hill VR. Comparison of real-time PCR methods for the detection of Naegleria fowleri in surface water and sediment. Parasitol Res. 2015;114(5):1739–46.
16. Kang H, Seong GS, Sohn HJ, Kim JH, Lee SE, Park MY, et al. Effective PCR-based detection of Naegleria fowleri from cultured sample and PAM-developed mouse. Eur J Protistol. 2015;51(5):401–8.
17. Kao PM, Hsu BM, Hsu TK, Chiu YC, Chang CL, Ji WT, et al. Application of TaqMan qPCR for the detection and monitoring of Naegleria species in reservoirs used as a source for drinking water. Parasitol Res. 2014;113(10):3765–71.
18. Kao PM, Tung MC, Hsu BM, Chou MY, Yang HW, She CY, et al. Quantitative detection and identification of Naegleria spp. in various environmental water samples using real-time quantitative PCR assay. Parasitol Res. 2013;112(4):1467–74.
19. Wang W, Wei F, Li J, Li N, Liu Q. Isolation and identification of naegleria species from environmental water in Changchun, Northeastern China. Iran J Parasitol. 2014;9(2):254–9.
20. Mull BJ, Narayanan J, Hill VR. Improved method for the detection and quantification of Naegleria fowleri in water and sediment using immunomagnetic separation and real-time PCR. J Parasitol Res. 2013;2013:608367.
21. Qvarnstrom Y, Visvesvara GS, Sriram R, da Silva AJ. Multiplex real-time PCR assay for simultaneous detection of Acanthamoeba spp., Balamuthia mandrillaris, and Naegleria fowleri. J Clin Microbiol. 2006;44(10):3589–95.
22. De Jonckheere JF. Origin and evolution of the worldwide distributed pathogenic amoeboflagellate Naegleria fowleri. Infect Genet Evol. 2011;11(7):1520–8.
23. Zhou L, Sriram R, Visvesvara GS, Xiao L. Genetic variations in the internal transcribed spacer and mitochondrial small subunit rRNA gene of Naegleria spp. J Eukaryot Microbiol. 2003;50(Suppl):522–6.
24. Cope JR, Conrad DA, Cohen N, Cotilla M, DaSilva A, Jackson J, et al. Use of the novel therapeutic agent miltefosine for the treatment of primary amebic meningoencephalitis: report of 1 fatal and 1 surviving case. Clin Infect Dis. 2016;62(6):774–6.
25. Linam WM, Ahmed M, Cope JR, Chu C, Visvesvara GS, da Silva AJ, et al. Successful treatment of an adolescent with Naegleria fowleri primary amebic meningoencephalitis. Pediatrics. 2015;135(3):e744–8.
26. Vargas-Zepeda J, Gomez-Alcala AV, Vasquez-Morales JA, Licea-Amaya L, De Jonckheere JF, Lares-Villa F. Successful treatment of Naegleria fowleri meningoencephalitis by using intravenous amphotericin B, fluconazole and rifampicin. Arch Med Res. 2005;36(1):83–6.
27. Goswick SM, Brenner GM. Activities of azithromycin and amphotericin B against Naegleria fowleri in vitro and in a mouse model of primary amebic meningoencephalitis. Antimicrob Agents Chemother. 2003;47(2):524–8.

28. Colon BL, Rice CA, Guy RK, Kyle DE. Phenotypic screens reveal posaconazole as a rapidly acting amebicidal combination partner for treatment of primary amoebic meningoencephalitis. J Infect Dis. 2019;219(7):1095–103.
29. Schuster FL, Yagi S, Gavali S, Michelson D, Raghavan R, Blomquist I, et al. Under the radar: balamuthia amebic encephalitis. Clin Infect Dis. 2009;48(7):879–87.
30. Visvesvara GS, Schuster FL, Martinez AJ. Balamuthia mandrillaris, N. G., N. Sp., agent of amebic meningoencephalitis in humans and other animals. J Eukaryot Microbiol. 1993;40(4):504–14.
31. Cope JR, Landa J, Nethercut H, Collier SA, Glaser C, Moser M, et al. The epidemiology and clinical features of Balamuthia mandrillaris disease in the United States, 1974–2016. Clin Infect Dis. 2019;68(11):1815–22.
32. Farnon EC, Kokko KE, Budge PJ, Mbaeyi C, Lutterloh EC, Qvarnstrom Y, et al. Transmission of Balamuthia mandrillaris by organ transplantation. Clin Infect Dis. 2016;63(7):878–88.
33. Gupte AA, Hocevar SN, Lea AS, Kulkarni RD, Schain DC, Casey MJ, et al. Transmission of Balamuthia mandrillaris through solid organ transplantation: utility of organ recipient serology to guide clinical management. Am J Transplant. 2014;14(6):1417–24.
34. Bravo FG, Seas C. Balamuthia mandrillaris amoebic encephalitis: an emerging parasitic infection. Curr Infect Dis Rep. 2012;14(4):391–6.
35. Huang ZH, Ferrante A, Carter RF. Serum antibodies to Balamuthia mandrillaris, a free-living amoeba recently demonstrated to cause granulomatous amoebic encephalitis. J Infect Dis. 1999;179(5):1305–8.
36. Booton GC, Carmichael JR, Visvesvara GS, Byers TJ, Fuerst PA. Identification of Balamuthia mandrillaris by PCR assay using the mitochondrial 16S rRNA gene as a target. J Clin Microbiol. 2003;41(1):453–5.
37. Kiderlen AF, Radam E, Lewin A. Detection of Balamuthia mandrillaris DNA by real-time PCR targeting the RNase P gene. BMC Microbiol. 2008;8:210.
38. Ahmad AF, Andrew PW, Kilvington S. Development of a nested PCR for environmental detection of the pathogenic free-living amoeba Balamuthia mandrillaris. J Eukaryot Microbiol. 2011;58(3):269–71.
39. Yagi S, Schuster FL, Visvesvara GS. Demonstration of Balamuthia and Acanthamoeba mitochondrial DNA in sectioned archival brain and other tissues by the polymerase chain reaction. Parasitol Res. 2008;102(3):491–7.
40. Cope JR, Roy S, Ali I. 865. *Acanthamoeba Disease* associated with the practice of nasal rinsing in immunocompromised patients. Open Forum Infect Dis. 2018;5(Suppl 1):S22.
41. Schuster FL, Visvesvara GS. Amebae and ciliated protozoa as causal agents of waterborne zoonotic disease. Vet Parasitol. 2004;126(1–2):91–120.
42. Karsenti N, Lau R, Purssell A, Chong-Kit A, Cunanan M, Gasgas J, et al. Development and validation of a real-time PCR assay for the detection of clinical acanthamoebae. BMC Res Notes. 2017;10(1):355.
43. Riviere D, Szczebara FM, Berjeaud JM, Frere J, Hechard Y. Development of a real-time PCR assay for quantification of Acanthamoeba trophozoites and cysts. J Microbiol Methods. 2006;64(1):78–83.
44. Booton GC, Visvesvara GS, Byers TJ, Kelly DJ, Fuerst PA. Identification and distribution of Acanthamoeba species genotypes associated with nonkeratitis infections. J Clin Microbiol. 2005;43(4):1689–93.

Part V
Disorders of the Spinal Cord

Chapter 13
Bacterial Infections of the Spine

Maja Babic and Claus Simpfendorfer

Infections of the Spine

The heterogeneity of clinical syndromes associated with spine infections reflects the structural complexity of the spinal column. Historically, all infections of the osteoarticular elements of the spine were categorized as vertebral osteomyelitis. Spinal epidural abscesses were investigated as a distinct entity, and not as part of the anatomic continuum of an evolving infectious process.

The majority of spine infections arise from hematogenous seeding during episodes of bacteremia. A minority is related to direct inoculation of pathogenic microorganisms during spinal instrumentation. Unlike the hematogenous seeding of the long bones in the pediatric population, which has seen a significant decrease in the antibiotic era, spine infections in the adult population are on the rise.

The reason is likely multifactorial, and includes an expanding elderly population with significant comorbidities subject to frequent invasive procedures, predisposed thereby to recurrent bacteremic episodes. The widespread availability of advanced imaging likely adds to the increase in diagnosis of spine infections. Despite recent advances in our understanding of spine infections, well defined clinical presentations and easier access to cross sectional imaging, the diagnostic delay of this potentially life-threatening infection remains unacceptably long. Once the diagnosis is established, the main therapeutic dilemma remains whether to operate or not. In recent years, the conservative approach with antimicrobial therapy only, has proven

M. Babic (✉)
Department of Infectious Disease, Cleveland Clinic, Cleveland, OH, USA
e-mail: babicm@ccf.org

C. Simpfendorfer
Imaging Institute, Cleveland Clinic, Cleveland, OH, USA

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_13

safe and successful for an increasing number of cases. Patients with overt neurologic deficits and spinal instability require surgery, in addition to antimicrobial therapy.

Anatomy of Spine Infections

Intervertebral discs (IVD) link adjacent vertebral bodies, represent the main amphiarthrodial joints of the spinal column and occupy one third of its height. They are composed of the outer thick ring of fibrous cartilage called annulus fibrosus, the inner gelatinous core or nucleus pulposus and the hyaline endplates. In children, the IVD is vascularized, with numerous capillaries originating from interosseous arteries of the vertebral body traversing the endplates. In adults, the vascular channels obliterate, making the IVD the largest avascular structure of the human body [1].

Vertebral bodies are the main weight bearing elements of the vertebral column. They incorporate physiologic equivalents of metaphyseal plates located along the bone-cartilage interface and supplied by terminal arteriolar archades. Metaphyseal equivalents are targets of hematogenous bacterial seeding, responsible for establishing the nidus for osteomyelitis [2].

Facet joints are diarthrodial, meniscoid containing, synovial joints interlocking adjacent vertebral bodies posteriorly. Facet joints are part of the weight bearing tripod of the spine, comprised of the anterior column and bilaterally symmetric facets posteriorly. Along with the IVD, they transfer load and constrain spine movement [3].

Epidural space is a potential space between the periosteum of the vertebral column and the spinal dura mater. It extends from the foramen magnum to the sacral hiatus. It contains fat, spinal blood vessels, lymphatics and nerve roots with their dural sleeves which extend into paravertebral space [4].

Pathophysiology of Spine Infections

In adults, the infections of the axial skeleton are caused by hematogenous seeding. The blood vessels supplying the vertebral end plates are terminal, and therefore bacteria laden platelet clots lodge in the end arteriolar arcades causing a septic ischemic infarct in bone. As the IVD is an avascular structure which receives nutrients through diffusion from the adjacent vertebral end plate, the infection spreads to engulf the IVD as well (Fig. 13.1). In children, the IVD is vascularized and can be an isolated target for hematogenous bacterial seeding, causing primary discitis without involvement of adjacent vertebral end-plates. Facet joints of adults can be a target for hematogenous seeding as well. As in other synovial joints of the body, it is unclear whether the lack of a basement membrane in the synovium is the entry point for bacteria or the obliterated blood vessels of the closed growth plates

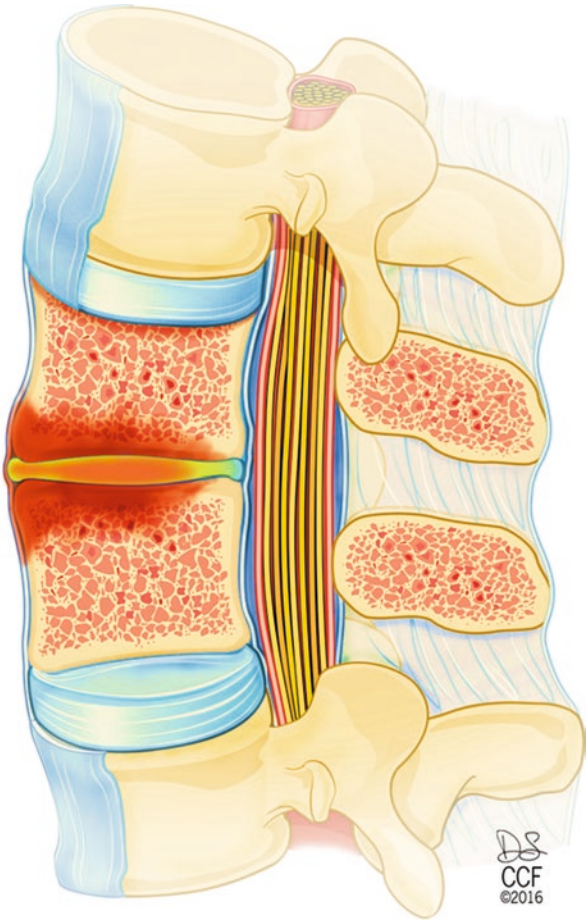


Fig. 13.1 Illustration of early spondylodiscitis, involving the intervertebral disc and two adjacent vertebral endplates. (Reprinted with permission Cleveland Clinic Center for Medical Art & Photography © 2016–2020. All Rights Reserved)

facilitate bacterial entry through microscopic infarcts. Posterior spread of infection from the affected IVD and vertebral bodies into the epidural space results in an epidural abscess (Fig. 13.2). If infection spreads antero-laterally, it extends into the retropharyngeal space in the cervical spine, into the space limited by the endothoracic fascia in the thoracic spine, along the costovertebral joints and ribs, or into the psoas muscles in the lumbar spine causing psoas muscle abscesses. Spread of infection from the facet joints anteriorly extends into an epidural abscess. Posterior spread decompresses into the paravertebral musculature (Fig. 13.3). A simplified classification of spine infections and their nomenclature is presented in Table 13.1.

A minority of spinal infections are caused by direct expansion of infection from adjacent structures, like infected aortic grafts, fistulous tracts and abscesses related to inflammatory bowel disease, or contiguous sites of osteomyelitis in areas of decubitus ulcers.

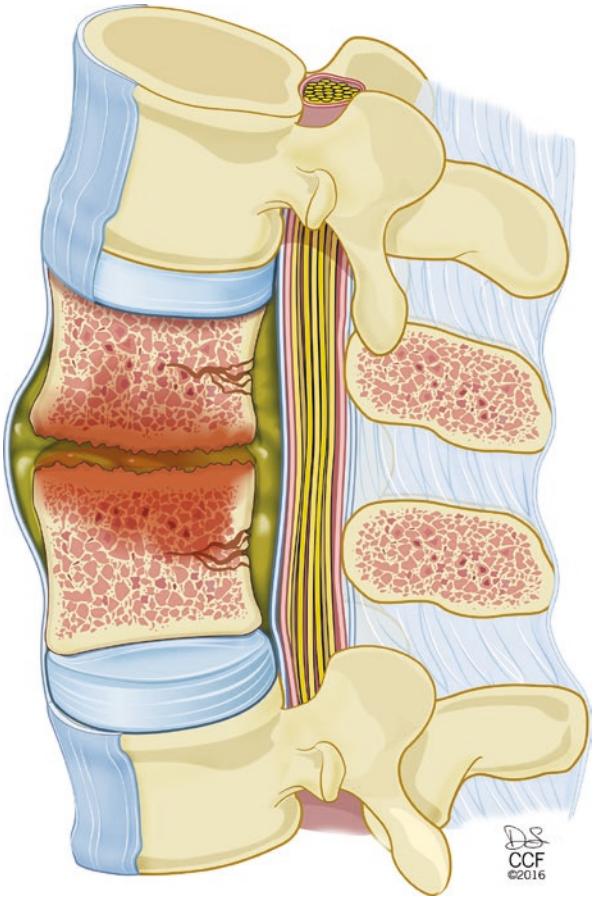


Fig. 13.2 Illustration of advanced spondylodiscitis with associated epidural abscess and prevertebral abscess. (Reprinted with permission Cleveland Clinic Center for Medical Art & Photography © 2016–2020. All Rights Reserved)

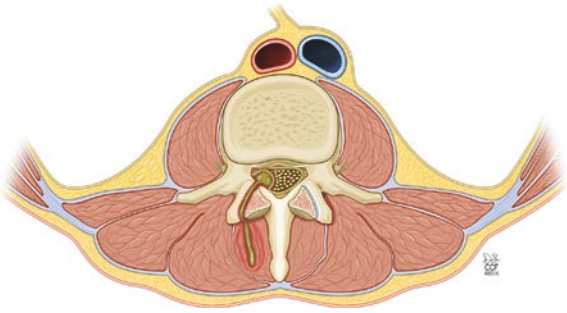


Fig. 13.3 Illustration of septic facet joint with associated epidural abscess and paravertebral abscess. (Reprinted with permission Cleveland Clinic Center for Medical Art & Photography © 2016–2020. All Rights Reserved)

Table 13.1 Nomenclature of spine infections

Nomenclature of spine infections	Pathology	Characteristics
Discitis	Isolated disc infection	Hematogenous bacterial seeding of vascularized disc in children
Spondylitis	Vertebral end plate infection	Earliest osteomyelitis of VB in adults
Spondylodiscitis	Discitis with adjacent vertebral body infection	Extent of most spine infections at presentation
Septic facet joint	Hematogenous septic arthritis of facet joints	Increasingly recognized entity in era of MRI
Epidural abscess	Purulence in epidural space	Contiguous spread of infection from infected disc space or septic facet joint

Epidemiology of Spine Infections

The incidence of spine infections is steadily increasing. Reports on annual incidence of vertebral osteomyelitis range from 1 per 100,000 to as high as 7 per 100,000 inhabitants [5–7]. In a Danish study the incidence tripled from 2/100,000 to 6/100,000 over a period from 1995 through 2008 [5]. A subsequent 2013 report from the Danish Civil Registration system, focused on a 1 year cross section in a single region confirmed a 5.3/100,000 cases in the general population, if adjusted for age >65 however, the incidence increased to 16.5 per 100,000 [8]. According to the Japanese Diagnosis Procedure Combination Database from 2007 to 2010 the incidence increased from 5.3 to 7.4 per 100,000 inhabitants. In Spain the incidence more than doubled from 0.6 to 1.5 per 100,000 from 1991 to 2009 [7].

The most recent retrospective review of the epidemiology of vertebral osteomyelitis in the United States calculated the average incidence of 4.7/100,000 cases of vertebral osteomyelitis annually [9]. In contrast to prior European studies, which reported a steady increase in incidence by age, with a peak incidence among patients 70 years of age and older, the majority of cases (49.5%) in the Unites States series are younger than 59 years old. The reason for this discrepant finding remains unclear, but could be related to a combination of increased awareness of practitioners, easier access to more accurate detection methods, i.e. widespread availability of MRI and the ongoing opioid crisis.

Microbiology

The majority of infections of the spine, in keeping with the rest of osteoarticular infections, is caused by gram positive bacteria, Staphylococci and Streptococci. In large series of pyogenic spine infections account for 60–90% of all cases [10–12].

In recent series that focus on presence of epidural abscess, gram positive organisms account for 90% of pathogens [13]. *Staphylococcus aureus* remains the single, most frequently isolated organism in cases of native spine infections [10–16]. The percentage of methicillin-resistant *S. aureus* (MRSA) varies, and seems to correlate with the incidence of IVDA and community acquisition.

Streptococci spp. are the second most frequent pathogen isolated from cases of spine infections [10, 11, 17]. Streptococci are a heterogenous group, encompassing virulent pathogens akin *to Staphylococcus aureus, i.e Steptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae* as well as less virulent organisms like viridans streptococci. Interestingly, these low virulent organisms are frequently implicated in cases of coinfections of spine and endocarditis [18].

Coagulase negative staphylococci (CNS) are less virulent pathogens. They are capable of seeding the spine and establishing overt infect during episodes of prolonged bacteremia. Prolonged CNS bacteremia is usually related to artificial material infection, like line infections, prosthetic valve endocarditis cases or intravascular shunts infections [19].

Gram negative bacilli historically accounted for 15–30% of pathogens in series of spine infections [10, 17]. Gram negative spine infections, like *E coli*, Proteus spp. or Klebsiella spp., can be seen following procedures or infections involving the genito-urinary or gastro-intestinal tract [20, 21]. It is unclear why the percentage has decreased in recent series, with gram positive organisms accounting for almost 90% of all microbiologically confirmed infections [13, 16, 22]. Our institution registry concurs with the more recent data, with less than 5% of spinal infections caused by gram negative pathogens (unpublished data). It is unclear whether a true shift in etiology has happened over the past 30 years or whether the extent of gram-negative infections has been overestimated in older case series. From an antimicrobial stewardship point, it is crucial to reevaluate the percentage of gram-negative spine infections and address empirical antimicrobial regimens that were designed to provide coverage for both gram positive and gram-negative organisms. Evidence for a particular choice of empiric antibiotic treatment in culture-negative cases is very limited.

Fungal infections, including Candida and Aspergillus species, present a minority of spine infections mostly limited to patients with injection drug abuse and immunocompromised hosts [23].

Tuberculosis of the spine and Brucella spp infections are found in endemic areas. Hematogenous seeding of the spine usually results in monomicrobial infections. Contiguous infections, originating from pelvic abscesses or overlying dehisced surgical wounds, are frequently polymicrobial.

Risk Factors and Clinical Presentation

Spinal infections remain a diagnostic challenge, since the classical presentation of progressive back pain in a patient with fever is frequently masked by concomitant distant infections or use of anti-inflammatory medications.

A high index of suspicion is required, especially in patients with risk factors for transient bacteremias, including those with chronic indwelling catheters, dialysis – dependent patients, intravenous drug abusers and patients subject to frequent medical procedures. Diabetes, malignancy, alcoholism and immunocompromised status are reported in most studies to be risk factors for spinal infections [10, 12, 14, 24].

The *sine qua non* of spinal infections is back pain, present in more than 80% of cases in most series [25–27]. The features of back pain associated with spine infections differ based on the anatomical location involved and extent of spread. Discitis and spondylodiscitis usually present as indolent midline pain exacerbated by movement that slowly progresses to unremitting, nocturnal pain at rest. In cases of lumbar spine spondylodiscitis with spread of infection into a psoas abscess, the pain can radiate into the side of the involved psoas muscle and can be exacerbated by flexion of the hip, as the psoas muscle is a major hip flexor. In thoracic spine spondylodiscitis, apart from the midline pain, the adjacent costovertebral joint can be involved, and the pain can radiate along the ipsilateral rib, mimicking the pain of herpes zoster, pleurisy or pancreatitis [28]. Cervical spondylodiscitis with anterior prevertebral spread of infection can present with neck pain associated with dysphagia and dysphonia [29]. Involvement of the posterior elements, as in the case of isolated hematogenously seeded facet joints, present more acutely, frequently as distinctly unilateral pain [30].

Fever is an inconsistent finding in spine infection, present on average in 2/3rds of cases, but ranging from 16% to 97% between series [10, 12, 31]. Given the ubiquitous use of anti-inflammatories for back pain, febrile episodes likely remain masked.

Neurological deficits in the form of motor weakness, sensory deficits, radicular pain or cauda equina syndrome, are present in 10–50% of cases and are caused by the development of an epidural abscess [32–34].

Diagnosis

The unacceptably long diagnostic delay in establishing spine infection as the cause of back pain remains a problem even in today's era of widespread MRI availability. Work up for new onset back pain should always include inflammatory markers. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in particular, are helpful in screening for serious causes of back pain, i.e. infection, fractures and metastatic lesions [35]. CRP is the only factor found to significantly shorten the diagnostic delay in pyogenic spine infections [36].

Imaging

Radiographs are frequently the initial examination performed. Changes of spine infection on X-ray lag several weeks following symptom onset and include decreased bone density, disc space narrowing, end plate destruction followed

ultimately by subluxation and instability. The imaging of choice for establishing a diagnosis of spine infection is MRI [37]. MRI findings include disc space narrowing and increased signal on fluid sensitive, or T2 weighted, sequences with enhancement following contrast administration. The endplates show low T1 signal, increased T2 signal and enhancement post contrast administration.

End-plate enhancement is the earliest sign of acute spondylodiscitis on MRI [38]. Paraspinal soft tissue inflammation is seen as increased T2 signal with enhancement and is crucial in differentiating infection from degenerative disc changes [39]. When possible, gadolinium should be administered, as it is essential in differentiating epidural abscess formation from phlegmonous inflammation [40]. Uniform enhancement is seen in phlegmonous inflammatory changes lacking a central liquid component. In contrast, an abscess is seen as a rim enhancing hypointense collection. The central low intensity signal on T1 weighted images represents the necrotic portion of the abscess, while the surrounding rim of granulation tissue is well perfused and enhances following contrast administration [41]. These two distinct MRI patterns correlate with intraoperative findings of gross purulence that can be surgically evacuated in cases of epidural abscesses, versus inflamed granulomatous tissue in phlegmon which cannot [42]. When an MRI cannot be obtained and the suspicion for epidural abscess is high, a CT myelogram is recommended. The block in free contrast flow indicates the level of compression, but can frequently not delineate the extent of an epidural abscess or whether it originates from an infected disc space or a septic facet joint [43]. It is also an invasive procedure associated with risks of infection and bleeding. Typical MRI findings of spondylodiscitis are shown in Fig. 13.4. Typical findings of epidural abscess on MRI are shown in Fig. 13.5.

In cases where MRI is contraindicated, contrast enhanced CT scan, PET scan, or combined gallium/T99c bone scan can help establish the diagnosis [44, 45]. Boney structures are better evaluated on CT compared to MRI, like end plate erosions and extent of destruction of vertebral bodies. CT is the modality of choice for evaluating for possible biopsy to help establish the diagnosis. The addition of intravenous contrast to CT makes soft tissue inflammation and abscesses more conspicuous. Unfortunately, a major limitation of CT is its inability to delineate epidural abscesses [46].

The best alternative to MRI, albeit limited by cost and availability, is FDG-PET-CT. It reliably identifies paraspinal soft tissue inflammation and psoas abscesses, as well as end-plated changes characteristic of spondylodiscitis. Its major drawback is lack of reliable identification of epidural abscesses [47, 48].

A frequently overlooked entity and underreported imaging finding is the septic facet joint. Radiographs are not helpful and typically only show degenerative changes. CT findings include erosive changes in the affected facets that are difficult to differentiate from degenerative changes, unless additional soft tissue inflammation, paraspinal or psoas muscle abscesses are present [49]. MRI is the imaging of choice for establishing a diagnosis of a septic facet joint, as early as 5 days after onset of symptoms [50]. On MRI, fluid in a facet joint with associated edema in the surrounding soft tissues of the paraspinal muscles should raise suspicion for

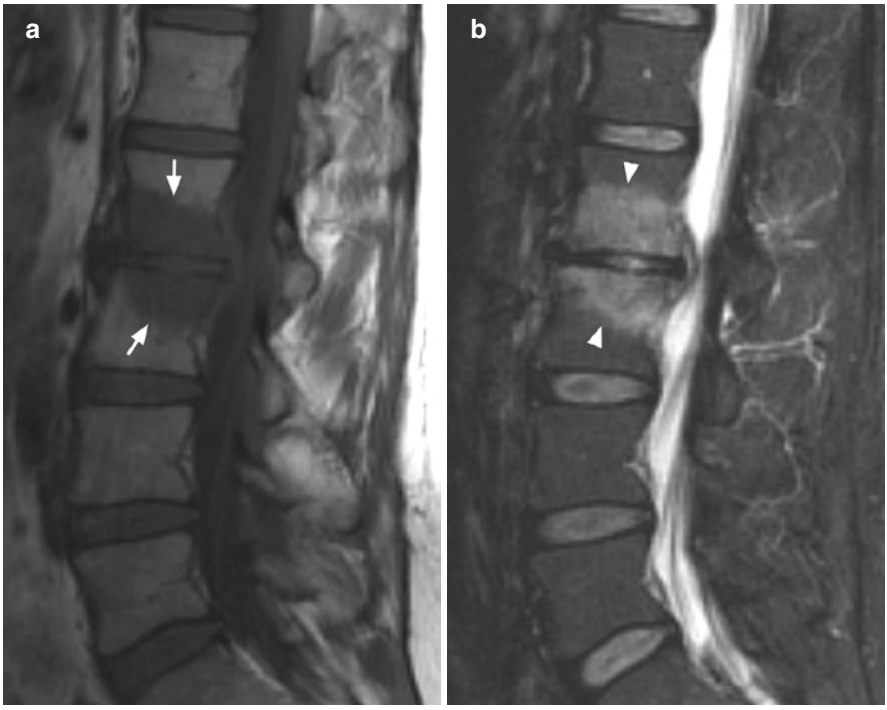


Fig. 13.4 (**a**) Findings of spondylodiscitis on T1W MRI imaging, arrows pointing to edema in adjacent vertebral bodies as hypo-intense signal area. (**b**) Findings of spondylodiscitis on STIR MRI, arrowheads pointing to edema of adjacent vertebral bodies as bright signal area

infection. Edema is more conspicuous on fat suppressed fluid sensitive sequence, T2WI or STIR (Fig. 13.6). The addition of gadolinium is preferred as it can delineate the presence of an epidural abscess originating from the culprit septic facet joint. The reported frequency of epidural abscesses originating from septic facet joints ranges from 25% to 60% and typically, though not uniformly, involve the posterior epidural space, forming a dorsal epidural abscess [30, 51].

Establishing Microbiological Etiology

Every effort should be made to confirm the microbiological etiology prior to initiating antibiotic therapy.

Blood cultures should be routinely obtained in patients with back pain who are febrile or have imaging findings suspicious for infection. They are positive in roughly 60% of bacterial spine infection cases, the yield ranging from 30% to 72% [52]. Empiric antibiotics should be withheld until the microbiological diagnosis is established in all but critically ill patients with signs of sepsis. In patients with

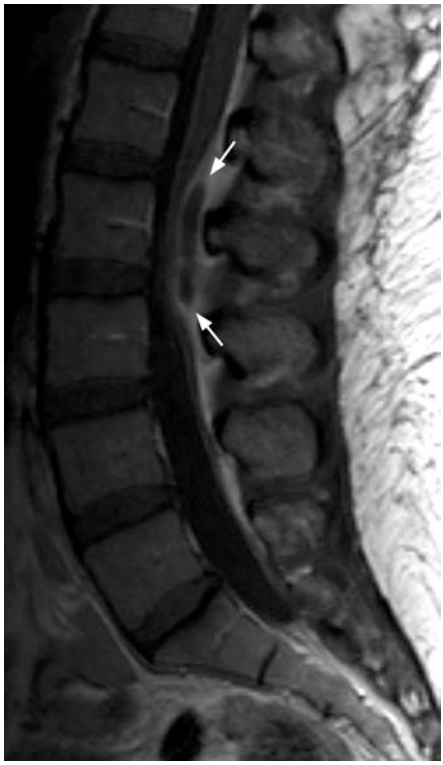


Fig. 13.5 Findings of epidural abscess on gadolinium-enhanced T1W MRI, arrows delineating the proximal and distal end of the dorsally located epidural abscess

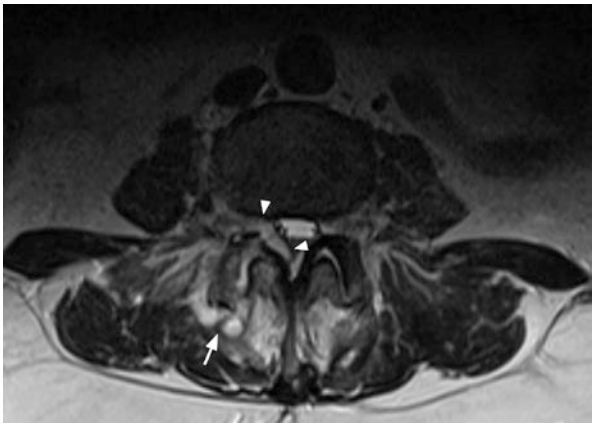


Fig. 13.6 Findings of a right sided septic facet joint on T2W MRI, arrowheads pointing to epidural extension and arrow pointing to paravertebral spread of infection

negative blood cultures or a single set isolate of a contaminant organisms like coagulase negative Staphylococcus, a CT guide or open biopsy is indicated. The yield of biopsy ranges from 30% to 75% and is compromised by prior administration of antibiotics [53–55]. Given the indolent course, side effects of empiric antimicrobial therapy and increased awareness of the need for antimicrobial stewardship, it is

deemed reasonable to withhold therapy for up to 2 weeks in stable patients [56]. A standard biopsy specimen should include an aspirate from the disc space or adjacent paraspinal collections, and a core specimen of the affected end plates. Samples are sent for both microbiology and pathology. Routine bacterial and fungal stains and cultures are done. In cases of exposure history, mycobacterial stains and cultures are requested. Pathology evaluation can be helpful in culture negative cases, where the presence of white blood cells indicates pyogenic osteomyelitis, or granulomatous lesions point towards mycobacterial etiology or Brucellosis [57]. Pathology can also be helpful in culture negative cases where imaging findings are equivocal and cannot differentiate between infection and non-infectious etiology. The absence of white blood cells on pathology can point away from infection in favor of degenerative Modic changes, ankylosing spondylitis, neuropathic-Charcot joint deformities of the spine or hemodialysis-associated spondylo-arthropathy [58]. Occasionally, crystal deposits can be found on histology, establishing a diagnosis of gout or pseudogout in the spine, entities indistinguishable from infection on both imaging and clinical presentation [59].

Cases where no pathogen is identified, either from blood cultures or tissue obtained by biopsy, are deemed as culture negative and placed on empiric antibiotic therapy. Recent guidelines recommend a second CT guided or open biopsy attempt at establishing the pathogen [56]. The yield of a second biopsy ranges from 0% to 60% and its applicability has been a topic of intense debate [60]. Though post-biopsy blood cultures had shown some promise as an adjunct tool to establish a microbiologic diagnosis, its overall low yield has made it an obsolete diagnostic test [61].

Broad-range PCR has emerged in recent years as an additional tool available in cases where microbiological cultures are not sufficiently sensitive, as in patients who have previously received antibiotics or when fastidious organisms are present. Limitations of these advanced diagnostic techniques are high rate of false positive results and lack of susceptibility testing to guide treatment [62, 63].

Treatment

Once the diagnosis of spine infection is established and the microbiological cause is confirmed, antimicrobials can be initiated. The goal of treatment is to eradicate infection, relieve back pain and prevent further complications, like cord compression and progressive bone loss leading to an unstable spine. Uncomplicated cases of spine infection, including discitis, spondylodiscitis, septic facet joints without significant boney erosions and epidural abscesses without significant neurologic deficits, are treated conservatively with good outcome. Six weeks of targeted antibiotic therapy suffices in most cases [64]. More extensive infections with spread into paraspinal tissue and associated psoas muscle abscesses may benefit from extended courses of up to 8–12 weeks [65]. Initial intravenous antibiotic regimens can safely be switched to oral antibiotics with high bioavailability once the CRP has decreased by 50%, if the pain has resolved and no residual neurological deficits are present

[66]. The therapeutic response is monitored clinically and with serial inflammatory markers. End of treatment cross-sectional imaging is not recommended if pain has resolved and inflammatory markers have normalized [56]. MRI findings can lag up to 4–6 weeks behind clinical improvement, and persistence of findings on imaging can create a conundrum for the treating physician and the patient. Only in cases where back pain persists or recurs, or inflammatory markers fail to improve, should repeat imaging be performed [67].

Some patients will require surgery. Surgical indications include acute neurological deficits caused by cord compression from epidural abscesses and mechanical instability of the vertebral column due to loss of bone stock to infectious osteolysis (Figs. 13.7 and 13.8). Occasionally, unremitting pain and prolonged bacteremia can present a relative surgical indications. Historically, the treatment of choice for all epidural abscesses was surgical decompression [68, 69]. Currently, the dilemma is whether or not to proceed with surgical decompression of an epidural abscess. Over the past two decades, conservative management of epidural abscesses, with antibiotics alone has become a viable option for an increasing number of patient. Epidural

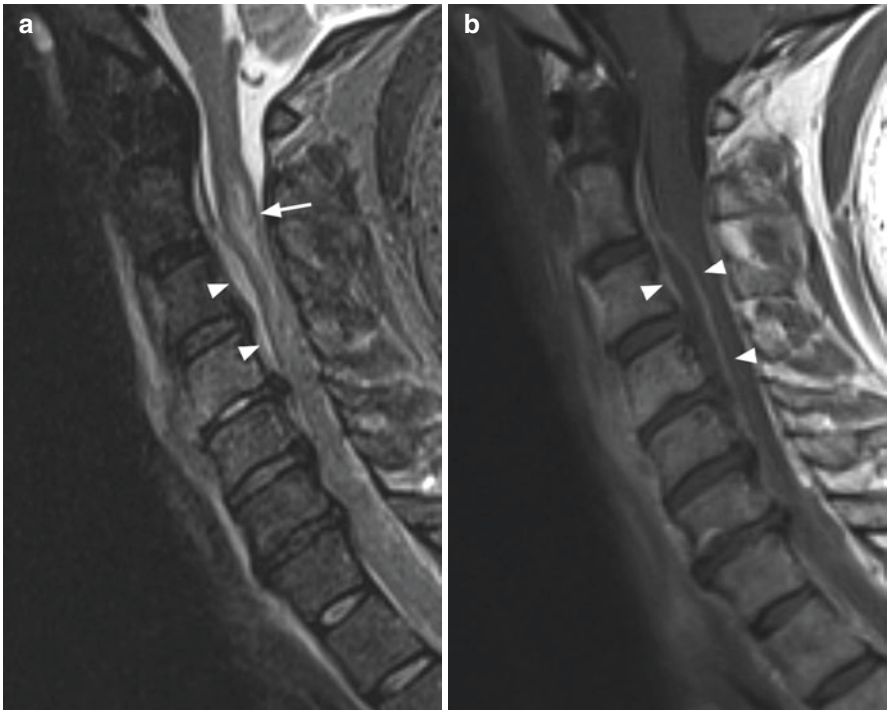


Fig. 13.7 (**a**) Findings of cervical spondylodiscitis associated prevertebral and epidural extension on STIR MRI. Arrowheads delineate epidural collection causing cord compression with marked cord edema, arrow pointing to bright signal in spinal cord. (**b**) Typical finding of a ventrally located epidural abscess on gadolinium-enhanced T1W MRI. Arrowheads delineating rim enhancement of the abscess

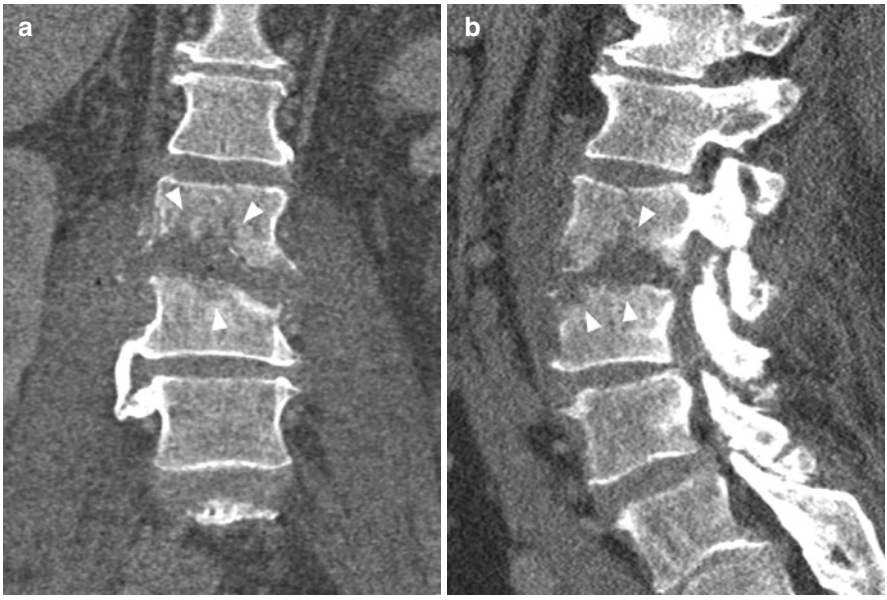


Fig. 13.8 (**a**) Coronal CT imaging findings of advanced vertebral body destruction due to spondylodiscitis. Arrowheads pointing to extensively eroded vertebral endplates. (**b**) Sagittal CT imaging findings of advanced vertebral body destruction with fracture of proximal vertebral body (arrowheads)

abscesses of known causative organism and without neurological deficits can safely be managed conservatively, with antibiotics alone [70, 71]. Patients with neurological deficits should undergo immediate decompression, as it is not known at which point in time the deficits become irreversible [71]. It is acceptable to proceed with conservative management in cases of mild neurological deficits with close follow up. The failure rate of conservative management ranges from 30% to 40% [72, 73]. The outcome of delayed surgery following conservative management failure is suboptimal. It is therefore important to be able to predict which patients are at risk for failure. Numerous algorithms for non-operative management failure of epidural abscesses have been published, all based on retrospective cohort studies [16, 72, 74]. Models are based on the presence of risk factors like diabetes, neoplasm, old age, presence of methicillin-resistant *Staphylococcus aureus*, elevated CRP and white blood cells. Most of the models were not validated in subsequent cohorts and are of limited clinical utility.

Isolated case reports of CT-guide aspiration of epidural collections, as an adjunct to conservative management, confirm its feasibility but the practice is not widespread in clinical setting [75, 76]. The concept is based on aspiration and irrigation of multilevel epidural abscesses under CT guidance. Only dorsally located epidural abscesses with a confirmed liquid component on MRI and absence of significant bony destruction associated with spondylodiscitis qualify for percutaneous drainage [77]. Routine CT guided procedures can provide therapeutic support. Psoas

abscesses associated with lumbar spondylodiscitis, if not multiloculated and with diameters greater than 3 cm, can be successfully drained to decrease infectious load. The optimal therapeutic approach to septic facet joints is unknown. Most are treated in accordance with vertebral osteomyelitis guidelines. If they are associated with an epidural abscess, the presence of neurological deficits determines the therapeutic approach. Occasionally, a septic facet joint can be the source of prolonged bacteremia, especially with *Staphylococcus aureus*. Aspiration under CT guidance of purulent content from the facet joint space can relieve symptoms and help manage source control [30].

Surgical management involves radical debridement of all infected tissue and reconstruction of lost bone support. Debrided bone defects are filled in with bone grafts or, in recent years, titanium mesh cages.

In addition to foregoing the morbid procedure of harvesting bone graft, Titanium is more resistant to bacterial adherence compared to other metals, and results in higher fusion rates and better sagittal alignment [78–80]. A significant shift in management occurred when it became evident that placement of metal into an actively infected spine did not compromise outcome [79, 81]. Neither the use of Rifampin or chronic suppressive antibiotics are needed following hardware placement in acute cases of spine infection, as they do not impact long term outcome or failure rate [82]. The majority of treatment failures happen within the first postoperative year, thus continuing chronic suppressive antibiotics beyond the initial year is unlikely beneficial [82]. Intraoperative use of topical antibiotic delivery systems have found its applications in surgical management of spine infections. Injectable antibiotic eluting bone graft substitutes have been used successfully to eradicate infection and promote fusion [83].

Outcome

Over the course of the past century, spine infection has evolved from an acute, life threatening illness of the young, with associated high mortality rates, to a more prolonged, indolent disease of the older population, associated with chronic disabling sequelae and lower mortality rates [10]. Estimates of mortality range widely between 1.2% and 20% in prior studies, but is reported as 2.1% in-hospital mortality in the U.S. by Issa et al. [5, 7, 9, 34, 52, 84, 85]. It appears that long-term mortality in spine infections is relates to comorbidities as shown in Table 13.2.

Prior studies of long term functional outcomes of spine infection found significant morbidity and high rates of adverse outcomes [86, 87]. Recent data supports better recovery rates following eradication of infection and restoration of mechanical stability of the spine [88]. Impaired quality of life is attributable to residual pain, paralysis and associated more frequently with female gender. It has been noted previously by Hadjipavlou et al. that residual back pain, attributable to kyphosis or pseudoarthrosis, was more prevalent in cases of spine infection managed non-operatively [11]. Certain features of spine infection may relate to worse outcomes.

Table 13.2 Mortality of spine infections and associated factors

Study	Mortality (%)	Factors associated with mortality
McHenry (2002) [10]	11%	Diagnostic delay, motor weakness, paralysis, nosocomial acquisition
Akiyama (2013) [7]	6%	Older age, diabetes, dialysis, cirrhosis, endocarditis, malignancy
Kehrer (2015) [5]	20%	Epidural abscess, neurodeficits, comorbidities
Kokabu (2017) [88]	3% vs 15%	No comorbidities vs comorbidities

Infections involving the cervical spine seem to have higher mortality compared to lumbar and thoracic locations [89]. Extreme elevation of inflammatory markers, i.e. CRP values above 100 mg/L on presentation was found to relate to higher mortality [22]. Though spine infections caused by MRSA where associated with prolonged bacteremia and more frequent recurrences, compared to MSSA infections, the overall mortality did not differ significantly [90]. Most importantly, a diagnostic delay exceeding 60 days was associated with poor outcome [91].

Summary

Infections of the spine are becoming an increasing occurrence in developed countries with an aging population. Advanced instrumentation predisposes patient to frequent transient episodes of bacteremia. The spectrum of spinal infections is a result of hematogenous bacterial or rarely fungal seeding of vertebral end plates and facet joints. Unopposed infection spreads into adjacent anatomic structures of the spine and causes phlegmons or abscesses in the epidural space, paraspinal and psoas muscles and prevertebral soft tissue spaces. Back pain is universally present as the main complaint, but given its ubiquitous nature adds to the pitfalls of diagnosing a spine infection in a timely manner. Though significant progress has been made in the treatment of spine infections, the diagnostic delay remains unacceptably long. CRP is the sole inflammatory marker that aids in establishing a diagnosis of serious causes of back pain and shortens the diagnostic delay in infections of the spine. The imaging of choice for diagnosing spine infections is Gadolinium enhanced MRI. FGD PET CT scan is a viable option in patients with contraindications to MRI. CT myelograms are used for locating a spinal epidural abscess if MRI not feasible and clinical suspicion is high. The most frequent etiologic agents are gram positive bacteria, namely Staphylococcus aureus. A minority of cases are caused by enterobacteriaceae. Fungal infections are mostly restricted to injection drug use and severely immunocompromised patients. In today's era of antimicrobial stewardship, a concerted effort has to be made to establish the microbiological diagnosis. In hemodynamically stable patients, empiric antimicrobial therapy should be withheld until a microbiological agent is recovered either from blood cultures or CT guided biopsy samples. Targeted antibiotic therapy can be initiated thereafter. The standard

duration of therapy in uncomplicated cases is 6 weeks. Response to therapy is monitored clinically and by following serial inflammatory markers. Initial antibiotic therapy is administered intravenously, but a switch to highly bioavailable oral agents is acceptable in cases of clinical improvement and with down-trending inflammatory markers. End of treatment imaging studies are not recommended. Repeat imaging is reserved for cases with suboptimal therapeutic response, with ongoing symptoms or persistently elevated inflammatory markers. An increasing number of spine infections are managed conservatively, with antibiotic therapy only. In the acute setting, onset of neurologic deficits and mechanical instability of the spine require surgical intervention. Following completion of therapy, residual mechanical instability may be the cause of chronic pain and is eventually managed surgically as well. A number of models predicting the failure rate of conservative management as a tool to assess the need for early surgery are available. Their applicability in real time clinical setting remains to be determined.

References

1. Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. Pain Pract. 2008;8(1):18–44.
2. Nixon GW. Hematogenous osteomyelitis of metaphyseal-equivalent locations. AJR Am J Roentgenol. 1978;130(1):123–9.
3. Jaumard NV, Welch WC, Winkelstein BA. Spinal facet joint biomechanics and mechanotransduction in normal, injury and degenerative conditions. J Biomech Eng. 2011;133(7):071010.
4. Parkin IG, Harrison GR. The topographical anatomy of the lumbar epidural space. J Anat. 1985;141:211–7.
5. Kehrer M, Pedersen C, Jensen TG, Lassen AT. Increasing incidence of pyogenic spondylodiscitis: a 14-year population-based study. J Infect. 2014;68(4):313–20.
6. Lora-Tamayo J, Euba G, Narvaez JA, Murillo O, Verdaguer R, Sobrino B, et al. Changing trends in the epidemiology of pyogenic vertebral osteomyelitis: the impact of cases with no microbiologic diagnosis. Semin Arthritis Rheum. 2011;41(2):247–55.
7. Akiyama T, Chikuda H, Yasunaga H, Horiguchi H, Fushimi K, Saita K. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. BMJ Open. 2013;3(3):e002412.
8. Brummerstedt M, Bangstrup M, Barfod TS. High mortality from pyogenic vertebral osteomyelitis: a retrospective cohort study. Spinal Cord Ser Cases. 2018;4:59.
9. Issa K, Diebo BG, Faloon M, Naziri Q, Pourtaheri S, Paulino CB, et al. The epidemiology of vertebral osteomyelitis in the United States from 1998 to 2013. Clin Spine Surg. 2018;31(2):E102–E8.
10. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis. 2002;34(10):1342–50.
11. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ. Hematogenous pyogenic spinal infections and their surgical management. Spine (Phila Pa 1976). 2000;25(13):1668–79.
12. Carragee EJ. Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am. 1997;79(6):874–80.
13. Artenstein AW, Friderici J, Holers A, Lewis D, Fitzgerald J, Visintainer P. Spinal epidural abscess in adults: a 10-year clinical experience at a tertiary care academic medical center. Open Forum Infect Dis. 2016;3(4):ofw191.
14. Aguilar-Company J, Pigrau C, Fernandez-Hidalgo N, Rodriguez-Pardo D, Falco V, Lung M, et al. Native vertebral osteomyelitis in aged patients: distinctive features. An observational cohort study. Infection. 2018;46(5):679–86.

15. Gupta A, Kowalski TJ, Osmon DR, Enzler M, Steckelberg JM, Huddleston PM, et al. Long-term outcome of pyogenic vertebral osteomyelitis: a cohort study of 260 patients. Open Forum Infect Dis. 2014;1(3):ofu107.
16. Kim SD, Melikian R, Ju KL, Zurakowski D, Wood KB, Bono CM, et al. Independent predictors of failure of nonoperative management of spinal epidural abscesses. Spine J. 2014;14(8):1673–9.
17. Nolla JM, Ariza J, Gomez-Vaquero C, Fiter J, Bermejo J, Valverde J, et al. Spontaneous pyogenic vertebral osteomyelitis in nondrug users. Semin Arthritis Rheum. 2002;31(4):271–8.
18. Murillo O, Grau I, Gomez-Junyent J, Cabrera C, Ribera A, Tubau F, et al. Endocarditis associated with vertebral osteomyelitis and septic arthritis of the axial skeleton. Infection. 2018;46(2):245–51.
19. Bucher E, Trampuz A, Donati L, Zimmerli W. Spondylodiscitis associated with bacteraemia due to coagulase-negative staphylococci. Eur J Clin Microbiol Infect Dis. 2000;19(2):118–20.
20. Khan IA, Vaccaro AR, Zlotolow DA. Management of vertebral diskitis and osteomyelitis. Orthopedics. 1999;22(8):758–65.
21. Gasbarrini AL, Bertoldi E, Mazzetti M, Fini L, Terzi S, Gonella F, et al. Clinical features, diagnostic and therapeutic approaches to haematogenous vertebral osteomyelitis. Eur Rev Med Pharmacol Sci. 2005;9(1):53–66.
22. Loibl M, Stoyanov L, Doenitz C, Brawanski A, Wiggermann P, Krutsch W, et al. Outcome-related co-factors in 105 cases of vertebral osteomyelitis in a tertiary care hospital. Infection. 2014;42(3):503–10.
23. Yang H, Shah AA, Nelson SB, Schwab JH. Fungal spinal epidural abscess: a case series of nine patients. Spine J. 2019;19(3):516–22.
24. Hadjipavlou AG, Berguist S, Chen J, Necessary JT, Muffoletto AJ. Vertebral osteomyelitis. Curr Treat Options Infect Dis. 2000;2:226–37.
25. Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian University Hospital 1987–97: clinical features, laboratory findings and outcome. Scand J Infect Dis. 1998;30(2):147–51.
26. Priest DH, Peacock JE Jr. Hematogenous vertebral osteomyelitis due to Staphylococcus aureus in the adult: clinical features and therapeutic outcomes. South Med J. 2005;98(9):854–62.
27. Bateman JL, Pevzner MM. Spinal osteomyelitis: a review of 10 years' experience. Orthopedics. 1995;18(6):561–5.
28. Luney M, Adiamah A, Pearson L. Thoracic spondylodiscitis presenting as abdominal pain. BMJ Case Rep. 2016;2016
29. Ghaly G, Espeso A, Fish B. Idiopathic cervical osteomyelitis presenting as dysphagia. J Surg Case Rep. 2010;2010(3):6.
30. Muffoletto AJ, Ketonen LM, Mader JT, Crow WN, Hadjipavlou AG. Hematogenous pyogenic facet joint infection. Spine (Phila Pa 1976). 2001;26(14):1570–6.
31. Jensen AG, Espersen F, Skinhoj P, Rosdahl VT, Frimodt-Moller N. Increasing frequency of vertebral osteomyelitis following Staphylococcus aureus bacteraemia in Denmark 1980–1990. J Infect. 1997;34(2):113–8.
32. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. QJM. 2001;94(9):465–70.
33. Legrand E, Flipo RM, Guggenbuhl P, Masson C, Maillefert JF, Soubrier M, et al. Management of nontuberculous infectious discitis. Treatments used in 110 patients admitted to 12 teaching hospitals in France. Joint Bone Spine. 2001;68(6):504–9.
34. Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, Reguera JM, Palomino-Nicas J, Martos F, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. Ann Rheum Dis. 1997;56(12):709–15.
35. Siemionow K, Steinmetz M, Bell G, Ilaslan H, McLain RF. Identifying serious causes of back pain: cancer, infection, fracture. Cleve Clin J Med. 2008;75(8):557–66.
36. Jean M, Irisson JO, Gras G, Bouchand F, Simo D, Duran C, et al. Diagnostic delay of pyogenic vertebral osteomyelitis and its associated factors. Scand J Rheumatol. 2017;46(1):64–8.
37. Dagirmanjian A, Schils J, McHenry M, Modic MT. MR imaging of vertebral osteomyelitis revisited. AJR Am J Roentgenol. 1996;167(6):1539–43.

38. Dunbar JA, Sandoe JA, Rao AS, Crimmins DW, Baig W, Rankine JJ. The MRI appearances of early vertebral osteomyelitis and discitis. Clin Radiol. 2010;65(12):974–81.
39. Diehn FE. Imaging of spine infection. Radiol Clin N Am. 2012;50(4):777–98.
40. Ledermann HP, Schweitzer ME, Morrison WB, Carrino JA. MR imaging findings in spinal infections: rules or myths? Radiology. 2003;228(2):506–14.
41. Parkinson JF, Sekhon LH. Spinal epidural abscess: appearance on magnetic resonance imaging as a guide to surgical management. Report of five cases. Neurosurg Focus. 2004;17(6):E12.
42. Suppiah S, Meng Y, Fehlings MG, Massicotte EM, Yee A, Shamji MF. How best to manage the spinal epidural abscess? A current systematic review. World Neurosurg. 2016;93:20–8.
43. Gerstein N. Spinal epidural abscess. N Engl J Med. 2007;356(6):638; author reply -9.
44. Love C, Palestro CJ. Nuclear medicine imaging of bone infections. Clin Radiol. 2016;71(7):632–46.
45. Ohtori S, Suzuki M, Koshi T, Yamashita M, Yamauchi K, Inoue G, et al. 18F-fluorodeoxyglucose-PET for patients with suspected spondylitis showing Modic change. Spine (Phila Pa 1976). 2010;35(26):E1599–603.
46. Prodi E, Grassi R, Iacobellis F, Cianfoni A. Imaging in spondylodiskitis. Magn Reson Imaging Clin N Am. 2016;24(3):581–600.
47. Prodromou ML, Ziakas PD, Poulou LS, Karsaliakos P, Thanos L, Mylonakis E. FDG PET is a robust tool for the diagnosis of spondylodiscitis: a meta-analysis of diagnostic data. Clin Nucl Med. 2014;39(4):330–5.
48. Smids C, Kouijzer IJ, Vos FJ, Sprong T, Hosman AJ, de Rooy JW, et al. A comparison of the diagnostic value of MRI and (18)F-FDG-PET/CT in suspected spondylodiscitis. Infection. 2017;45(1):41–9.
49. Tali ET, Gultekin S. Spinal infections. Eur Radiol. 2005;15(3):599–607.
50. Andre V, Pot-Vaucel M, Cozic C, Visee E, Morrier M, Varin S, et al. Septic arthritis of the facet joint. Med Mal Infect. 2015;45(6):215–21.
51. Narvaez J, Nolla JM, Narvaez JA, Martinez-Carnicero L, De Lama E, Gomez-Vaquero C, et al. Spontaneous pyogenic facet joint infection. Semin Arthritis Rheum. 2006;35(5):272–83.
52. Mylona E, Samarkos M, Kakalou E, Fanourgiakis P, Skoutelis A. Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. Semin Arthritis Rheum. 2009;39(1):10–7.
53. de Lucas EM, Gonzalez Mandly A, Gutierrez A, Pellon R, Martin-Cuesta L, Izquierdo J, et al. CT-guided fine-needle aspiration in vertebral osteomyelitis: true usefulness of a common practice. Clin Rheumatol. 2009;28(3):315–20.
54. Kim CJ, Song KH, Park WB, Kim ES, Park SW, Kim HB, et al. Microbiologically and clinically diagnosed vertebral osteomyelitis: impact of prior antibiotic exposure. Antimicrob Agents Chemother. 2012;56(4):2122–4.
55. Rankine JJ, Barron DA, Robinson P, Millner PA, Dickson RA. Therapeutic impact of percutaneous spinal biopsy in spinal infection. Postgrad Med J. 2004;80(948):607–9.
56. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61(6):e26–46.
57. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med. 2010;362(11):1022–9.
58. Hong SH, Choi JY, Lee JW, Kim NR, Choi JA, Kang HS. MR imaging assessment of the spine: infection or an imitation? Radiographics. 2009;29(2):599–612.
59. Bridges KJ, Bullis CL, Wanchu A, Than KD. Pseudogout of the cervical and thoracic spine mimicking infection after lumbar fusion: case report. J Neurosurg Spine. 2017;27(2):145–9.
60. Kasalak O, Adams HJA, Jutte PC, Overbosch J, Dierckx R, Wouthuyzen-Bakker M, et al. Culture yield of repeat percutaneous image-guided biopsy after a negative initial biopsy in suspected spondylodiscitis: a systematic review. Skelet Radiol. 2018;47(10):1327–35.
61. Gras G, Buzele R, Parienti JJ, Debiais F, Dinh A, Dupon M, et al. Microbiological diagnosis of vertebral osteomyelitis: relevance of second percutaneous biopsy following initial negative biopsy and limited yield of post-biopsy blood cultures. Eur J Clin Microbiol Infect Dis. 2014;33(3):371–5.

62. Fuursted K, Arpi M, Lindblad BE, Pedersen LN. Broad-range PCR as a supplement to culture for detection of bacterial pathogens in patients with a clinically diagnosed spinal infection. Scand J Infect Dis. 2008;40(10):772–7.
63. Fenollar F, Roux V, Stein A, Drancourt M, Raoult D. Analysis of 525 samples to determine the usefulness of PCR amplification and sequencing of the 16S rRNA gene for diagnosis of bone and joint infections. J Clin Microbiol. 2006;44(3):1018–28.
64. Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet. 2015;385(9971):875–82.
65. Park KH, Cho OH, Lee JH, Park JS, Ryu KN, Park SY, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. Clin Infect Dis. 2016;62(10):1262–9.
66. Lam KS, Webb JK. Discitis. Hosp Med. 2004;65(5):280–6.
67. Kowalski TJ, Berbari EF, Huddleston PM, Steckelberg JM, Osmon DR. Do follow-up imaging examinations provide useful prognostic information in patients with spine infection? Clin Infect Dis. 2006;43(2):172–9.
68. Heusner AP. Nontuberculous spinal epidural infections. N Engl J Med. 1948;239(23): 845–54.
69. Curry WT Jr, Hoh BL, Amin-Hanjani S, Eskandar EN. Spinal epidural abscess: clinical presentation, management, and outcome. Surg Neurol. 2005;63(4):364–71; discussion 71.
70. Butler JS, Shelly MJ, Timlin M, Powderly WG, O'Byrne JM. Nontuberculous pyogenic spinal infection in adults: a 12-year experience from a tertiary referral center. Spine (Phila Pa 1976). 2006;31(23):2695–700.
71. Tuchman A, Pham M, Hsieh PC. The indications and timing for operative management of spinal epidural abscess: literature review and treatment algorithm. Neurosurg Focus. 2014;37(2):E8.
72. Patel AR, Alton TB, Bransford RJ, Lee MJ, Bellabarba CB, Chapman JR. Spinal epidural abscesses: risk factors, medical versus surgical management, a retrospective review of 128 cases. Spine J. 2014;14(2):326–30.
73. Stratton A, Gustafson K, Thomas K, James MT. Incidence and risk factors for failed medical management of spinal epidural abscess: a systematic review and meta-analysis. J Neurosurg Spine. 2017;26(1):81–9.
74. Shah AA, Ogink PT, Nelson SB, Harris MB, Schwab JH. Nonoperative management of spinal epidural abscess: development of a predictive algorithm for failure. J Bone Joint Surg Am. 2018;100(7):546–55.
75. Lyu RK, Chen CJ, Tang LM, Chen ST. Spinal epidural abscess successfully treated with percutaneous, computed tomography-guided, needle aspiration and parenteral antibiotic therapy: case report and review of the literature. Neurosurgery. 2002;51(2):509–12; discussion 12.
76. Rust TM, Kohan S, Steel T, Lonergan R. CT guided aspiration of a cervical spinal epidural abscess. J Clin Neurosci. 2005;12(4):453–6.
77. Ran B, Chen X, Zhong Q, Fu M, Wei J. CT-guided minimally invasive treatment for an extensive spinal epidural abscess: a case report and literature review. Eur Spine J. 2018;27(Suppl 3):380–5.
78. Sundararaj GD, Amritanand R, Venkatesh K, Arockiaraj J. The use of titanium mesh cages in the reconstruction of anterior column defects in active spinal infections: can we rest the crest? Asian Spine J. 2011;5(3):155–61.
79. Rayes M, Colen CB, Bahgat DA, Higashida T, Guthikonda M, Rengachary S, et al. Safety of instrumentation in patients with spinal infection. J Neurosurg Spine. 2010;12(6):647–59.
80. Koptan W, Elmiligui Y, Elsharkawi M. Single stage anterior reconstruction using titanium mesh cages in neglected kyphotic tuberculous spondylodiscitis of the cervical spine. Eur Spine J. 2011;20(2):308–13.
81. Skaf GS, Domloj NT, Fehlings MG, Bouclaous CH, Sabbagh AS, Kanafani ZA, et al. Pyogenic spondylodiscitis: an overview. J Infect Public Health. 2010;3(1):5–16.

82. Arnold R, Rock C, Croft L, Gilliam BL, Morgan DJ. Factors associated with treatment failure in vertebral osteomyelitis requiring spinal instrumentation. Antimicrob Agents Chemother. 2014;58(2):880–4.
83. Bostelmann R, Steiger HJ, Scholz AO. First report on treating spontaneous infectious spondylodiscitis of lumbar spine with posterior debridement, posterior instrumentation and an injectable calcium sulfate/hydroxyapatite composite eluting gentamicin: a case report. J Med Case Rep. 2016;10(1):349.
84. Sapico FL, Montgomerie JZ. Vertebral osteomyelitis. Infect Dis Clin N Am. 1990;4(3):539–50.
85. Grammatico L, Baron S, Rusch E, Lepage B, Surer N, Desenclos JC, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002–2003. Epidemiol Infect. 2008;136(5):653–60.
86. O'Daly BJ, Morris SF, O'Rourke SK. Long-term functional outcome in pyogenic spinal infection. Spine (Phila Pa 1976). 2008;33(8):E246–53.
87. Solis Garcia del Pozo J, Vives Soto M, Solera J. Vertebral osteomyelitis: long-term disability assessment and prognostic factors. J Infect. 2007;54(2):129–34.
88. Kokabu T, Takahata M, Ishiguro N, Iwasaki N. Long-term prognosis of hematogenous vertebral osteomyelitis: mortality, quality of life, and pain. J Orthop Sci. 2017;22(5):822–7.
89. Urrutia J, Zamora T, Campos M. Cervical pyogenic spinal infections: are they more severe diseases than infections in other vertebral locations? Eur Spine J. 2013;22(12):2815–20.
90. Park KH, Chong YP, Kim SH, Lee SO, Choi SH, Lee MS, et al. Clinical characteristics and therapeutic outcomes of hematogenous vertebral osteomyelitis caused by methicillin-resistant Staphylococcus aureus. J Infect. 2013;67(6):556–64.
91. D'Agostino C, Scorzolini L, Massetti AP, Carnevalini M, d'Ettorre G, Venditti M, et al. A seven-year prospective study on spondylodiscitis: epidemiological and microbiological features. Infection. 2010;38(2):102–7.

Chapter 14
Infectious Primary Myelitis

Rohini D. Samudralwar and Rodrigo Hasbun

Myelitis

Myelitis is an inflammation of the spinal cord and can be either be a primary myelitis (directly involving the cord) or a secondary myelopathy due to compression of an adjacent epidural abscess [1]. Myelitis can also have an infectious or a noninfectious cause. Magnetic resonance imaging (MRI) of the spinal cord can be used to distinguish infectious versus non-infectious causes of myelitis, such as multiple sclerosis or neuromyelitis optica spectrum disorder (NMOSD). For the purpose of this chapter, we will focus on infectious primary myelitis (see other chapters for noninfectious, post infectious myelopathies, or secondary myelopathies).

Primary myelitis can present as either: (1) anterior myelitis, affecting primarily gray matter (2) leukomyelitis, affecting white matter, many times in the dorsal region or (3) transverse myelitis, involving an entire cross section of the spinal cord (Table 14.1) [1]. The most common clinical manifestations of myelitis are pain; motor deficits; sensory deficits; abnormalities of reflexes and muscle tone; and bowel/bladder dysfunction. The distribution of neurologic deficits depends on the spinal segment(s) affected and pattern of involvement. Weakness is present in virtually all spinal cord disorders, and may progress over hours, days, or weeks. Tone can be helpful in conjunction with weakness. The tone is usually decreased when the anterior horn cells of the gray matter are affected in "poliomyelitis" (e.g., polio virus, West Nile virus, Enterovirus D68). Involvement elsewhere in the spinal cord creates increased tone and spasticity. If the patient has associated radiculopathy, the local pain can follow the nerve roots involved. Spinal shock is sudden, characterized by areflexia

R. D. Samudralwar
Department of Neurology, University of Texas Health Science Center, Houston, TX, USA

R. Hasbun (✉)
UT Health McGovern Medical School, Houston, TX, USA
e-mail: Rodrigo.Hasbun@uth.tmc.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_14

Table 14.1 Infectious myelitis syndromes

Syndrome	Organism	Symptoms, signs, and neurologic findings	Other findings	Risk factors
Anterior "polio myelitis" syndrome	Poliovirus 1, 2, 3	*Onset:* Acute *Clinical patterns:* Spinal and bulbar paralysis *Common features:* Asymmetric flaccid paralysis (AFP)	"Minor illness" (3–4 d) influenza-like syndrome "Major illness" (5–7 d) aseptic meningitis, myeloencephalitis	Absence of protective immunity and travel in endemic areas
Acute flaccid paralysis	Nonpolio viruses Coxsackie A, Enterovirus D68 Enterovirus71, West Nile virus (WNV)	*Onset:* Acute *Clinical patterns:* Similar to polio	CNS phase aseptic meningitis, encephalitis, encephalomyelitis	Seasonal incidence in temperate climates (summer), year-round in tropical climates WNV: Vector borne (*mosquito*)
Ascending myelitis syndrome (leukomyelitis)	HIV-1	*Onset:* Acute/subacute		See Table 13.2
	HTLV-1	*Onset:* Subacute/chronic *Clinical patterns*: tropical spastic paraparesis (TSP) or HAM	"Rosette cells" in CSF lymphocytes Coinfection with HIV in IVDUs	Injecting drug use Prior residence in endemic areas
	Herpesviruses: CMV, EBV HSV, VZV	*Onset:* Acute *Clinical patterns:* Ascending pattern w/initial plexitis Asymmetric commonly	Primarily in immunosuppressed	
	Herpes B virus (Monkey B)	*Onset:* Subacute (5–30 d) *Clinical pattern:* Aseptic meningitis Ascending encephalomyelitis	Prodromal illness: Early (*vesicles*); Intermediate (*numbness, weakness, hiccups*)	Macaque monkey bite or exposure to tissues Laboratory exposure
Transverse myelitis syndrome	Primary myelitis VZV Dengue Spirochetes[a] Schistosoma	*Onset:* Acute (after prodrome) *Clinical patterns:* Sensory motor level		

Abbreviations: *CMV* cytomegalovirus, *CNS* central nervous system, *CSF* cerebrospinal fluid, *EBV* Epstein–Barr virus, *HAM* HTLV-1-associated myelopathy, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *HTLV* human T-cell lymphotropic virus, *IDUs* injecting drug users, *IVDU* intravenous drug use, *PNS* parasympathetic nervous system, *VZV* varicella-zoster virus, *WNV* West Nile virus

[a]Spirochetes include: *Borrelia* species (*B. burgdorferi* – Lyme, *B. recurrentis* – relapsing fever), *Leptospira* spp., *Treponema pallidum*

and loss of tone below the level of the lesion. Bladder dysfunction is usually not an early sign of spinal cord disease unless there is spinal shock. Chronic myelopathies cause a spastic bladder and result in urgency, frequency, and incontinence [1]. In this review; we will discuss the most common infectious causes of primary myelitis.

Viruses

Herpesviruses

All human herpesviruses have been implicated in myelitis, especially in the setting of immunosuppression. Herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and less commonly human herpesviruses 6 and 7 (HHV-6 and HHV-7) can cause myelitis. In adults, the most common herpes virus causing myelitis is HSV-2 with reactivation in sacral dorsal root ganglia resulting in lumbosacral radiculitis in addition to the myelitis (Elsberg syndrome) [2]. The diagnosis is usually made by a positive CSF VZV polymerase chain reaction (PCR). The presentation of HSV myelitis may be acute or subacute and intravenous high dose acyclovir should be given as soon as possible. The addition of adjunctive steroids should be considered as it may decrease the risk of ascending myelitis [3].

VZV can cause varicella in children or zoster (shingles) in adults. VZV can occur with an associated vesicular rash in a dermatomal distribution or without a rash (Zoster sine herpete) [4]. It can affect either immunosuppressed or immunocompetent patients and the presentation may be acute or subacute with asymmetric weakness and sensory deficits at the level where VZV reactivated. MRI may show spinal cord T2 hyperintensities, cord enhancement, and nerve root enhancement [4]. Patients should be treated with IV acyclovir at 10 mg/kg every 8 hours and in patients with severe cord edema or severe deficits, adjunctive steroids should be considered.

CMV is almost exclusively seen in immunosuppressed individuals such as those with acquired immunodeficiency syndrome (AIDS) or in solid or bone marrow transplant recipients [3, 4]. In can also cause a lumbosacral polyradiculitis in addition to the myelitis. CSF sometimes shows a neutrophilic pleocytosis, elevated protein, and a mild hypoglycorrachia. The diagnosis is done by obtaining a CSF CMV PCR and the treatment is intravenous ganciclovir with or without foscarnet [4]. Other herpes viruses that can rarely cause myelitis are Epstein Barr Virus (EBV), and human herpesviruses 6 and 7 (HHV-6 and HHV-7). EBV myelitis can occur concomitantly or after an infectious mononucleosis and diagnosis should be made both by serologies and by a CSF EBV PCR. HHV-6 is most commonly reported in the setting of allogeneic hematopoietic stem cell transplantation. The use of mycophenolate mofetil can be an important risk factor for HHV-6 myelitis and the treatment usually consists of IV ganciclovir or foscarnet. HHV-7 has been seen as isolated case reports of myelitis and can be treated with IV foscarnet [3, 4].

Herpes B virus or Cercopithecine herpesvirus 1 (or also known as *Herpesvirus simiae*), is a naturally occurring virus among primates of the genus *Macaca* that can cause fatal encephalomyelitis in humans following a bite, cage scratch, or other

exposure [5]. Patients may develop vesicular lesions at the site of the bite before developing neurologic manifestations. In addition to thorough washing, prophylactic oral acyclovir or valacyclovir should be considered after an at-risk exposure. In patients with disease, the Centers for Disease Control and Prevention (CDC) should be consulted and intravenous acyclovir or ganciclovir should be considered with evidence of any disease that can lower the mortality from 80% to 20% [5].

Enteroviruses

The enteroviruses are well-known causes of infectious myelitis, of which poliovirus has been the most historically significant. Poliovirus infection may present with fever, meningismus, and muscle spasms followed by acute flaccid paralysis (AFP) from infection of anterior horn cells. Largely due to effective vaccination programs, poliovirus cases have decreased by 99% and are now only seen in three countries (Pakistan, Afghanistan, and Nigeria). Other enteroviruses – such as Coxsackie A and B, echovirus, and enteroviruses D68, 70 and 71 – are now one of the most common causes of AFP. AFP refers to the development of decreased tone and weakness secondary to inflammation in the spinal cord that is seen more commonly in children and young adults between the months of August and October. The characteristic features include preceding febrile or respiratory illness, limb weakness and/or cranial nerve involvement. MRI shows gray matter involvement spanning >1 vertebral segment, and CSF analysis with pleocytosis. Limb weakness in AFP is caused by involvement of the anterior horn cells (gray matter in spinal cord), located at the ventral aspect of the spinal cord, controlling strength and hypertonicity. Damage in this area leads to the flaccid, decreased tone, and loss of strength, distinctive of this entity.

Enterovirus 71 – the causative agent of hand-foot-and-mouth disease – is an important exception and may mimic poliovirus in severity. Besides aseptic meningitis and encephalitis, EV 71 can cause myelitis; it may be difficult to distinguish between post infectious, immune-mediated cord injury and direct viral invasion. Detection of virus in CSF is supportive of direct viral invasion. Enteroviruses can be recovered from CSF as well as from blood, respiratory secretions, and stool. The most reliable diagnostic test is the enteroviral polymerase chain reaction (PCR) either in the respiratory secretions. Enterovirus is rarely detected by a CSF enterovirus PCR [6].

Flaviviruses

Since the appearance of *West Nile virus* (WNV) in the United States in 1999 until 2018, more than 50,000 WNV disease cases have been reported to the CDC. Although most WNV infection is asymptomatic or self-limited, neuroinvasive disease (NID) also occurs. AFP is one of the most serious presentations of NID and mimics poliomyelitis with injury to spinal cord anterior horn cells [2, 4]. AFP commonly accompanies WNV encephalitis, appears abruptly, and often results in asymmetric lower

extremity weakness. Areflexia, loss of bladder and bowel function, and signs of denervation may develop. In addition to acute flaccid myelitis, WNV can also present with cauda equina involvement or posterior cord related involvement leading to proprioceptive and sensory ataxia [7]. MRI of the spine many times can appear normal despite focal neurological examination. CSF typically demonstrates pleocytosis; diagnosis is done by serologic and CSF testing for WNV IgM. The WNV CSF PCR is not reliable. There is no human vaccine and no agents available to treat WNV disease.

Dengue can have several types of neurologic complications including meningitis, encephalitis, mono- and poly-neuropathies, Guillain–Barré syndrome (GBS) acute disseminated encephalomyelitis (ADEM), and myelitis [2, 4, 8]. The latter three complications are immune-mediated phenomena versus direct viral invasion [8]. CSF may demonstrate pleocytosis and elevated protein. Diagnosis is supported by serologic studies, CSF antibody testing or PCR, or by isolating the virus in the CSF. Care is supportive.

Other flaviviruses that have been associated with myelitis include Japanese encephalitis, tick-borne encephalitis, St. Louis encephalitis, Zika, and Hepatitis C [2, 4].

Retroviruses

Two retroviruses can cause myelopathy: HIV and human T-cell lymphotropic virus (HLTV-1) (Table 14.2) [2, 4]. HIV can cause vacuolar myelopathy but this is a diagnosis of exclusion. Although of distinctive neuropathology, it often coexists with the acquired immunodeficiency syndrome (AIDS)-associated dementia complex, also known as HIV encephalopathy or encephalitis. Vacuolar myelopathy was found in up to 50% of AIDS patients undergoing autopsy before the highly active antiretroviral therapy (HAART) era. In severe cases patients develop spastic paraparesis of the lower extremities with or without involvement of the arms. The weakness, which may be asymmetric, evolves over weeks. Coexisting neuropathy is often present. A discrete sensory level is unusual. Sphincter dysfunction occurs late in the course of the disease.

HTLV-1 is a retrovirus associated with adult T-cell leukemia/lymphoma and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). It is endemic in the Caribbean, Japan, Africa, and Italy but can be seen in the US [1, 9]. HTLV-1 can cause a chronic meningomyelitis with focal destruction of gray matter as well as demyelination of white matter primarily within the posterior columns and corticospinal tracts. A characteristic pattern is a longitudinally extensive transverse myelitis (LETM) referring to a transverse myelitis that spans at least three vertebral bodies. Neurologic disease usually begins in the fifth decade; women are more commonly affected than men. Patients have bilateral lower extremity weakness, stiffness, and back pain causing difficulty in walking. Neurogenic bladder and neuropathy can occur. Exam shows spastic paraparesis, hyperreflexia, extensor plantar reflexes, and reduced vibratory sensation and proprioception. Typically, the disease is slowly progressive and may ultimately leave patients wheelchair dependent; the upper extremities are usually not affected. HAM/TSP may be preceded,

Table 14.2 Infectious neurologic syndromes

Organism	Symptoms, signs, and neurologic findings	Other findings	Risk factors
HIV-1	*Onset:* Acute, subacute, and chronic *Clinical patterns*: Acute*:* GBS, Bell's palsy, mononeuritis multiplex Subacute/chronic: Vacuolar myelopathy: progressive spasticity; Ascending myelitis (leukomyelitis); Sensory peripheral neuropathy (CIDP)	*Acute* infection: aseptic meningitis, infectious mononucleosis syndrome *Late disease:* concurrent HIV encephalopathy	IVDU, sexual transmission, exposure to contaminated blood or body fluids
Dengue virus	*Onset:* acute or postinfectious *Clinical patterns:* Myelitis (transverse), Guillain–Barré syndrome, mono- or polyneuropathy, brachial neuritis, ADEM, encephalitis	Fever, headache, myalgia, arthralgia, rash, headache, leukopenia, thrombocytopenia, elevated liver transaminases	Mosquito exposure in endemic region
Mycoplasma pneumoniae	*Onset:* acute *Clinical patterns:* Ascending myelitis (leukomyelitis), polyradiculitis	Commonly associated with encephalitis	Recent upper respiratory infection in child or young adult
Brucella spp.	*Onset:* Subacute/chronic *Clinical patterns:* Radiculitis, myelitis, CNS palsies	Encephalitis, meningitis, mycotic aneurysm; Leukoclastic vasculitis, thrombocytopenia and splenomegaly in children	Unpasteurized milk products, occupational exposure to livestock and cattle parturition
Borrelia burgdorferi	*Onset:* Acute and chronic *Clinical patterns:* Acute: Bell's palsy, aseptic meningitis, encephalitis, transverse myelitis Chronic: weakness, paresthesias	*Acute*: Erythema chronicum migrans	Tick-bite travel or residence in endemic areas

Organism	Symptoms, signs, and neurologic findings	Other findings	Risk factors
Treponema pallidum	*Onset:* Acute and chronic *Clinical patterns:* Acute syphilitic meningitis Chronic asymptomatic Chronic symptomatic (meningovascular, behavioral, tabes dorsalis, myelopathy)	Dementia Gumma (cord/meninges) Uveitis, optic atrophy Deafness	Asymptomatic (abnormal CSF) and symptomatic neurosyphilis occurs after early syphilis. Higher risk with HIV infection
Mycobacterium tuberculosis	*Clinical patterns:* Meningitis, vasculitis, cord infarction, granulomatous myeloradiculitis, intramedullary tuberculoma, cord compression from vertebral collapse	Pulmonary disease, meningitis, fever	Travel to or residence in high prevalence region, homelessness, incarceration, institutionalization, contacts with known tuberculosis
Schistosoma spp.	*Clinical patterns:* Transverse myelitis, subacute myeloradiculopathy, encephalitis	Fever, abdominal pain, hepatosplenomegaly	Travel to or residence in endemic region
VZV	*Onset:* Acute *Clinical patterns:* Bell's palsy, Ramsey Hunt syndrome Sensory radiculitis (CNS and PNS) Ascending and transverse myelitis	Dermatomal vesicles Encephalitis Uveitis, corneal ulcer	Immunosuppression (with recrudescent VZV)
HSV	*Onset:* Acute and recurrent *Clinical patterns:* HSV-1: Bell's palsy; HSV-2: sacral radiculitis (Elsberg syndrome)	Ascending necrotizing myelitis Mollaret's meningitis	AIDS Primary genital HSV

Abbreviations: *ADEM* acute demyelinating encephalomyelitis, *CNS* central nervous system, *CSF* cerebrospinal fluid, *HSV* herpes simplex virus, *HIV* human immunodeficiency virus, *PNS* peripheral nervous system, *VZV* varicella-zoster virus, *IVDU* intravenous drug use, *GBS* Guillain–Barré syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy

more commonly in children, by infective dermatitis, a recurrent erythematous, scaly, and crusted rash of the scalp, face, neck, axilla, and groin. Diagnosis is established by the presence of HTLV-1 seropositivity. No effective antiretroviral or adjunctive therapies have been established to date.

Other Viruses

Other viruses that can occasionally be associated with myelitis include chikungunya virus, influenza virus, mumps, measles, hepatitis A and E, JC virus and rabies viruses [2, 4].

Bacteria

Syphilis

Treponema pallidum can cause four different types of spinal cord infections. (1) Tabes dorsalis is the best known manifestation that consists of degeneration of the dorsal roots and the posterior column of the spinal cord. Patients present clinically with lancinating pains, ataxic gait, paresthesias, and bladder dysfunction. On exam they can have Argyll Robertson pupils, diminished reflexes, impaired vibration and propiorception impaired pain and temperature with development of Charcot joints and extraocular muscle palsies [2, 4]. (2) Meningovascular syphilis causes an endarteritis of vessels that can cause thrombosis and infarction of spinal arteries. (3) Spinal cord compression from gummas of the meninges and cord and (4) Syphilitic meningomyelitis [1, 10]. Because of its varied presentations, syphilis should be considered in the differential diagnosis of nearly all diseases of the spinal cord. The serum rapid plasma reagin (RPR) titer is usually above 1:32 in neurosyphilis [10], and the CSF usually shows a lymphocytic pleocytosis, elevated protein, and normal glucose; HIV infection with or without HAART may impact these parameters. The CSF Venereal Disease Research Laboratory (VDRL) test is specific but generally insensitive. CSF fluorescent treponemal antibody test may also aid diagnosis. Steroids may be added to intravenous penicillin to prevent cord edema, ischemia, or Jarisch–Herxheimer reaction associated with treatment [1].

Mycoplasma Pneumoniae

CNS complications of *M. pneumoniae* infection are probably the most frequent extrapulmonary manifestation of infection. Although encephalitis is the most common neurologic complication, meningitis, polyradiculitis, ADEM, and transverse myelitis also occur. The exact pathogenesis of CNS disease is unknown, but it may

be secondary to direct invasion, elaboration of neurotoxins, autoimmune complexes, molecular mimicry, or vasculitis. A recent respiratory tract infection, especially in a child or young adult, should suggest the diagnosis [1, 2]. Diagnosis can be confirmed with positive CSF *M. pneumoniae* PCR or by retrospectively observing a four-fold rise in antibody titers. If active infection is present, antibiotic therapy may be effective. Doxycycline penetrates the CNS more effectively than macrolides but is contraindicated in young children. Steroids, plasmapheresis, and intravenous immunoglobulin (IVIG) have also been advocated but remain controversial.

Brucellosis

Brucellosis is a zoonotic disease caused by an aerobic, Gram-negative coccobacillus that is acquired by drinking unpasteurized dairy products [2]. Neurobrucellosis can present as chronic meningitis with cranial nerve palsies, an encephalitis or as a myelitis. Myelopathy typically involves the corticospinal tracts and produces a pure upper motor neuron syndrome without sensory findings. Secondary myelitis can occur from granulomatous spondylitis and epidural abscess. Radiculopathy due to chronic inflammation of intrathecal nerve roots complicates neurobrucellosis in an eighth of patients. CSF usually reveals a lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia. CSF cultures are positive in fewer than 50% of cases. Cultures of blood and tissue fluids may become positive in 2–4 days with modern automated liquid culture systems, particularly when specimens are first processed to release intracellular organisms. PCR methods are reportedly more sensitive than culture. Serum tube agglutination (TA) testing can support a diagnosis of brucellosis. CSF TA testing can help confirm a diagnosis of neurobrucellosis; however, there is no commonly agreed upon titer cut-point for CSF TA titers. Treatment of neurobrucellosis consists of intravenous ceftriaxone in combination with doxycycline and rifampin [2]. Surgical exploration and decompression may be warranted for symptomatic epidural abscess. Adjunctive steroids early in meningitis may reduce complications from vasculitis [1, 2].

Neuroborreliosis

Neuroborreliosis are tick-borne illnesses that are caused by *Borrelia burgdorferi* in the US (Lyme disease) and by *Borrelia garinni* in Europe. Neurological manifestations of neuroborreliosis include cranial nerve palsies (seventh palsy more commonly), radiculitis, peripheral neuropathy, aseptic meningitis and less frequently encephalopathy and myelitis. In Europe, neuroborreliosis may present with a painful meningoradiculitis known as Bannwarth syndrome. Skin manifestations that can be a clue for neuroborreliosis are erythema migrans (Lyme disease) and acrodermatitis chronica atrophicans in Europe [2, 4]. MRI of the spine in myelitis may be normal or demonstrate a centromedullary involvement pattern usually affecting the

midthoracic or lumbar levels. The CSF has a mild lymphocytic pleocytosis, with a normal glucose and a mildly elevated protein [2, 4]. The diagnosis is established with a screening enzyme-linked immunosorbent assay followed by a confirmatory Western Blot. An elevated CSF antibody index (quantitative comparison of serum to CSF Lyme-specific antibody levels) may support the diagnosis [2, 4]. The treatment of choice is ceftriaxone 2 gm IV daily for a 14–28 day course.

Tuberculosis

Mycobacterium tuberculosis may have several ways that can cause spinal cord involvment [2, 4]. Patients with tuberculosis meningitis can have radiculomyelitis (arachnoiditis), intradural extramedullary tuberculomas, acute or transverse myelitis, vasculitis with cord infarction, vertebral tuberculosis (Pott's disease), and syringomelia [2, 4]. Necrotizing tuberculous granulomas may directly affect spinal arteries. The thoracic cord is the most commonly affected followed by the cervical region [2]. The CSF typically shows a lymphocytic pleocytosis with hypoglycorrachia and significantly elevated protein (secondary to spinal block). Besides obtaining a CSF mycobacterial culture, a CSF *M. tuberculosis* PCR should be obtained that can give a rapid diagnosis and check for rifampin resistance [2, 4]. In the absence of drug resistance, the treatment is four drug therapy (rifampin, isoniazid, pyrazinamide, ethambutol) for 2 months followed by and additional 7–10 months of two-drug therapy (rifampin, isoniazid) with adjunctive steroids.

Parasites

Schistosomiasis

Schistosomiasis, a trematode, affects more than 230 million people worldwide [4]. Neuroschistosomiasis should be considered in the differential diagnosis of acute myelopathy in regions where *Schistosoma* species are prevalent. Myelitis is most common with *S. mansoni* and *S. haematobium* infection that are endemic in Africa, Middle East, and in Central and South America [2, 4]. Schistosoma ova spread hematogenously and invade the CNS where the host inflammatory response, including granuloma formation, can lead to acute myelopathy. The lower thoracic and lumbar cords are most commonly affected. Patients may present with lower extremity weakness, cauda equina syndrome, or lumbar or radicular pain. Spinal artery infarction may be found. Diagnosis is challenging; schistosomal ova are found in stool or urine in fewer than half of cases of neuroschistosomiasis [1, 2, 4]. CSF findings may be nonspecific, but may show eosinophils and elevated protein levels. Visualization of schistosomal forms in biopsy specimens provides definitive

diagnosis. Treatment is with steroids, to reduce inflammatory response, followed by praziquantel, though optimal treatment doses and duration are not established.

Toxocara canis and *T. catis* are round worms and the cause of visceral larva migrans and have occasionally been reported as a cause of myelitis. Patients present with typical symptoms of myelitis; lower extremity weakness is most common. MRI findings often reveal a single inflammatory lesion. Symptoms generally improve after albendazole therapy.

Other parasitic diseases found to cause spinal cord disease include gnathostomiasis, Acanthamoeba sp, *Taenia solium*, *Toxoplasma gondii*, and *Echinococcus granulosus*.

Fungal Diseases

Fungal infections rarely cause spinal cord disease, and present most commonly among immunosuppressed persons. Secondary myelopathy from epidural abscess, granuloma, or vertebral compression fracture is most commonly from *Aspergillus*, *Cryptococcus*, or *Candida* species. *Blastomyces* and *Coccidioides* also causes spinal and paraspinal disease. Fungal myelopathy may result from direct iatrogenic inoculation; cauda equina syndrome was noted in 17% of patients in an outbreak of *Exserohilum rostratum* from contaminated glucocorticoid injections. Iatrogenic paraspinal aspergillus infection has also been described [1].

Conclusions

Primary infectious myelitis has several causes that are treatable and a cause should be aggressively investigated. The most common causes are viruses such as the herpes viruses, arboviruses, enteroviruses and less likely retroviruses such as HIV and HTLV-1. The majority of the bacterial, mycobacterial, parasitic and fungal etiologies are treatable but diagnosis may be challenging. An MRI of the spine and CSF examination should be done on patients to help diagnose and guide therapy.

References

1. Percak J, Hasbun R. Chapter 78: myelitis and peripheral neuropathy. In: Schlossberg D, editor. Clinical infectious diseases. 2nd ed. Cambridge: Cambridge University Press; 2015. p. 510–23.
2. Grill MF. Infectious myelopathies. Continuum (Minneap Minn). 2018;24(2):441–73.
3. Berger J, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008;65(5):596–600.
4. Montalvo M, Cho T. Infectious myelopathies. Neurol Clin. 2018;36:789–808.

5. Johnston WF, Yeh J, Nierenberg R, Procopio G. Exposure to macaque monkey bite. J Emerg Med. 2015;49(5):634–7.
6. Messacar K, Schreiner TL, Van Haren K, Yang M, Glaser CA, et al. Acute flaccid myelitis: a clinical review of US cases 2012–2015. Ann Neurol. 2016;80(3):326–38.
7. Athar P, Hasbun R, Nolan MS, et al. Long-term neuromuscular outcomes of West nile virus infection: a clinical and electromyographic evaluation of patients with a history of infection. Muscle Nerve. 2018;57(1):77–82.
8. Almeida BA, Kroon EG, Romanelli RMC. Neurological manifestations of pediatric arboviral infections in the Americas. J Clin Virol. 2019;116:49–57.
9. Eusebio-Ponce E, Candel FJ, Anguita E. Human T-Cell Lymphotropic virus Type 1 and associated diseases in Latin America. Tropical Med Int Health. 2019;24(8):934–53.
10. Marra CM. Neurosyphils. Continuum (Minneap Minn). 2015;6:1714–28.

Chapter 15
Post-infectious Encephalomyelitis

Setty M. Magaña and Ariane G. Soldatos

Acute disseminated encephalomyelitis (ADEM), also known as post-infectious encephalomyelitis, is a rare, multifocal inflammatory demyelinating disease of the central nervous system (CNS). Historically, it has been classified as post-infectious ADEM, post-vaccination ADEM or sporadic ADEM based on suspected etiology [1]. The earliest reports of post-infectious ADEM in association with measles and smallpox date back to the eighteenth century [2]. Subsequent development of vaccinations against measles, mumps and rubella resulted in marked decrease of ADEM and neurologic sequelae secondary to those infections [1, 3]. However, ADEM continues to be among the most frequent pediatric inflammatory CNS demyelinating disorders and must be distinguished from infectious meningoencephalitides as well as chronic CNS demyelinating diseases, the latter of which require maintenance immunomodulatory therapies.

S. M. Magaña · A. G. Soldatos (✉)
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
e-mail: ariane.soldatos@nih.gov

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_15

Epidemiology

International population-based studies approximate the annual incidence of ADEM to be 0.3–0.6/100,000, with one study from California reporting an incidence of 0.4/100,000 children per year [4, 5]. ADEM occurs more frequently in children than adults, with a median age of onset of 5–8 years, and exhibits a male predominance [6, 7].

ADEM is commonly preceded by viral or bacterial infection in up to 75% of cases, manifesting mostly as a nonspecific upper respiratory infection. There is a latency up to 1 month between the antigenic trigger and the onset of neurological symptoms. Numerous viruses have been associated with ADEM, including cytomegalovirus, Epstein-Barr, herpes simplex, human herpes virus-6, hepatitis A, coxsackie, coronavirus, HIV, influenza (Fig. 15.1), varicella, West Nile virus, measles and rubella. Other pathogens implicated in ADEM include borrelia burgdorferi, chlamydia, leptospira, mycoplasma pneumoniae, rickettsia and beta hemolytic streptococcus [8–18]. Further evidence for an infectious trigger in ADEM is supported by seasonal peaks that have been observed in some studies [19, 20].

Post-vaccination ADEM represents less than 5% of all cases and is currently most often associated with measles, mumps, and rubella vaccination. Notably, the incidence of ADEM previously associated with measles virus infection was approximately 1 in 1000 cases whereas the incidence associated with the live measles vaccine is 1–2 per one million cases [18].

Given the high frequency of intercurrent infections in childhood, the observation that there is often a prodromal antigenic trigger, such as upper respiratory infection

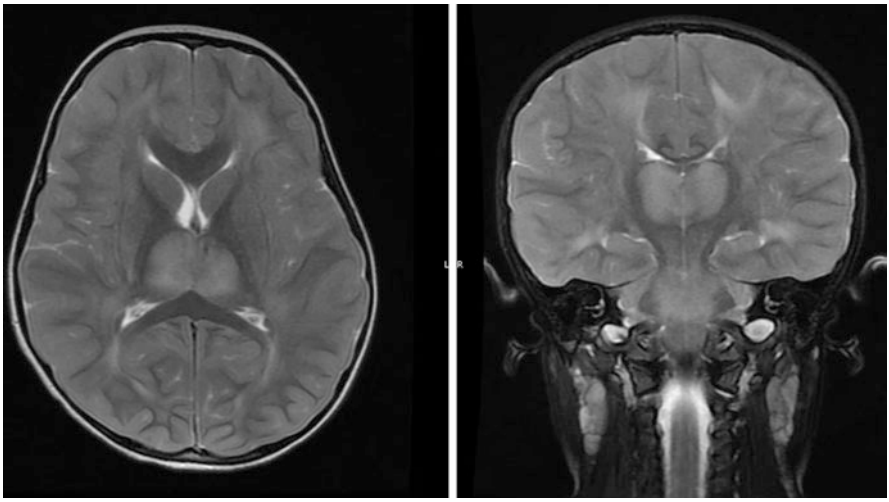


Fig. 15.1 ADEM Mimics. Axial T2 and coronal T2 showing bithalamic inflammation in a 3-year-old diagnosed with post-influenza "ADEM," found to have RANBP2-associated acute necrotizing encephalopathy (ANE)

or immunization, associated with the onset of ADEM is not surprising and thus confounds establishment of causality.

Clinical Features

ADEM presents acutely with encephalopathy (behavioral change or altered level of consciousness), rapidly progressive polyfocal neurologic deficits and is preceded by febrile prodromal illness (e.g. malaise, headache, nausea, vomiting, behavioral and mentation changes) in 50–75% of children. The presence of encephalopathy was added as a required diagnostic criterion in 2007 [21] such that case series prior to that change may be difficult to compare given that the antecedent cohorts may include more divergent patients. In cases with identifiable infectious trigger or vaccination, neurologic symptoms typically occur 4–13 days after the inciting trigger and can reach maximal deficits within 2–5 days from onset [19, 20, 22, 23]. Common neurological manifestations include pyramidal (long-tract) signs such as hemiparesis, cranial neuropathies from brainstem involvement, optic neuritis, speech difficulties, seizures, cerebellar ataxia, and spinal cord involvement (myelitis). Less common features include movement disorders, sensory symptoms, and very rarely, peripheral nervous system involvement [24]. Severe cases requiring intensive care unit admission have been reported in up to 25% of children with ADEM [25].

Diagnostic Testing

Neuroimaging

Although magnetic resonance imaging is the preferred modality, a computed tomography of the brain may need to be performed acutely to exclude causes of altered mental status such as space-occupying lesions (e.g. brain abscess) or severe cerebellitis causing posterior fossa swelling and fourth ventricular compression with risk of herniation, and ensure a lumbar puncture is safe to perform.

ADEM can affect the brain and spinal cord and result in ill-defined, large confluent demyelinating lesions with associated edema and swelling. T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) brain lesions classically reveal multifocal, bilateral, asymmetric, patchy hyperintense lesions that can involve: central and subcortical white matter, cortical gray-white matter junction, deep gray matter nuclei (thalami, basal ganglia) [26], cerebellum and brainstem. This contrasts with multiple sclerosis (MS) lesions which are classically periventricular, ovoid, juxtacortical, corpus callosal and well-defined [24, 27]. Gadolinium enhancement occurs in up to 30% of ADEM cases [23, 24, 28] and when present an open-ring pattern of enhancement can be seen. Leptomeningeal enhancement should prompt evaluation for an alternate diagnosis.

Spinal cord lesions are observed in 1/3 of patients and are often longitudinally extensive lesions (≥3 vertebral segments). Therefore, it is important to look for demyelination in other parts of the neuraxis such as with spine MRI to evaluate for myelitis, orbital imaging and optical coherence tomography (OCT) for optic neuritis.

Lumbar Puncture

Cerebrospinal fluid (CSF) analyses in ADEM are required to rule out infectious etiologies such as bacterial meningitis and herpes simplex encephalitis. If there is pleiocytosis it is usually lymphocytic; neutrophilic pleiocytosis can be seen in NMOSD. CSF leukocyte count has been reported normal in 42–72% of pediatric ADEM cases. CSF oligoclonal bands (OCBs), a marker of intrathecal clonal IgG synthesis and characteristically elevated in multiple sclerosis patients, are notably rare in pediatric ADEM cases [29]. Other associated features such as IgG index, are also unremarkable in the majority of ADEM patients. CSF protein may be elevated in 23–62% of ADEM cases.

Laboratory Studies

Nonspecific markers of inflammation as evidenced by leukocytosis, elevated erythrocyte sedimentation rate and C-reactive protein can be present in up to 2/3 of patients [19, 20, 22].

Infectious work-up, including viral and bacterial cultures of nasopharyngeal, oropharynx and stool specimens, as well as serological testing is important [17]. It is recommended to store a serum sample before IVIg treatment or plasmapheresis in the event that additional serology testing is needed.

Immunopathogenesis

The pathogenesis of ADEM remains incompletely understood, however, several pathomechanistic hypotheses have been proposed due to pathologic similarities between ADEM and the monophasic experimental autoimmune (allergic) encephalomyelitis (EAE) animal model. EAE is the most common rodent model for studying acute monophasic inflammatory demyelination and can be induced by immunization with myelin proteins and peptides [27, 30, 31]. It has been posited that ADEM is an autoimmune disorder triggered by an environmental stimulus (e.g.

infection) in a genetically susceptible host through molecular mimicry of autoreactive, myelin-specific T cells activated against shared antigenic determinants between myelin proteins and the infecting pathogen [8, 9]. Since many cases of ADEM have no identifiable infectious trigger, it has also been suggested that ADEM is caused by activation of T cells in a nonspecific inflammatory manner [27].

Pathology

The pathological hallmark of ADEM lesions consists of perivenular sleeves of demyelination in association with inflammatory infiltrates of B and T lymphocytes, neutrophils, myelin-laden macrophages, microglia and occasional granulocytes and plasma cells [32]. In some cases, perivenous lesions can coalesce to form large confluent demyelinated lesions. Edema and swelling can be seen in brain and spinal cord, however they may also appear grossly normal. Axonal damage has been reported in fatal cases of ADEM and its hyperacute variant, acute hemorrhagic leukoencephalitis (AHL) [33]. Additionally, ADEM can exhibit diffuse cortical microglial aggregates, independent of cortical demyelinated lesions, that may serve as the pathologic substrate for the depressed level of consciousness classically observed in ADEM patients [32].

Diagnosis

ADEM diagnosis relies on clinical criteria, MRI supportive features, and remains a diagnosis of exclusion. It is crucial to differentiate infective encephalomyelitis from immune-mediated ADEM. In 2013, the International Pediatric Multiple Sclerosis Group (IPMSG) updated the diagnostic criteria and case definitions to incorporate the widening spectrum of immune-mediated CNS inflammatory demyelinating disorders [21].

Diagnostic Criteria

ADEM is a heterogenous entity and perhaps best viewed as a ‘syndrome’ rather than a specific disorder [21]. The majority of ADEM cases are monophasic, however diagnostic confusion occurs with recurrent ADEM-like symptoms and determining whether a relapse is heralding a chronic demyelinating disease such as multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSD) [34]. The latter can only be determined in retrospect and with longitudinal monitoring.

Monophasic ADEM

Monophasic ADEM represents most pediatric cases of ADEM and requires all the following criteria to be met: [21].

1. A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause.
2. Encephalopathy is present and cannot be explained by fever.
3. Brain MRI is abnormal during the acute (3- month) phase. MRI typically shows diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter; deep gray matter lesions (e.g. thalamus, basal ganglia) can be present; T1 hypointense white matter lesions are rare.
4. No new clinical or MRI findings emerge within ≥3 months of ADEM onset.

Multiphasic ADEM

The term "multiphasic" ADEM has replaced the previous classification of "recurrent" ADEM. Multiphasic ADEM is defined as two episodes consistent with ADEM occurring at least 3 months apart but without subsequent events. The second ADEM event can involve new neurologic symptoms or re-emergence of previous neurologic symptoms, signs or MRI findings. Importantly, relapses beyond the second ADEM event are no longer consistent with multiphasic ADEM and indicate a chronic CNS demyelinating disorder such as multiple sclerosis or NMO-spectrum disorders.

Variant and Recurrent Forms of ADEM (Fig. 15.2)

As noted above, a subset of ADEM patients will go on to be diagnosed with relapsing, chronic CNS demyelinating disorders. These include ADEM followed by optic neuritis (ADEM-ON), multiple sclerosis (ADEM-MS), neuromyelitis optica spectrum disorders (ADEM-NMOSD). Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been identified in a spectrum of pediatric and adult CNS demyelinating disorders [35, 36]. Small case series have found increased relapse rates in patients with persistent anti-MOG titers compared to transient titers or seronegative patients [37]. In a cohort of MOG antibody-associated demyelination, presence of ADEM at some point in the clinical course was common in children (52%), but rare in adults (4%) in whom a relapsing optic neuritis or a NMOSD phenotype is predominant [38]. Autoimmune GFAP (an intracellular astrocytic intermediate filament) disease is a more recently described entity and can be tumor-associated [39].

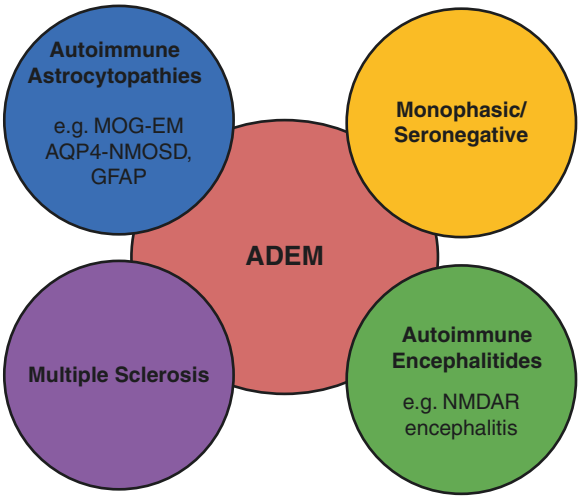


Fig. 15.2 Types of relapsing autoimmune demyelinating disorders. MOG-EM = MOG-IgG-associated encephalomyelitis (myelin oligodendrocyte glycoprotein); GFAP = autoimmune glial fibrillary acidic protein astrocytopathy; AQP4-associated NMOSD = aquaporin 4-associated neuromyelitis optica spectrum disorders; NMDAR = N-Methyl-D-aspartate receptor encephalitis

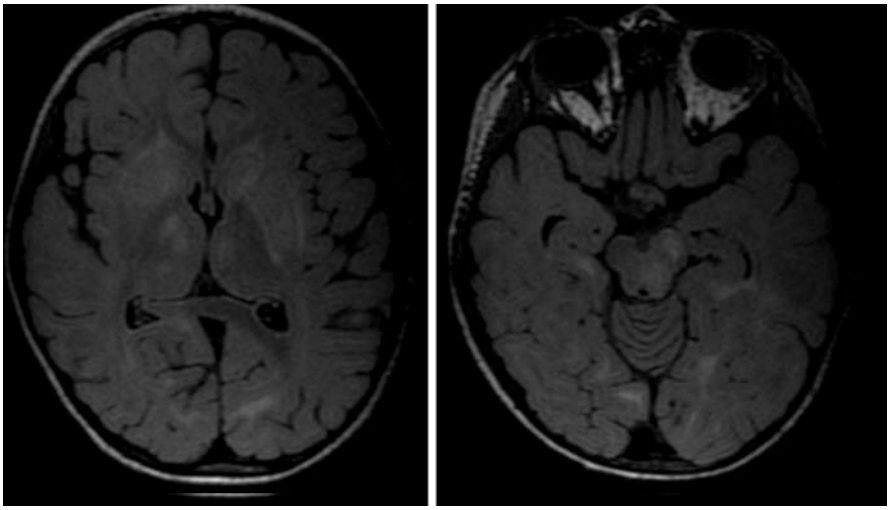


Fig. 15.3 MOG-positive ADEM. Axial FLAIR MRI in a 4-year-old ADEM patient showing diffuse involvement of basal ganglia, thalami, deep and subcortical white matter, and brainstem

Differential Diagnosis and Evaluation

As noted previously, the diagnosis of ADEM is made on clinical grounds after thorough exclusion of alternative diagnoses. Priority should be placed on ruling out treatable infectious etiologies. Brain and spine MRI (Fig. 15.3) with contrast-enhancement, CSF studies including opening pressure, cell count and differential,

protein, glucose, bacterial culture, polymerase chain reaction (PCR) for herpesviruses, lactate, IgG index, and oligoclonal bands (compared with paired serum) should be obtained. Screening for infectious agents should be guided by clinical and exposure history and include herpes simplex virus and others such as enterovirus, Epstein-Barr virus (EBV), mycoplasma and arboviruses. Blood work should include complete blood count, basic metabolic panel, erythrocyte sedimentation rate, C-reactive protein, and consideration of Lyme serology, EBV serologies, NMO-IgG, and anti-MOG antibodies.

Distinguishing ADEM from MS and NMOSD (Fig. 15.4) is of prognostic and therapeutic importance. Additionally, many autoimmune encephalitides can present with overlap of ADEM. Thus, specific testing for neuronal autoantibodies (e.g. NMDA-receptor IgG) should be considered [40] (commercially available as so-called "paraneoplastic panels" though in children often these autoimmune syndromes are not tumor-associated). NMDAR encephalitis can occur after infectious encephalitis, most classically Herpes Simplex encephalitis but also has been described more widely after multiple other infectious encephalitides [41]. A prominent movement disorder is a classic accompanying feature of this. Most of these brain cell surface antibody biomarkers are sensitive in serum (except for GFAP-IgG which has best sensitivity in the CSF).

If there is a relapsing course or some atypical feature, it is important to reconsider possible mimics of ADEM (Table 15.1). For example, primary hemophagocytic lymphohistiocytosis (HLH) in children can present with isolated CNS manifestations [42]. It is caused by genetic defects impairing the cytotoxicity of CD8 T-lymphocytes and natural killer cells. Patients can be asymptomatic until a trigger, e.g. EBV, induces the uncontrolled activation of CD8+ T-lymphocytes and macrophages (Fig. 15.5).

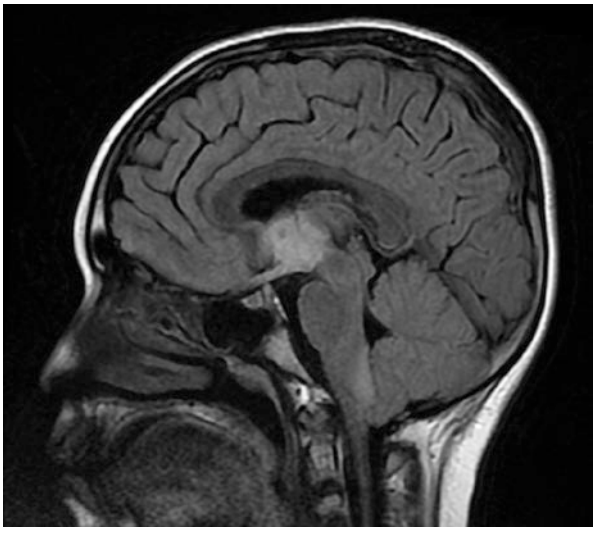


Fig. 15.4 NMO. Sagittal T2 MRI in a 9-year-old female with NMO, demonstrating characteristic involvement of aquaporin 4-rich regions on the brain (e.g. hypothalamus and area postrema of the medulla)

Table 15.1 Differential diagnosis for ADEM

Category	Examples	Diagnostic tests or clues
Infectious [54]	Acute bacterial meningitis	CSF gram stain and culture
	Herpesviral encephalitis	HSV PCR EBV PCR
	Progressive multifocal leukoencephalopathy (*PML*)	JC virus PCR
	Flaviviruses (e.g. West Nile)	Serology
	Lyme	Serology
	Mycoplasma	Nasopharyngeal swab PCR (IgM is not specific)
	Rabies	Nuchal skin biopsy
Rheumatologic	Behcet's	Oral/genital ulcers
	Neurosarcoid	Elevated ACE, chest X-ray for hilar adenopathy
	Small vessel childhood primary angiitis of the CNS (SVcPACNS)	Lumbar puncture Brain biopsy (conventional angiography is often insensitive)
	Vasculitides secondary to systemic autoimmune disorders (e.g. lupus) or triggered by infections such as VZV.	ANA, dsDNA, ANCA, ENA, vWFAg
Autoinflammatory	Hemophagocytic Lymphohystiocytosis (HLH) or Macrophage Activation syndrome (MAS) (Fig. 15.5) *Neurological symptoms may be the first and only manifestation of the disease [42]	↑sIL2R (CD25), ↓NK cell function, ↑ferritin, ↑triglycerides, ↓fibrinogen, cytopenias, hepatosplenomegaly *Laboratory parameters may be normal in CNS-isolated cases Genetic testing for HLH genes Look for triggers of secondary HLH such as EBV, rheumatologic disease or malignancy
Autoimmune	Neuronal antibody-mediated encephalitides (e.g. NMDAR) [40, 55]	Anti-neuronal ("paraneoplastic") antibody panels
	Multiple sclerosis	CSF Oligoclonal bands
Oncologic	Gliomatosis cerebri, primary CNS lymphoma, astrocytoma	CSF cytology and flow cytometry for clonal B or T cells, biopsy
Genetic/metabolic	Mitochondriopathies [56]	CSF lactate, MR spectroscopy, genetic testing

ACE angiotensin-converting enzyme, *ANA* antinuclear antibodies, *dsDNA* double-stranded DNA, *ANCA* antineutrophil cytoplasmic antibodies, *ENA* anti-extractable nuclear antigen, *vWFAg* von Willebrand Factor Ag

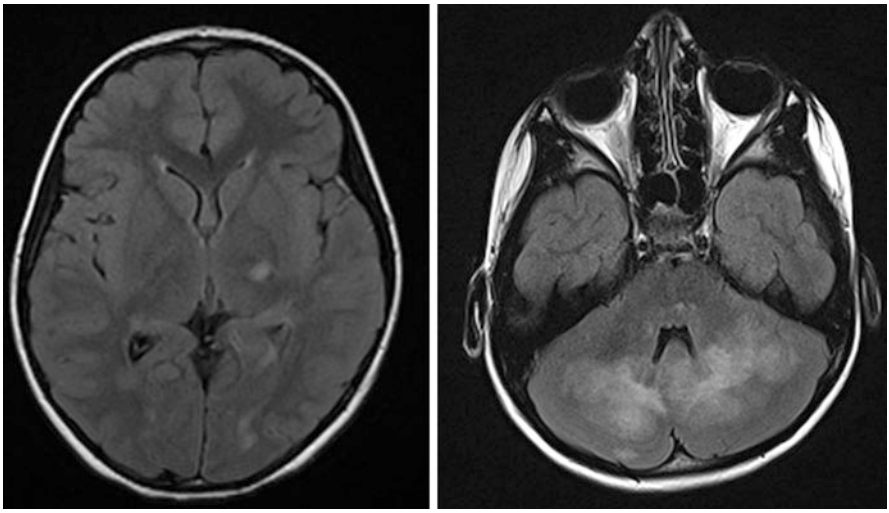


Fig. 15.5 ADEM Mimics. Axial FLAIR showing white matter involvement in the deep white matter and cerebellum in a 5-year-old female with CNS-isolated HLH due to perforin 1 gene mutation, who was initially diagnosed as relapsing ADEM triggered by Varicella immunization

Treatment (Fig. 15.6)

Acute Treatment

Although ADEM often has an immunological trigger, it does not represent an active CNS infection and thus the mainstay of treatment is immunomodulation. Once an active infection has been reasonably excluded, typically first-line agents such as steroids and intravenous immunoglobulin (IVIg) are most commonly used. Plasma exchange can be considered in more severe cases if the patient remains significantly symptomatic despite first-line treatments. ADEM without associated astrocyte antibodies (e.g. MOG or NMO) is typically monophasic and thus maintenance immunomodulation is not recommended empirically.

Commonly used regimens for acute treatment of ADEM consist of intravenous methylprednisolone 30 mg/kg/day for <30 kg of body weight, or 1 g/day for >30 kg body weight, over 3–5 consecutive days followed by an oral prednisolone taper over a few weeks [23]. A taper could consist of prednisolone at a starting dose of 1 mg/kg/day and tapered over 14–28 days. Potential side-effects include hyperglycemia, hypertension, behavioral dysregulation, insomnia, and gastritis such that prophylaxis with an H2-antagonist should be considered. There are case reports using additionally IVIg with a total dose of 1–2 g/kg divided over 2–5 days.

In cases of corticosteroid-refractory patients with fulminant disease, plasma exchange has been used, five to seven treatments every 2 days. In a Mayo Clinic cohort of patients with CNS demyelination, ten of these patients had ADEM and were treated with plasma exchange [43]. Patients received a median of seven exchanges.

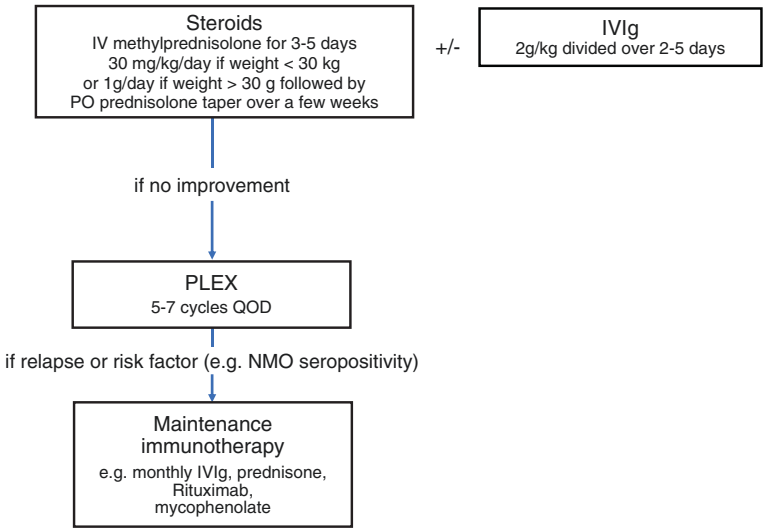


Fig. 15.6 ADEM treatment algorithm

Patients who noted improvement did so within three exchanges and 5 days of treatment in 75% of those responders. For the ADEM patients, marked improvement occurred in 40%, mild improvement in 10%, and no improvement in 50%.

There are no clinical treatment trials of ADEM except for a randomized controlled trial of plasma exchange after corticosteroid failure in acute CNS demyelinating disease, but only one patient in that cohort had ADEM [44]. In that trial, moderate or greater improvement in neurological disability occurred during 42% of active treatment courses compared to 6% courses of sham treatment. Possible adverse effects of plasma exchange include: anemia, hypotension, hypocalcemia, heparin-associated thrombocytopenia, and catheter-related complications.

In rare cases of significant tumefactive lesions, decompressive craniectomy has been performed.

Maintenance Immunosuppression If High Risk for Relapse

In cases of NMO-associated encephalomyelitis, the risk of relapse is high, and the potential sequelae severe given the typically associated optic neuritis (with sequelae of visual impairment) and myelitis (with sequelae of paraparesis and bowel/bladder dysfunction). Thus, maintenance immunotherapy is often instituted, commonly with rituximab [45, 46].

Prognosis

Despite the often dramatic presentation, most children with ADEM achieve full recovery, with neurologic improvement appreciated within days of treatment initiation. However, long-term cognitive deficits have been increasingly reported, particularly in children afflicted with ADEM before 5 years of age, and may include impaired attention, executive function, verbal processing, intellectual quotient and behavioral dysregulation [47, 48].

Mortality rates are lower in children than adults with ADEM and range between 1% and 3% [25, 49]. Mortality is low except in patients with fulminant variants such as acute hemorrhagic leukoencephalitis. Brainstem involvement (rhombencephalitis, *Bickerstaff's*) with dysphagia, respiratory suppression, or autonomic dysfunction, requires close monitoring and possible cardiorespiratory support in an intensive care setting.

Risk of Relapse

Despite its dramatic clinical and radiological presentations, seronegative ADEM is usually monophasic with excellent outcomes. MOG-associated encephalomyelitis can follow a relapsing course especially in adults. These patients can often experience exacerbation of their symptoms upon steroid cessation, therefore a gradual taper is recommended.

Motor Sequelae

Outcome studies often utilize validated standardized scales to measure functional status. One example which is commonly used in multiple sclerosis studies is the Expanded Disability Status Scale (EDSS.) EDSS heavily emphasizes primarily lower extremity motor deficits with regard to ambulation. In a large cohort of children with ADEM from Argentina who were followed by the same clinician for a mean duration of 6.6 ± 3.8 years [23], 90% had a monophasic course (clinically and by serial neuroimaging). Of the 10% having biphasic disease, the second episode (new lesions) occurred between 2 months and 8 years. Cranial MRI follow-up showed near resolution at a mean of 7.2 months. 89% of the patients had an Expanded Disability Status Scale (EDSS) [50] of 0–2.5 (normal neurologic examination or abnormal signs without disability,) while 11% had an EDSS of 3–6.5 (abnormal signs plus some degree of disability). The patients who relapsed still had complete neurologic recovery with EDSS scores 0–2.5.

Neuropsychological Sequelae

Neurocognitive sequelae in ADEM patients is likely underreported. Executive functioning and metacognition domains seem to be more vulnerable. A meta-analysis [51] suggested possible attentional, reduced processing speed and elevated internalizing symptoms. This suggests that more proactive neuropsychological testing of patients who recover from ADEM would be important to maximize educational potential. In addition to motor rehabilitation, cognitive rehabilitation and school individualized education plans should also be emphasized in patients post-ADEM.

Age of ADEM onset and impact on the developing nervous system versus the adult mature nervous system results in different sequelae. Given that ADEM is predominantly a disorder of children and young adults, large case series describing outcomes are reflective of that population. A serial neuroimaging volumetric study demonstrated an impact of monophasic acute demyelinating events with onset during childhood and adolescence on age-expected growth of the cerebrum and cerebellum [52], though this was not associated with any alteration in clinical outcome.

Risk of Evolution to Multiple Sclerosis

A follow-up study of 40 adult patients in Germany shows there is a higher rate of conversion to multiple sclerosis in adults presenting with ADEM [53]. In this cohort with a mean follow-up of 38 months, 35% of patients were diagnosed with MS after a second demyelinating episode which occurred within the first year of initial presentation in all patients.

Conclusion

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system characterized by encephalopathy and polyfocal CNS neurological deficits, with higher incidence in children. It can be triggered by an immunological stressor such as an infection. It is important to differentiate ADEM from acute infectious encephalomyelitis because the mainstay of therapy for ADEM is immunosuppression such as with corticosteroids.

ADEM is typically a monophasic syndrome with favorable outcome. However, recently described variants with auto-antibody or paraneoplastic-associated disease may portend a relapsing course or require tumor screening. Examples of these include autoimmune astrocytopathies such as myelin oligodendrocyte glycoprotein (MOG)-IgG-associated encephalomyelitis and aquaporin 4 (AQP4)-associated

neuromyelitis optica spectrum disorders (NMOSD), as well as autoimmune encephalitides associated with antibodies against neuronal surface antigens such as N-Methyl-D-aspartate (NMDAR) receptor encephalitis. Additionally, it is critical to differentiate ADEM from a first attack of a chronic demyelinating disorder such as multiple sclerosis (MS).

There are multiple mimics to consider in the differential diagnosis of ADEM especially in patients with relapses or atypical features (Table 15.1).

References

1. McAlpine D. Acute disseminated encephalomyelitis: its sequela and its relation to disseminated sclerosis. Lancet. 1931;217:846–52.
2. Lucas J. An account of uncommon symptoms succeeding measles: with some additional remarks on the infection of measles and smallpox. Lond Med J. 1790;11:325–31.
3. Gibbons JL, Miller HG, Stanton JB. Para-infectious encephalomyelitis and related syndromes; a critical review of the neurological complications of certain specific fevers. Q J Med. 1956;25(100):427–505. PubMed PMID: 13379602. eng.
4. Torisu H, Kira R, Ishizaki Y, Sanefuji M, Yamaguchi Y, Yasumoto S, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka prefecture. Jpn Brain Dev. 2010;32(6):454–62. PubMed PMID: 19942388. Epub 2009/11/25. eng.
5. Leake JA, Albani S, Kao AS, Senac MO, Billman GF, Nespeca MP, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J. 2004;23(8):756–64. PubMed PMID: 15295226. eng.
6. Tenembaum S, Chitnis T, Ness J, Hahn JS, Group IPMS. Acute disseminated encephalomyelitis. Neurology. 2007;68(16 Suppl 2):S23–36. PubMed PMID: 17438235. eng.
7. Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr. 2007;166(5):405–12. PubMed PMID: 17219129. Epub 2007/01/12. eng.
8. Pohl-Koppe A, Burchett SK, Thiele EA, Hafler DA. Myelin basic protein reactive Th2 T cells are found in acute disseminated encephalomyelitis. J Neuroimmunol. 1998;91(1–2):19–27. PubMed PMID: 9846815. eng.
9. Stüve O, Zamvil SS. Pathogenesis, diagnosis, and treatment of acute disseminated encephalomyelitis. Curr Opin Neurol. 1999;12(4):395–401. PubMed PMID: 10555827. eng.
10. Caldemeyer KS, Smith RR, Harris TM, Edwards MK. MRI in acute disseminated encephalomyelitis. Neuroradiology. 1994;36(3):216–20. PubMed PMID: 8041443. eng.
11. David P, Baleriaux D, Bank WO, Amrom D, De Temmerman D, Babusiaux C, et al. MRI of acute disseminated encephalomyelitis after coxsackie B infection. J Neuroradiol. 1993;20(4):258–65. PubMed PMID: 8308544. englfre.
12. Kim SC, Jang HJ, Han DJ. Acute disseminated encephalomyelitis after renal transplantation in patients with positive Epstein-Barr virus antibody. Transplant Proc. 1998;30(7):3139. PubMed PMID: 9838388. eng.
13. Shoji H, Kusuhara T, Honda Y, Hino H, Kojima K, Abe T, et al. Relapsing acute disseminated encephalomyelitis associated with chronic Epstein-Barr virus infection: MRI findings. Neuroradiology. 1992;34(4):340–2. PubMed PMID: 1326729. eng.
14. Apak RA, Köse G, Anlar B, Turanli G, Topaloğlu H, Ozdirim E. Acute disseminated encephalomyelitis in childhood: report of 10 cases. J Child Neurol. 1999;14(3):198–201. PubMed PMID: 10190272. eng.

15. Huber S, Kappos L, Fuhr P, Wetzel S, Steck AJ. Combined acute disseminated encephalomyelitis and acute motor axonal neuropathy after vaccination for hepatitis A and infection with Campylobacter jejuni. J Neurol. 1999;246(12):1204–6. PubMed PMID: 10653319. eng.
16. Murthy JM. MRI in acute disseminated encephalomyelitis following Semple antirabies vaccine. Neuroradiology. 1998;40(7):420–3. PubMed PMID: 9730339. eng.
17. Stonehouse M, Gupte G, Wassmer E, Whitehouse WP. Acute disseminated encephalomyelitis: recognition in the hands of general paediatricians. Arch Dis Child. 2003;88(2):122–4. PubMed PMID: 12538312. PMCID: PMC1719460. eng.
18. Fenichel GM. Neurological complications of immunization. Ann Neurol. 1982;12(2):119–28. PubMed PMID: 6751212. eng.
19. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. Neurology. 2001;56(10):1308–12. PubMed PMID: 11376179. eng.
20. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000;123(Pt 12):2407–22. PubMed PMID: 11099444. eng.
21. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261–7. PubMed PMID: 23572237. Epub 2013/04/09. eng.
22. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics. 2002;110(2 Pt 1):e21. PubMed PMID: 12165620. eng.
23. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology. 2002;59(8):1224–31. PubMed PMID: 12391351. eng.
24. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenembaum S, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38–45. PubMed PMID: 27572859. eng.
25. Absoud M, Parslow RC, Wassmer E, Hemingway C, Duncan HP, Cummins C, et al. Severe acute disseminated encephalomyelitis: a paediatric intensive care population-based study. Mult Scler. 2011;17(10):1258–61. PubMed PMID: 20876155. Epub 2010/09/27. eng.
26. Baum PA, Barkovich AJ, Koch TK, Berg BO. Deep gray matter involvement in children with acute disseminated encephalomyelitis. AJNR Am J Neuroradiol. 1994;15(7):1275–83. PubMed PMID: 7976938. eng.
27. Koelman DL, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. J Neurol. 2015;262(9):2013–24. PubMed PMID: 25761377. Epub 2015/03/13. eng.
28. Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: comparison of presenting features. Dev Med Child Neurol. 2009;51(6):480–6. PubMed PMID: 19018840. PMCID: PMC2704249. Epub 2008/10/24. eng.
29. Sinclair AJ, Wienholt L, Tantsis E, Brilot F, Dale RC. Clinical association of intrathecal and mirrored oligoclonal bands in paediatric neurology. Dev Med Child Neurol. 2013;55(1):71–5. PubMed PMID: 23095051. Epub 2012/10/24. eng
30. Aubert-Broche B, Fonov V, Narayanan S, Arnold DL, Araujo D, Fetco D, et al. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. Neurology. 2014;83(23):2140–6. PubMed PMID: 25378667. PMCID: PMC4276405. Epub 2014/11/05. eng.
31. Waksman BH. Experimental allergic encephalomyelitis and the “auto-allergic” diseases. Int Arch Allergy. 1959;14:1–87.
32. Young NP, Weinshenker BG, Parisi JE, Scheithauer B, Giannini C, Roemer SF, et al. Perivenous demyelination: association with clinically defined acute disseminated encephalomyelitis and

comparison with pathologically confirmed multiple sclerosis. Brain. 2010;133(Pt 2):333–48. PubMed PMID: 20129932. PMCID: PMC2822631. Epub 2010/02/03. eng.
33. Ghosh N, DeLuca GC, Esiri MM. Evidence of axonal damage in human acute demyelinating diseases. J Neurol Sci. 2004;222(1–2):29–34. PubMed PMID: 15240192. eng.
34. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177–89. PubMed PMID: 26092914. PMCID: PMC4515040. Epub 2015/06/19. eng.
35. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: how clinically useful are they? Curr Opin Neurol. 2017;30(3):295–301. PubMed PMID: 28248700. eng.
36. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nat Rev Neurol. 2019;15(2):89–102. PubMed PMID: 30559466. eng.
37. López-Chiriboga AS, Majed M, Fryer J, Dubey D, McKeon A, Flanagan EP, et al. Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders. JAMA Neurol. 2018;75(11):1355–63. PubMed PMID: 30014148. PMCID: PMC6248120. eng.
38. Ramanathan S, Mohammad S, Tantsis E, Nguyen TK, Merheb V, Fung VSC, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry. 2018;89(2):127–37. PubMed PMID: 29142145. PMCID: PMC5800335. Epub 2017/11/15. eng.
39. Fang B, McKeon A, Hinson SR, Kryzer TJ, Pittock SJ, Aksamit AJ, et al. Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA Neurol. 2016;73(11):1297–307. PubMed PMID: 27618707. eng.
40. Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med. 2018;378(9):840–51. PubMed PMID: 29490181. eng.
41. Cavaliere E, Nosadini M, Pelizza MF, Ventura G, Toldo I, Sartori S. Anti-NMDAR encephalitis preceded by non-herpetic central nervous system infection: systematic literature review and first case of tick-borne encephalitis triggering anti-NMDAR encephalitis. J Neuroimmunol. 2019;332:1–7. PubMed PMID: 30913507. Epub 2019/03/19. eng.
42. Benson LA, Li H, Henderson LA, Solomon IH, Soldatos A, Murphy J, et al. Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. Neurol Neuroimmunol Neuroinflamm. 2019;6(3):e560.
43. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58(1):143–6. PubMed PMID: 11781423. eng.
44. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46(6):878–86. PubMed PMID: 10589540. eng.
45. Nosadini M, Alper G, Riney CJ, Benson LA, Mohammad SS, Ramanathan S, et al. Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2016;3(1):e188. PubMed PMID: 26819962. PMCID: PMC4723136. Epub 2016/01/21. eng.
46. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83(2):142–50. PubMed PMID: 24920861. PMCID: PMC4117174. Epub 2014/06/11. eng.
47. Jacobs RK, Anderson VA, Neale JL, Shield LK, Kornberg AJ. Neuropsychological outcome after acute disseminated encephalomyelitis: impact of age at illness onset. Pediatr Neurol. 2004;31(3):191–7. PubMed PMID: 15351018. eng.
48. Suppiej A, Cainelli E, Casara G, Cappellari A, Nosadini M, Sartori S. Long-term neurocognitive outcome and quality of life in pediatric acute disseminated encephalomyelitis. Pediatr Neurol. 2014;50(4):363–7. PubMed PMID: 24630282. Epub 2013/12/12. eng
49. Ketelslegers IA, Visser IE, Neuteboom RF, Boon M, Catsman-Berrevoets CE, Hintzen RQ. Disease course and outcome of acute disseminated encephalomyelitis is more severe

in adults than in children. Mult Scler. 2011;17(4):441–8. PubMed PMID: 21148017. Epub 2010/12/08. eng.
50. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444–52. PubMed PMID: 6685237. eng.
51. Burton KLO, Williams TA, Catchpoole SE, Brunsdon RK. Long-term neuropsychological outcomes of childhood onset acute disseminated encephalomyelitis (ADEM): a meta-analysis. Neuropsychol Rev. 2017;27(2):124–33. PubMed PMID: 28364141. Epub 2017/03/31. eng
52. Aubert-Broche B, Weier K, Longoni G, Fonov VS, Bar-Or A, Marrie RA, et al. Monophasic demyelination reduces brain growth in children. Neurology. 2017;88(18):1744–50. PubMed PMID: 28381515. PMCID: PMC5409842. Epub 2017/04/05. eng.
53. Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology. 2001;56(10):1313–8. PubMed PMID: 11376180. eng.
54. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57(8):1114–28. PubMed PMID: 23861361. PMCID: PMC3783060. Epub 2013/07/15. eng.
55. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54(7):899–904. PubMed PMID: 22281844. PMCID: PMC3297648. Epub 2012/01/26. eng.
56. Wolf NI, Toro C, Kister I, Latif KA, Leventer R, Pizzino A, et al. DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder. Neurology. 2015;84(3):226–30. PubMed PMID: 25527264. PMCID: PMC4335995. Epub 2014/12/19. eng.

Part VI
Miscellaneous Infections

Chapter 16
Tick-Borne Infections of the Central Nervous System

Michael J. Bradshaw and Karen C. Bloch

Tick-borne infections, a heterogenous group of diseases caused by bacteria, viruses, and protozoa, are under-appreciated causes of central nervous system (CNS) infection. A number of different tick species can transmit disease (several are shown in Fig. 16.1), each with a typical geographic range (Fig. 16.2). The incidence of tick-borne infections in the United States has more than doubled in the last decade, with >48,000 cases per year reported in 2016 [1, 2]. However, the true burden of tick-borne infection is likely significantly higher due to under-diagnosis and reporting. For instance, it is estimated that the actual number of Lyme disease infections annually are ten-fold higher than the number reported to the Centers for Disease Control and Prevention (CDC) [3, 4].

Several factors may explain the rising incidence of tick-borne infections. Increasing awareness of these infections, coupled with the increasing availability of molecular testing has improved recognition and diagnosis. The geographic range of known tick vectors has expanded into previously disease-naïve areas [5, 6], and the expansion of tick species beyond historically endemic regions has increased the population at risk for tick-borne infection (Figs. 16.2 and 16.3) [7, 8]. Finally, in the last decade several previously unknown tick-borne pathogens have been identified, some of which are neurotropic.

M. J. Bradshaw (✉)
Department of Neurology, University of Washington; Rosalind Franklin University of Medicine and Science; Billings Clinic, Billings, MT, USA

K. C. Bloch
Vanderbilt University Medical Center, Nashville, TN, USA

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_16

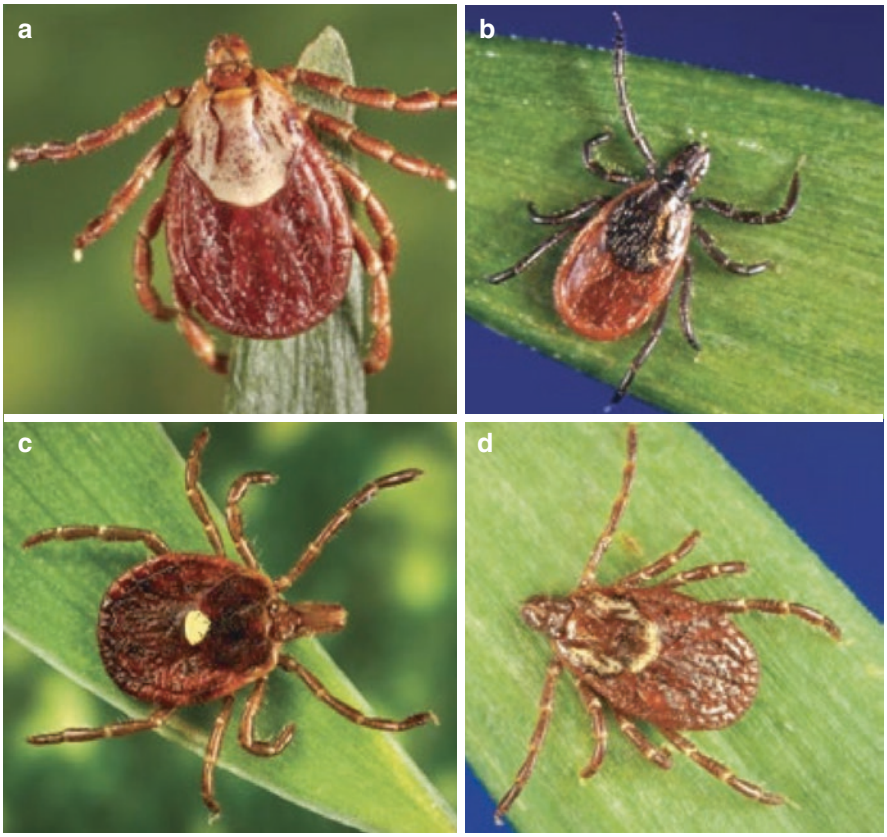


Fig. 16.1 Select ticks common in North America. (**a**) Rocky Mountain wood tick, *Dermcenter andersoni*, which transmits Rocky Mountain spotted fever, Colorado tick fever and tularemia. (**b**) Blacklegged tick, *Ixodes scapularis*, common in the northeastern and upper midwewstern USA and transmits Lyme, anaplasmosis, babesiosis and Powassan disease. (**c**) Lone star tick, *Amblyomma americanum*, common in the southeastern and southern USA and transmits *Ehrlichia chafeensis*, *Ehrlichia ewingii*, tularemia and STARI. (**d**) American dog tick (AKA wood tick), *Dermacentor verabilis*, common throughout the Rocky Mountains and some areas of the Pacific coast and transmits tularemia and Rocky Mountain spotted fever. Images are not to scale. (From https://www.cdc.gov/ticks/tickbornediseases/tickID.html)

This chapter focuses on tick-borne infectious agents that cause can involve the nervous system in the United States (Table 16.1). Powassan virus, a tick-borne infection that causes encephalitis, is discussed in the arboviral chapter. While the emphasis of this chapter is on diseases endemic to the United States, it is recognized that tick-borne infections are a significant cause of morbidity and mortality globally.

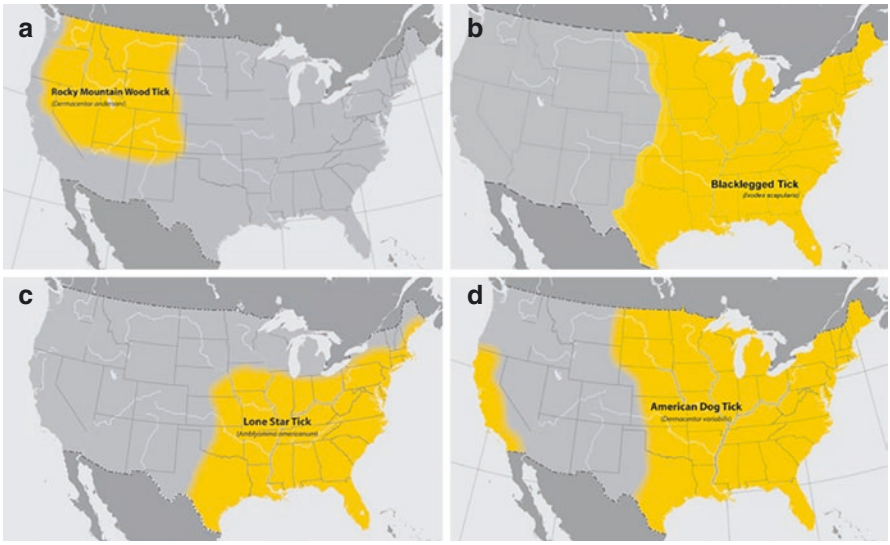


Fig. 16.2 (**a**–**d**) Geographic Distribution of select ticks causing human infection in the USA. (From https://www.cdc.gov/ticks/tickbornediseases/overview.html)

The evolving epidemiology and increasing burden of infections due to ticks requires a coordinated public health response as well as clinician education to optimize early recognition, diagnosis and treatment of these potentially life-threatening pathogens.

Bacterial Infections

Anaplasmosis

Epidemiology

Anaplasmosis, caused by the obligate intracellular bacterium *Anaplasma phagocytophilum*, is an increasingly recognized cause of tick-borne infection. Cases reported to the CDC increased almost five-fold between 2009 and 2017, with a 39% increase between 2016 and 2017 alone [9]. The vector for anaplasmosis is the *Ixodes* tick and therefore the geographic distribution of cases is similar to that of Lyme disease (Figs. 16.2 and 16.3). *Ixodes* is a competent reservoir for multiple human pathogens, and co-infections with *Anaplasma* and *Borrelia* or *Babesia* can occur. Although most infections are transmitted by tick bite, transfusion-associated transmission has been reported [10].

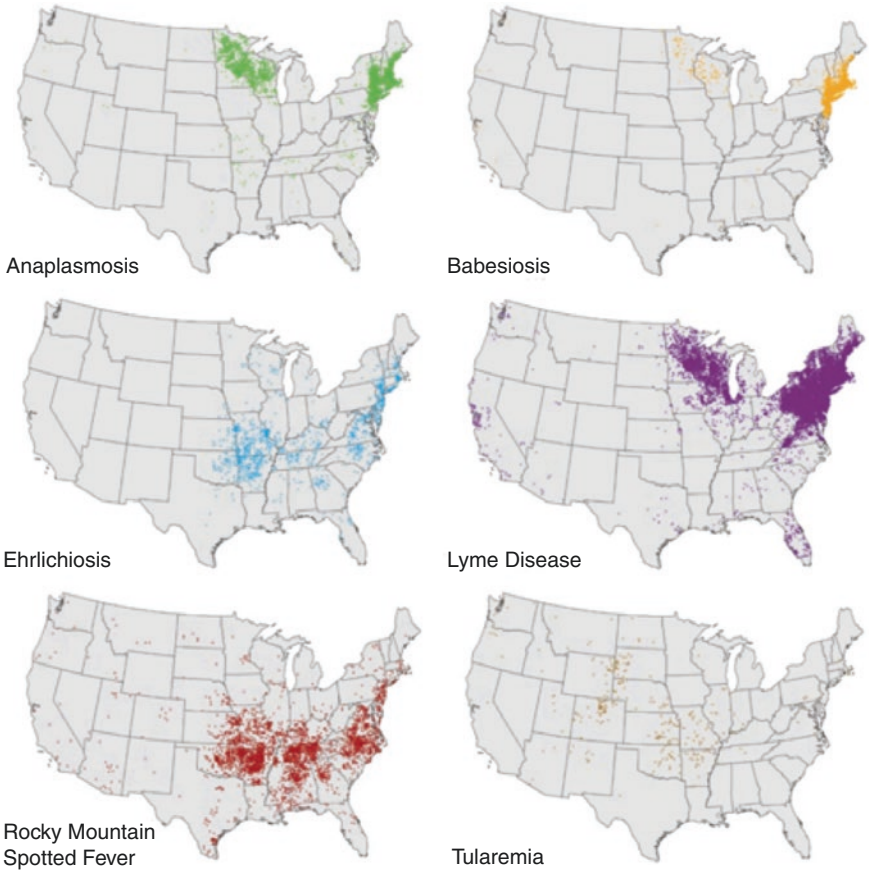


Fig. 16.3 Tick-borne infection distribution in the USA based on 2015 CDC data. For each case, a single dot is placed randomly in the reported county. (From https://www.cdc.gov/ticks/tickborne-diseases/overview.html)

Clinical

The onset of symptoms is typically 1–2 weeks after transmission through tick bite and typically manifests with fevers, chills, malaise, headache, myalgias and gastrointestinal symptoms. Infections range in severity from mild to life-threatening illness. Rash is present in <10% of cases and should prompt consideration of another etiology such as Lyme disease or Rocky Mountain spotted fever in the appropriate clinical context [11]. Although anaplasmosis is typically considered a milder illness than ehrlichiosis, in surveillance data 31% of cases required hospitalization, and the overall case fatality rate was 0.3% [12]. Treatment delay is a risk factor for severe illness, and is associated with renal or pulmonary failure, disseminated intravascular coagulopathy, rhabdomyolysis and central or peripheral nervous system

Table 16.1 CNS Manifestations of tick-borne infections

Disease	Reported cases 2017[a]	Frequency of CNS involvement	Organism/s	Clinical presentation	Diagnostic testing
Bacterial					
Ehrlichiosis	1642	20% with confusion 5% meningitis or encephalitis	*E chaffeensis*	Meningoencephalitis	Whole blood PCR Paired serology
Anaplasmosis	5762	17% confusion <1% meningoencephalitis	*Anaplasma phagocytophila*	Meningoencephalitis	Whole blood PCR Microscopy Paired serology
Lyme	42,743	15% Neuroborreliosis	*B burgdorferi*	Meningitis, cranial nerve palsy, mononeuritis multiplex	2-tier serology
Spotted fever rickettsiosis	6248	Unknown, ~17% (Bradshaw, Bloch, unpublished data)	*R rickettsia* *R parkeri*	Meningoencephalitis, cranial nerve palsy	Paired serology
Tularemia	Unknown	Unknown	*Francisella tularensis*	Meningitis, brainstem encephalitis	Paired serology
Viral					
	Unknown	Unknown (one reported case)	Heartland virus	Encephalitis (diagnosed on autopsy)	Not commercially available (can be performed through CDC; contact local health department for testing)
	Unknown	Unknown	Bourbon virus	Unknown	Not commercially available (can be performed through CDC; contact local health department for testing)
	Unknown	Unknown	Colorado tick fever	Meningoencephalitis	PCR or paired serologies
Protozoal					
Babesiosis	2358	Rare	Babesia spp	Encephalopathy	Whole blood PCR

[a]Cases in the United States reported to CDC for 2017, which is last year data available

involvement. Advanced age and immunosuppression are also risk factors for more severe illness.

Neurologic Manifestations

Neurologic manifestations including headache (82% of cases), neck stiffness (45%) and confusion (17%) are common [13]. Despite the frequency of these individual symptoms, however, meningoencephalitis was documented in less than 1% of anaplasmosis cases reported to the CDC between 2008 and 2012 [12]. The presenting features of *Anaplasma* meningoencephalitis are nonspecific and can include seizure [13, 14] and lymphocytic pleocytosis [15]. Uncommon neurologic presentations include facial diplegia [15], stroke [16], brachial plexopathy [17] and peripheral neuropathy [18].

Diagnosis

As with ehrlichiosis and the spotter fever rickettsioses, laboratory abnormalities including leukopenia, thrombocytopenia and elevated transaminase levels may be seen. Appropriate testing for *Anaplasma* is dependent on the stage of the infection. In acute infection, microscopy may identify morulae inside neutrophils in >20% of peripheral blood smears (Fig. 16.4) [13]. PCR of whole blood samples is increasingly available through commercial laboratories and is highly sensitive if performed prior to doxycycline therapy. *Anaplasma* PCR of CSF is rarely positive, likely due to the lower number of granulocytes in spinal fluid [15]. Serology performed on a single serum specimen is often misleading, with <50% of acute-phase samples seropositive [19]. However, testing of paired acute and convalescent serum specimens may allow a retrospective diagnosis.

Treatment

There have been no clinical trials specifically evaluating the optimal duration of treatment of patients with anaplasmosis. Guidelines developed through expert opinion suggest a 10-day course of doxycycline regardless of patient age [19, 20]. There

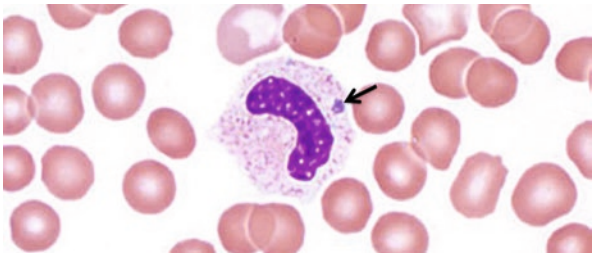


Fig. 16.4 Blood smear in a patient with anaplasmosis with a morula (arrow), which is a microcolony of the bacteria living within a modified lysosome in a neutrophil. (Courtesy of Bobbi Pritt, MD)

are no data suggesting a longer course is needed for CNS involvement. A hallmark of anaplasmosis is the rapid response to doxycycline, and fever persisting for >48 hours after treatment initiation makes the diagnosis unlikely.

Ehrlichiosis

Epidemiology

Ehrlichiosis refers to human disease caused by one of three closely related organisms: *Ehrlichia chaffeensis*, *E. ewingii* and a newly identified organism *E. muris eauclariensis*. CNS manifestations have only been reported with *E. chaffeensis*, the most common cause of ehrlichiosis. *E. chaffeensis* is transmitted by the lone star tick, *Amblyomma americanum* (Fig. 16.1), which is endemic throughout the Southeast and South-Central United States (Fig. 16.2). As with most tick-borne infections almost all cases are seasonal, occurring during Spring, Summer and Fall when ticks are most active in the environment.

Clinical

Clinical manifestations of ehrlichiosis range from asymptomatic infection to fulminant disease. Symptoms of ehrlichiosis typically develop after a 1–2 week incubation period and are nonspecific with fever, headache, and myalgias predominating. Rash is seen in 60% of pediatric cases but <30% of adults and, when present, typically develops about five days after symptom onset. The rash seen with ehrlichiosis can be either petechial or maculopapular and is non-pruritic. It most frequently resembles a nonspecific viral exanthem and is therefore not helpful in suggesting the diagnosis. Among cases of ehrlichiosis reported to the CDC through national surveillance, 57% required hospitalization. Severe disease can produce renal or liver failure, acute respiratory distress syndrome, disseminated intravascular coagulopathy and neurologic complications. Eleven percent of patients experience life-threatening complications and the case fatality rate is 1% [21]. As with anaplasmosis, immunocompromise, older age and delay in treatment are risk factors for more severe disease.

Neurologic Manifestations

Neurologic manifestations, particularly meningoencephalitis, are common in ehrlichiosis. Headache is almost universally present, and confusion is noted in approximately 20% of cases [22, 23]. In a series of 46 patients hospitalized with ehrlichiosis, nuchal rigidity was documented in 13% and an abnormal neurologic exam in 9% [24]. Meningoencephalitis was reported in 5% of all cases and 20% of hospitalized cases of *E. chaffeensis* between 2008 and 2012 [21].

Most information on CNS *Ehrlichia* infection is limited to case reports and small case series [25, 26]. The largest series of *Ehrlichia* meningoencephalitis included 15 patients who had clinical findings prompting cerebrospinal fluid (CSF) analysis, with abnormalities in 53% consistent with meningeal inflammation [22]. CSF nucleated cell counts ranged from 6 to 1400 cells/uL and nearly a quarter of cases were neutrophil predominant. Elevated protein and hypoglycorrhachia were present in 44% and 14% of cases, respectively. In that series, none of the 14 patients who underwent head CT had documented abnormalities. In addition to meningoencephalitis, other neurologic manifestations of ehrlichiosis include cranial neuropathy such as optic neuritis, seizures, ataxia, brachial plexopathy and peripheral neuropathy [23].

Diagnosis

Leukopenia, thrombocytopenia and elevated transaminases levels are frequently present and may provide indirect clues to the diagnosis of ehrlichiosis. However these findings are nonspecific, and are also common in anaplasmosis and Rocky Mountain spotted fever, as well as in acute viral infections. Laboratory confirmation of infection is required for diagnosis, with the preferred test methodology varying based on the stage of infection. *Ehrlichiae* are intraleukocytic pathogens, and therefore whole blood PCR is the most sensitive diagnostic test early in the course of disease. Detection in CSF by PCR has been reported, but the sensitivity is significantly lower than for blood, presumably due to the presence of fewer infected leukocytes [22]. Serologic testing has a sensitivity of only 30% during the acute illness, but increases to >90% for convalescent specimens obtained >2 weeks after onset of symptoms. Morulae can be seen inside monocytes on whole blood smear in up to 27% of cases of *E. chaffeensis* (Fig. 16.5), however the sensitivity is heavily dependent on the experience and tenacity of the microscopist.

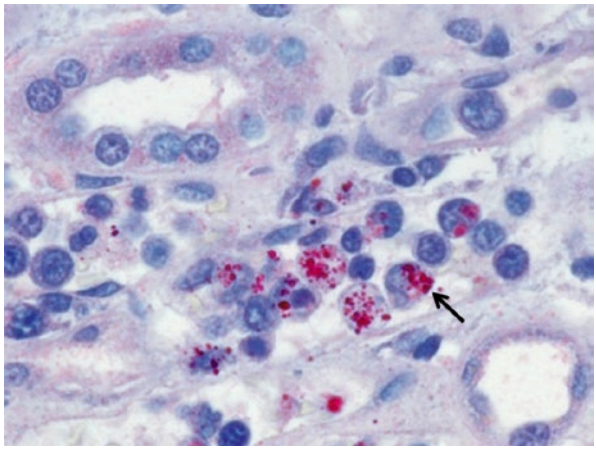


Fig. 16.5 Micrograph of kidney biopsy with *Ehrlichia chafeensis* immunohistochemical staining demonstrating morulae (arrow) within monocytes. (From https://www.cdc.gov/ticks/tickbornediseases/overview.html)

Treatment

The standard therapy for CNS ehrlichiosis is doxycycline. Due to the excellent bioavailability of this agent, oral therapy is as effective as parenteral treatment. Delay in initiation of therapy has been associated with more severe infection and adverse outcomes [24]. Doxycycline should therefore be started empirically when there is a suspicion for a tick-borne rickettsial infection [11]. Reticence among providers to prescribe doxycycline to young children due to the perceived risk of dental discoloration is unfounded and the American Academy of Pediatrics recommends empiric therapy in cases of suspected rickettsiosis (including ehrlichiosis) regardless of age [11, 27–29].

Lyme Disease

Epidemiology

The spirochete *Borrelia burgdorferi* causes Lyme disease, the most common tick-borne infection in the United States and Europe. In the United States, *Ixodes scapularis* is the primary vector (Fig. 16.1). Most cases result from the bite of an infected nymph, which is roughly the size of a poppy seed (adults are about the size of a sesame seed); so bites often go unnoticed. Highly endemic regions include the Northeast, Mid-Atlantic and Upper Midwest (Fig. 16.3) [30]. The reported incidence of Lyme disease tripled between 1992 and 2015 [31]. This appears to be related to a combination of climate change, land utilization and a marked increase in the deer population.

Clinical

Lyme disease is clinically divided into several stages including early localized, early disseminated and late disseminated. The early localized stage is characterized by the erythema migrans rash, which develops at the site of the initial bite in over 80% of patients within several days to weeks of transmission [32]. Erythema migrans lesions are macular, may be round or ovoid, and most often homogenous in color; the classic "Bull's eye" rash with central clearing is less common (Fig. 16.6). The rash gradually enlarges over days to weeks as the spirochetes migrate centrifugally. Systemic symptoms such as malaise, fevers/chills, headaches myalgias and arthralgias may accompany erythema migrans or may develop without the rash [32, 33]. Several days to weeks later, the bacteria disseminate hematogenously and patients may develop multiple erythema migrans lesions, cardiac, rheumatic or neurologic symptoms. In the late disseminated stage, Lyme arthritis, acrodermatitis chronica atrophicans (wherein the skin develops a purplish discoloration, becomes paper thin and wrinkled) or Lyme neuroborreliosis may be present.

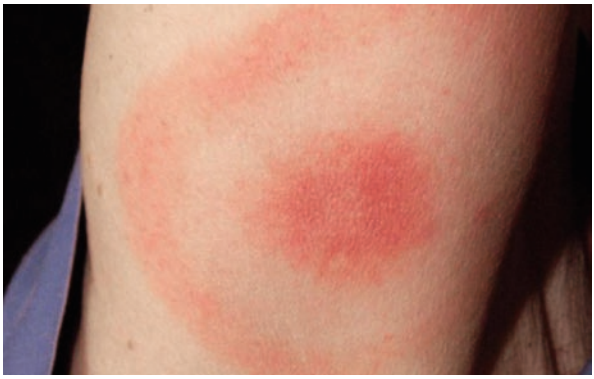


Fig. 16.6 Classic "bull's eye" erythema migrans of Lyme disease. Note that the bull's eye rash is uncommon. (From https://www.cdc.gov/ticks/tickbornediseases/overview.html)

Neurologic Manifestations

Roughly 15% of patients with untreated erythema migrans develop early Lyme neuroborreliosis, usually within several weeks of the rash. Erythema migrans may still be present at the time of symptom onset, therefore a full skin examination is important to perform. The peripheral nervous system is much more frequently affected than the CNS and the most common manifestations include cranial neuritis (most often the facial nerve, with either unilateral or bilateral palsy), painful meningoradiculitis (Bannwarth syndrome) and lymphocytic meningitis. Clues to Lyme neuroborreliosis include erythema migrans, radiculitis and presentation during the warm summer months, particularly in endemic areas. However, delay in onset of symptoms or presentation may lead to affected patients presenting in months when ticks are not active.

Given the availability of specific treatment, it is important to distinguish facial nerve palsy caused by Lyme disease from idiopathic Bell's palsy, a common misdiagnosis. Simultaneous or sequential bilateral facial palsy developing within a few days should raise concern for Lyme neuroborreliosis, particularly in children. Roughly 1/3 of patients with cranial neuritis from Lyme disease also have pleocytosis on CSF analysis [34–36].

Lyme meningitis most often presents with headache, and can develop acutely or subacutely. It is important to distinguish Lyme meningitis from other bacterial and viral causes. The "rule of 7s" can help distinguish among between Lyme meningitis and aseptic meningitis such as enteroviral meningitis, which also typically presents in the summer months [37, 38]. Children with less than 7 days of headache, less than 70% mononuclear cells on CSF analysis and no 7th (or other) cranial nerve palsy are considered to be low risk of having Lyme meningitis. Elevated intracranial pressure with headache, papilledema and transient visual changes can develop, particularly in children. Parenchymal CNS Lyme such as encephalitis and myelitis are exceptionally rare [39, 40].

Lyme radiculoneuritis typically presents initially with multifocal, asymmetric, severe, often sharp and lancinating deep muscular pain, which is worse at night and

unresponsive to analgesics. Neurologic deficits usually develop within a few weeks and mononeuropathies as well as plexopathies may occur [41]. This may eventually lead to a chronic mono- or polyneuritis which tends to manifest as sensory predominant distal axonal neuropathy, though any segment may be affected [42]. When present, chronic neuropathy of late Lyme disease characteristically presents with acrodermatitis chronica atrophicans.

Late Lyme neuroborreliosis is rare, constituting less than 2% of all cases. Patients may present with chronic meningitis, vague cognitive complaints and very rarely progressive encephalomyelitis or cerebral vasculitis [43–47].

Patients with Lyme neuroborreliosis respond well to antimicrobial treatment and objective neurologic deficits resolve in the vast majority of patients [48]. However, some patients develop subjective symptoms after treatment, most often fatigue, arthralgias, myalgias and perceived cognitive deficits. When such symptoms persist for more than 6 months after treatment, this is termed post-treatment Lyme disease syndrome. Post-treatment Lyme disease syndrome appears to be relatively rare (perhaps 3% of patients) as evinced by prospective studies of patients with erythema migrans [49, 50]. The literature does not support a role of persistent infection, nor does it support a role for morphological variants of *B. burgdorferi* in post-treatment Lyme disease syndrome [51, 52]. The true nature of this syndrome remains unclear, but evidence does not support a role for ongoing antimicrobial treatment [53, 54] and clinicians must consider a wide range of treatable explanations for such symptoms. Fortunately in most cases these symptoms improve over time with supportive care.

Diagnosis

When there is clinical concern for Lyme disease, serum testing should be pursued. The recommended testing strategy is a two-tiered approach, both tests can be performed on the same serum sample [55, 56]. The first test is a sensitive enzyme immunoassay (EIA) or indirect immunofluorescence (IFA) followed by a separate confirmatory Western blot if the initial test is positive or equivocal. If the screening test is negative, no further testing is needed. The IgM Western blot is only indicated for disease less than 4 weeks in duration, as the IgG may be negative early in the course of infection. Isolated IgM present more than 4 weeks after onset of symptoms is almost always a false positive result. IgM Western blot is considered positive if ≥2/3 bands are present, while IgG is considered positive when ≥5/10 bands are present. In Summer 2019, the FDA approved several EIA serological assays, which can be used in place of the Western blot as the second tier [55]. Because serologic testing is often negative early in the illness, patients with erythema migrans should be treated based on the clinical diagnosis.

When epidemiological and clinical features suggest Lyme neuroborreliosis affecting the CNS, in general MRI with and without contrast of the affected area should be obtained and CSF analysis should be pursued. A modest lymphocytic pleocytosis (usually <150 cells/uL) is typical, protein may be elevated (usually

<200 mg/dL), glucose is normal; oligoclonal bands may be present and IgG index may be elevated as well. Lyme antibody testing on both CSF and serum specimen should be performed. A CSF index of >1.3 indicates intrathecal synthesis and in the appropriate clinical context supports a diagnosis of Lyme neuroborreliosis with high sensitivity and specificity [57, 58]. In the absence of any clinical evidence of CNS involvement, CSF analysis is not generally valuable. Unfortunately, neither CSF PCR nor cultures are sufficiently sensitive. It is important to note that serum Lyme antibodies may remain elevated even long after appropriate treatment. Likewise, CSF index may remain elevated long after appropriate treatment.

Treatment

Early reports indicate that even without treatment, most cases of early Lyme neuroborreliosis are self-limited [59, 60]. Lyme disease is readily treatable and the overwhelming majority of patients with Lyme or Lyme neuroborreliosis respond well to a 2–4 week course of either intravenous ceftriaxone at a dose of 2 g daily or oral doxycycline, 100 mg twice per day, which appears to be equally effective, although in the rare instance of encephalitis, IV therapy should be given [45, 61, 62]. In the event that symptoms persist or new neurologic symptoms develop in or after the course of treatment, the clinician should consider repeat CSF analysis. If CSF pleocytosis persists, a repeat treatment course can be considered; however, antibodies can persist in the CSF for years after infection and should not be used in the absence of CSF pleocytosis to justify repeat therapy. The same is true of serum antibodies.

Rocky Mountain Spotted Fever

Epidemiology

Rocky Mountain spotted fever (RMSF) is a life-threatening infection caused by *Rickettsia rickettsii,* an obligate intracellular bacterium. Named for the Rocky Mountain lab in Montana where it was first identified, the syndrome was reclassified under the broader term "spotted fever rickettsioses" (SFR) in 2010 consequent to its serological indistinguishability from other closely related tick-borne rickettsial diseases [63]. As many as 60% of SFR occur in Tennessee, North Carolina, Missouri, Arkansas and Oklahoma; however, SFR have been reported throughout the continental United States [64]. After Lyme disease, SFR represent the most common cause of tick-borne infection in the United States and the incidence increased by more than 200% between 2004 and 2016 [1]. SFR are under-diagnosed, likely related to nonspecific clinical features, under-recognition by providers [65], and the low sensitivity of serologic testing at the onset of illness [11]. With early initiation of antibiotics and appropriate supportive care, the case fatality rate is

3–12% [5, 64, 66], while untreated mortality ranges from 25% to 70% [11]. Children and the elderly suffer disproportionally high mortality and morbidity [67–69].

Clinical

Following local inoculation by a feeding tick, hematogenous dissemination occurs and the bacterium infects endothelial and vascular smooth muscle cells in the gastrointestinal tract, skin, liver, lungs, kidneys and brain [68, 70]. After destroying the endothelial cells, the bacteria extend centripetally along the intima. Bacterial infection and host immune responses (particularly cytotoxic CD8+ T-cells) produce necrosis and apoptosis of widespread microvascular endothelial cells in all organs with consequent infarction/increased vascular permeability and the clinical manifestations of multi-system vasculitis [68].

After a 2–14 day incubation period (mean of 7 days), clinical illness develops, ranging from asymptomatic infection to a fulminant illness though most clinically apparent cases have moderate to severe illness [71]. Patients develop a wide range of systemic, cutaneous, cardiac, gastrointestinal, pulmonary, neurologic, renal and musculoskeletal manifestations. Early symptoms are nonspecific, including fever, malaise, headache, myalgias, arthralgias, nausea, vomiting and abdominal pain [71]. Sudden onset of high fever (often >38.9 °C), severe headache and significant malaise accompanied by myalgias, nausea/vomiting, abdominal pain and anorexia is typical and may be misdiagnosed as a viral illness. The clinical triad of fever, headache and rash is present in a small minority of patients during the first 3 days of symptom onset, however [71].

Cutaneous findings develop in approximately 60–70% of patients [71], typically within a week of fever (Fig. 16.7) [72]. The earliest skin lesions are blanching 1–5 mm erythematous macules that typically appear on the wrists and ankles, then the palms and soles and eventually the proximal extremities and trunk [73]. After ~7 days, the rash becomes petechial, and in severe cases may progress to purpura and ecchymosis [74] followed by skin necrosis and gangrene potentially necessitating amputation [75].

Neurologic Manifestations

CNS involvement is among the most serious manifestations of SFR, and is associated with a 19-fold increased risk of death [64]. In addition to headache, which is common in SFR, CNS involvement often manifests with meningoencephalitis, which may include meningismus, seizure, stroke, cranial neuropathy and other focal neurologic signs [76]. The “starry sky” MRI pattern (multifocal diffusion restricting or T2 hyperintense lesions scattered throughout the subcortical and deep white matter) likely represents miliary infarcts from arteriolar vasculitis/thrombosis [77] and is a readily recognizable clue to the diagnosis of SFR encephalitis (Fig. 16.7) [78]. In the largest series of patients with SFR meningoencephalitis to

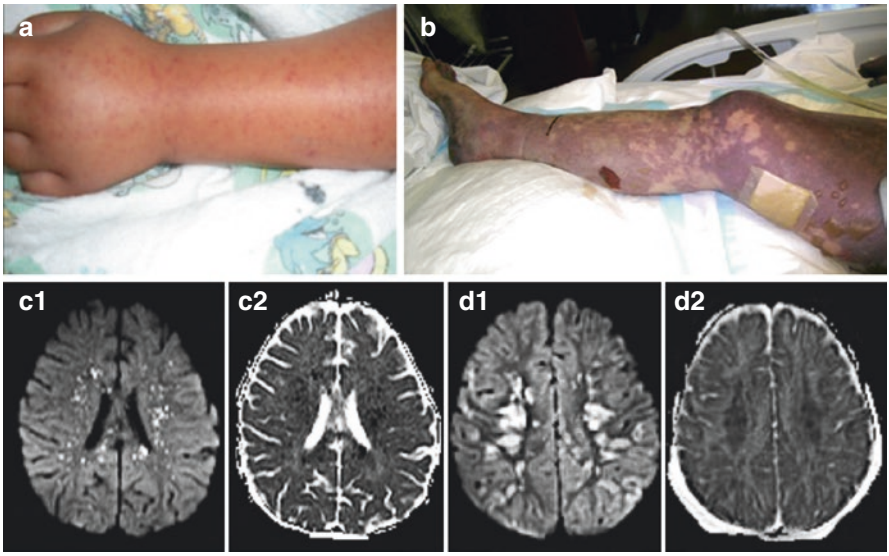


Fig. 16.7 The range of infectious vasculitis associated with Rocky Mountain spotted fever. (**a**) Petechial rash in a child with RMSF meningoencephalitis. (**b**) Widespread confluent rash in an adult with RMSF meningoencephalitis who eventually required amputation of the affected limbs. (**c1**) Axial diffusion weighted imaging (DWI) MRI of a child with RMSF meningoencephalitis demonstrating the "starry sky" pattern of multifocal, punctate, diffusion restricting lesions scattered throughout the white matter of both hemispheres, and (not shown) corpus callosum, brainstem and cerebellum. (**c2**) Axial apparent diffusion coefficient (ADC) MRI from the same patient. Autopsy studies from patients who died of RMSF meningoencephalitis have demonstrated vasculitis with arteriolar thromboses, which is the presumed mechanism of the starry sky sign on MRI. (**d1–2**) Axial DWI and ADC MRI from a child with RMSF meningoencephalitis with flame-like diffusion restriction in the subcortical white matter and (not shown) corpus callosum, brainstem and cerebellum. All patients survived their index hospitalization

date, the starry sky sign was seen in all children and no adults; however it is not exclusive to children and its absence does not exclude infection [76]. Brain MRI is recommended for the diagnosis of encephalitis, irrespective of cause, with abnormalities visualized in 86% of patients compared to only 6% on head CT [79]. In patients with SFR meningoencephalitis, CSF pleocytosis was seen in 87.5% (median 41 cells/uL, range 0–3250) and was neutrophil predominant in 33%; protein was elevated in 87.5% and hypoglycorrhachia present in 18.8% [76]. Ninety percent of patients with SFR meningoencephalitis require ICU admission and only 46% made a complete recovery by hospital discharge .

Diagnosis

Definitive diagnosis of SFR can be a challenge. There are no sensitive diagnostic biomarkers that might help the clinician identify cases early in the course of the illness. Therefore, the clinician must rely on clinical, laboratory, radiological and

epidemiologic clues that suggest the possibility of SFR infection [11]. Antibodies to SFR do not develop until 7–10 days after exposure and negative serologies do not exclude infection, thus the diagnostic utility of serologic testing early in the course of the disease is limited [80]. Laboratory confirmation typically requires acute and convalescent serum testing and cases are divided into confirmed or probable based on the results [81]. Polymerase chain reaction is insensitive [82] but may be helpful when combined with immunohistochemistry on biopsy specimens (e.g. skin biopsy of rash) [83]. The current gold-standard test is the indirect fluorescent antibody test, which is highly sensitive and specific for SFR, but does not distinguish among the rickettsiae [83]. Therefore, in the early phase of illness, a high clinical suspicion, appropriate historical and examination findings and supportive laboratories are needed. Non-specific but helpful laboratory findings include anemia, thrombocytopenia, elevated aminotransferases, elevated creatine kinase and hyponatremia [71].

Treatment

When the clinical concern for SFR is high, treatment should not await laboratory confirmation. Tetracyclines and chloramphenicol are the only antibiotics with definite efficacy for RMSF [71], and doxycycline is the preferred first-line agent, including for children [11, 27, 28]. Pediatric dosing of doxycycline is 2.2 mg/kg divided into two doses per day up to 100 mg BID for a minimum of 5–7 days or until the patient is afebrile for at least 2–3 days, whichever is longer. Adult dosing is 100 mg BID, oral or intravenous. Some clinicians will give a loading dose of 200 mg and may give doxycycline IV for more severe cases , although bioavailability of oral doxycycline approaches 100%.

Tularemia

Epidemiology

Tularemia is a zoonotic infection caused by *Francisella tularensis*, a highly infectious aerobic Gram-negative bacillus. Several animal species harbor *F. tularensis*, including rabbits, squirrels and muskrats. Tularemia has been reported throughout the USA (except Hawaii), but most often occurs in the South Central states. In 2015 there was a 975% increase in the incidence of tularemia in Colorado, Nebraska, South Dakota and Wyoming [84]. Humans can be infected by several mechanisms including direct contact with infected animals, ingestion of contaminated water or meat, inhalation of aerosolized bacteria or by the bite of an infected tick or deer fly [85]. The incidence is higher among men than women, presumably owing to greater outdoor exposure and transmission via tick vectors (most often *D. andersoni*, *D. variabilis*, and *A. americanum*) is now the most common means of infection [86].

Clinical

When inoculated into the skin bacteria multiply and cause a necrotic, purulent ulcerated lesion, which eventually evolves into a granuloma (Fig. 16.8). Hematogenous dissemination to the lymph nodes, spleen, liver, lungs and other organs can occur early or late in the course of the infection and bacteria may persist in tissues for prolonged periods producing a tendency to relapse after treatment. After an incubation period of 3–5 days, abrupt onset of fever, chills, malaise and headaches are common and myalgias, sore throat, vomiting and abdominal pain may also develop [87]. Interestingly, nearly half of patients are observed to have a lower pulse rate than expected for the degree of fever (termed pulse-temperature dissociation). Although clinical manifestations may overlap, six clinical categories have been described including ulceroglandular, glandular, oculoglandular, typhoidal, orophryngeal and pneumonic tularemia.

Neurologic Manifestations

Tularemic meningitis is very rare with only a handful of cases reported in the literature [88]. Neurologic manifestations typically develop 5 days after onset of the illness (range 3–30) and include headaches, confusion, meningismus and rarely seizure.

Diagnosis

CSF analysis usually demonstrates marked pleocytosis (mean 1788 cells/uL, range 2–13,200) and is usually monocyte predominant, often with hypoglycorrhachia with mean glucose 32 mg/dL (9–59 mg/dL). CSF Gram stain has low sensitivity

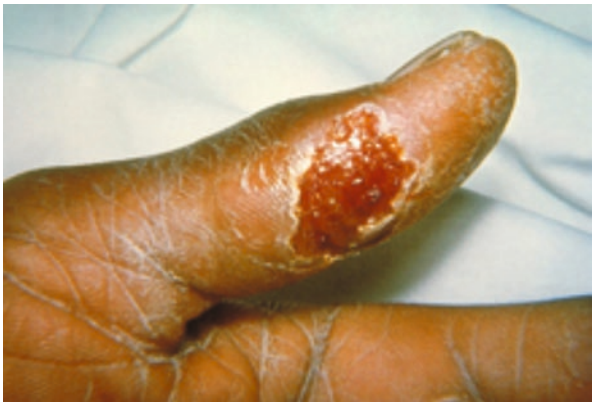


Fig. 16.8 Ulcerative lesion from tularemia. (From https://www.cdc.gov/ticks/tickbornediseases/overview.html)

(10%). Although human-human transmission has not been reported, tularemia is highly contagious including in the laboratory and laboratory personnel should be notified, both for their protection and to ensure that appropriate media are used when the diagnosis is suspected. Establishing the diagnosis includes serologic testing with tube agglutination, microagglutination or latex agglutination [89]. A presumptive diagnosis can be established in the appropriate clinical context with a single titer of 1:160, but confirmation requires a fourfold increase in the titer between acute and convalescent samples.

Treatment

The preferred antimicrobials for the treatment of tularemia include the aminoglycosides streptomycin (1 g IM BID) or gentamicin (5 mg/kg IV or IM daily) given for 10 days. Chloramphenicol and doxycycline (100 mg BID for 14–21 days) have been used in the past but are associated with higher rates of relapse than aminoglycocides. Ciprofloxacin 750 mg BID IV or PO has been used in recent years with some success. When CNS infection is diagnosed, an aminoglycoside should be combined with doxycycline or ciprofloxacin, as CSF aminoglycoside levels may be erratic [88, 90, 91].

Viral Infections

Colorado Tick Fever

Epidemiology

Colorado tick fever (CTF) is caused by the CTF virus, a non-enveloped, double-stranded RNA virus which is prototypical member of the *Coltivirus* genus. The vector, the Rocky Mountain wood tick (*Dermacentor andersoni*), is found throughout the western United States and western Canada at elevations of 4000–10,000 feet above sea level. CTF is specifically reportable in Arizona, Colorado, Montana, Oregon, Utah and Wyoming but not nationally reportable; cases occur not infrequently in individuals who have recently travelled to one of the endemic states. Between 2002 and 2012, 83 cases were reported to the CDC [92], which based on limited reporting is almost certainly an underestimate, with the true incidence more likely in the range of 200–400 [93]. Eighty percent of cases occurred between the months of May–July and the highest incidence was in Wyoming, followed by Montana and Utah [94]. Tick exposure is frequently reported prior to the illness although only roughly half of patients report a discreet tick attachment, an observation that suggests transmission may occur even with brief attachment. Roughly 20% of patients are hospitalized in the course of their illness [95].

Clinical

After an incubation period of roughly 2–3 days (range 0–14 days), nonspecific symptoms including malaise, fever, chills, headache and myalgias develop [96]. Sore throat, gastrointestinal upset and macular, maculopapular or petechial rash develops in 5–15% of patients [96]. Illness typically lasts several weeks and fever is biphasic in roughly half of patients, appropriately termed "saddleback" fever. Severe complications such as meningoencephalitis, hepatitis, pericarditis, myocarditis and pneumonia rarely develop. However, in the vast majority of cases, the illness is self-limited with rare reports of death associated with disseminated intravascular coagulopathy or meningoencephalitis in children. When they occur, neurologic symptoms most often develop in children and typically begin within a week of illness [93]. Neurologic complications range from meningismus to encephalitis including coma, but death is rare [97].

Diagnosis

Routine laboratory studies typically reveal leukopenia with atypical lymphocytes and thrombocytopenia. When meningoencephalitis develops, opening pressure is typically normal, a lymphocytic pleocytosis is common (range 0–372 cells/uL), protein may be normal or elevated and hypoglycorrhachia may occur [98]. PCR or serologies against CTFV can confirm the diagnosis although in the acute setting PCR is more sensitive as seroconversion may take 2–3 weeks. Diagnostic testing is available at some commercial and state health department laboratories as well as through the CDC.

Treatment

There is no specific treatment for CTF beyond general supportive care. There is currently no vaccine for CTF and prevention by avoiding tick exposure through best practices is recommended for people who engage in outdoor activities in areas of risk.

Emerging Tick-Borne Infections

In the last decade, a number of newly described tick-borne pathogens have been identified, however little is known about the clinical spectrum of these diseases. Heartland virus (HRTV), a phlebovirus spread by Lone star ticks, is clinically indistinguishable from ehrlichiosis. As of 2018, 35 cases have been confirmed in patients residing in the Southeast and South-central US. HRTV should be suspected in

patients with presumptive ehrlichiosis who fail to improve after 48 hours of doxycycline therapy.

In the few cases of HRTV reported in the literature, headache and fever are common, and confusion has also been reported [99]. A fatal case who presented with progressive confusion had normal cerebrospinal fluid and a negative MRI of the brain [100]. However, autopsy identified necrosis of the thalamus with viral antigen in glial cells by immunohistochemistry, consistent with encephalitis.

Bourbon virus is a tick-borne thogotovirus first identified in 2014. Very few cases have been reported in the literature, however the index case (who ultimately died of the infection) did not have clinical signs or symptoms suggestive of neurologic involvement.

Parasitic Infections

Babesiosis

Epidemiology

Babesiosis is caused by a single-celled intraerythrocytic parasite transmitted by *Ixodes* ticks, the same vector for Lyme disease and Anaplasomosis (Figs. 16.1 and 16.2) [101]. Less commonly infection can be acquired through transfusion of infected red cell products but the infection is not otherwise transmissible human to human. Babesiosis is not a nationally reportable disease. In 2017, the last year where incidence data are available, a total of 2358 cases were reported, a 24% increase from the previous year [102]. Almost 90% of cases occurred in residents of Connecticut, Massachusetts, New Jersey, New York, Rhode Island, Minnesota or Wisconsin. The number of reported cases is highest among older adults, likely reflecting a diagnostic bias towards more severely ill patients.

Clinical

Asymptomatic infection is common, particularly in healthy children and young adults. Symptomatic infections range from a mild febrile illness to fulminant disease. Older individuals, immunocompromised patients (including those with HIV/AIDS), and patients with asplenia are at risk for more severe disease. Mortality among hospitalized patients is >10% [103]. The hallmark of babesiosis is hemolysis, and many of the clinical findings and laboratory abnormalities are due to erythrocyte lysis. Symptomatic patients typically develop illness 1–4 weeks after exposure from tick bite or 1–9 weeks after exposure to contaminated blood products [101]. The illness usually begins with gradually worsening malaise (82%) followed by fever (89%), and may be accompanied by chills, sweats, headaches, myalgias, arthralgias, anorexia and nonproductive cough [104]. Uncommon manifestations

include sore throat, vomiting, conjunctival injection, hyperesthesia and in severe disease, jaundice and icterus may be present. Splenomegaly, hepatomegaly and retinopathy with splinter hemorrhages/retinal infarcts can occur. Although the illness typically lasts for several weeks, fatigue can persist for months.

Neurologic Complications

While headache is noted in 47% of patients with babesiosis, neurologic manifestations are seen almost exclusively with severe infections, correlating with high-level parasitemia [104]. A case series of patients hospitalized with severe babesiosis documented altered mentation in 6% of cases [103]. However, when encephalopathy is present, it is often due to hypoxia or uremia rather than direct neurologic involvement. Coma has been reported in patients with high levels of parasitemia. Theories to explain CNS symptoms with babesiosis include alterations in erythrocyte cytoadherence or cytokine production [105]. Autopsy studies have shown parasitized red cells in the brain confined to intravascular space, with no evidence of vasculitis or invasion of cerebral tissue.

Diagnosis

The cardinal laboratory abnormality is hemolytic anemia. Other laboratory findings variably present include thrombocytopenia, increased liver enzyme levels, elevated lactate dehydrogenase, and renal insufficiency. When there is high parasitemia, microscopic evaluation of thick and thin blood smears may reveal intraerythrocytic rings similar to those seen with *Plasmodium falciparum* malaria. Rarely tetrad forms resembling a Maltese cross may be present and are pathognomonic for babesiosis (Fig. 16.9). In cases with lower parasitemia levels, microscopy may be negative. In this setting, whole blood PCR is the preferred diagnostic investigation.

Treatment

Severe disease is treated with combination therapy of IV clindamycin (300–600 mg IV qid) and oral quinine (650 mg PO BID). The duration of treatment varies based on host characteristics, with longer duration of treatment often indicated in asplenic, elderly or immunocompromised patients. A minimum of 7 days of therapy is recommended; treatment should be extended until fever has abated and blood smears do not show residual parasitemia. In patients with parasites identified in $\geq$10% of cells or in whom severe hemolysis is present, exchange transfusion is indicated.

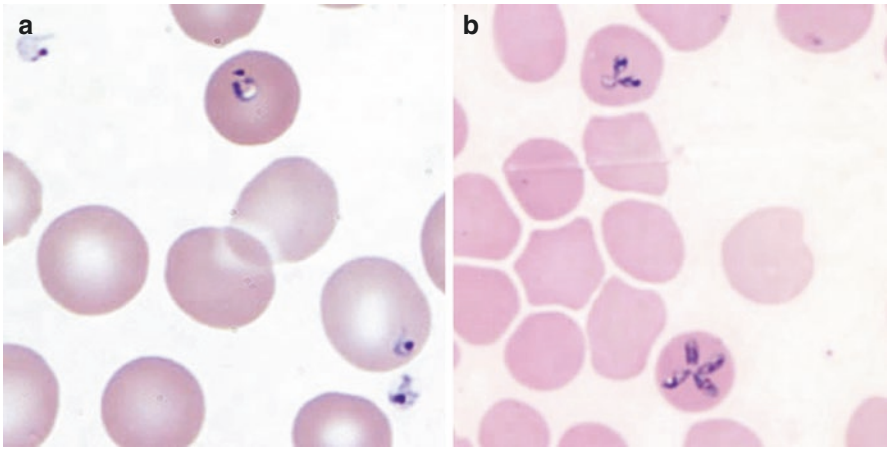


Fig. 16.9 Blood smear with Giemsa stain demonstrating (**a**) *Babesia microti* both intraerythrocytic and extracellular amoeboid forms. (**b**) *Babesia microti* Maltese cross. (From https://www.cdc.gov/ticks/tickbornediseases/overview.html)

References

1. Rosenberg R, Lindsey NP, Fischer M, et al. Vital signs: trends in reported vectorborne disease cases – United States and territories, 2004–2016. MMWR Morb Mortal Wkly Rep. 2018;67(17):496–501.
2. Paules CI, Marston HD, Bloom ME, Fauci AS. Tickborne diseases – confronting a growing threat. N Engl J Med. 2018;379(8):701–3.
3. Nelson CA, Saha S, Kugeler KJ, et al. Incidence of clinician-diagnosed Lyme disease, United States, 2005–2010. Emerg Infect Dis. 2015;21(9):1625–31.
4. Hinckley AF, Connally NP, Meek JI, et al. Lyme disease testing by large commercial laboratories in the United States. Clin Infect Dis. 2014;59(5):676–81.
5. Demma LJ, Traeger MS, Nicholson WL, et al. Rocky Mountain spotted fever from an unexpected tick vector in Arizona. N Engl J Med. 2005;353(6):587–94.
6. Drexler NA, Yaglom H, Casal M, et al. Fatal Rocky Mountain spotted fever along the United States-Mexico border, 2013–2016. Emerg Infect Dis. 2017;23(10):1621–6.
7. Kulkarni MA, Narula I, Slatculescu AM, Russell C. Lyme disease emergence after invasion of the blacklegged tick, Ixodes scapularis, Ontario, Canada, 2010–2016. Emerg Infect Dis. 2019;25(2):328–32.
8. Eddens T, Kaplan DJ, Anderson AJM, Nowalk AJ, Campfield BT. Insights from the geographic spread of the Lyme disease epidemic. Clin Infect Dis. 2019;68(3):426–34.
9. https://www.cdc.gov/anaplasmosis/index.html. Accessed 24 Oct 2019.
10. Goel R, Westblade LF, Kessler DA, et al. Death from transfusion-transmitted anaplasmosis, New York, USA, 2017. Emerg Infect Dis. 2018;24(8):1548–50.
11. Biggs HMBC, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis — United States. MMWR Recomm Rep. 2016;RR-2:1–44.
12. Dahlgren FS, Heitman KN, Drexler NA, Massung RF, Behravesh CB. Human granulocytic anaplasmosis in the United States from 2008 to 2012: a summary of national surveillance data. Am J Trop Med Hyg. 2015;93(1):66–72.

13. Bakken JS, Dumler JS. Human granulocytic anaplasmosis. Infect Dis Clin N Am. 2015;29(2):341–55.
14. Bakken JS, Krueth J, Wilson-Nordskog C, Tilden RL, Asanovich K, Dumler JS. Clinical and laboratory characteristics of human granulocytic ehrlichiosis. JAMA. 1996;275(3):199–205.
15. Lee FS, Chu FK, Tackley M, Wu AD, Atri A, Wessels MR. Human granulocytic ehrlichiosis presenting as facial diplegia in a 42-year-old woman. Clin Infect Dis. 2000;31(5):1288–91.
16. Kim SW, Kim CM, Kim DM, Yun NR. Manifestation of anaplasmosis as cerebral infarction: a case report. BMC Infect Dis. 2018;18(1):409.
17. Horowitz HW, Marks SJ, Weintraub M, Dumler JS. Brachial plexopathy associated with human granulocytic ehrlichiosis. Neurology. 1996;46(4):1026–9.
18. Bakken JS, Erlemeyer SA, Kanoff RJ, Silvestrini TC 2nd, Goodwin DD, Dumler JS. Demyelinating polyneuropathy associated with human granulocytic ehrlichiosis. Clin Infect Dis. 1998;27(5):1323–4.
19. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. JAMA. 2016;315(16):1767–77.
20. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089–134.
21. Nichols Heitman K, Dahlgren FS, Drexler NA, Massung RF, Behravesh CB. Increasing incidence of Ehrlichiosis in the United States: a summary of national surveillance of Ehrlichia chaffeensis and Ehrlichia ewingii infections in the United States, 2008–2012. Am J Trop Med Hyg. 2016;94(1):52–60.
22. Ratnasamy N, Everett ED, Roland WE, McDonald G, Caldwell CW. Central nervous system manifestations of human ehrlichiosis. Clin Infect Dis. 1996;23(2):314–9.
23. Hongo I, Bloch KC. Ehrlichia infection of the central nervous system. Curr Treat Options Neurol. 2006;8(3):179–84.
24. Hamburg BJ, Storch GA, Micek ST, Kollef MH. The importance of early treatment with doxycycline in human ehrlichiosis. Medicine (Baltimore). 2008;87(2):53–60.
25. Buzzard SL, Bissell BD, Thompson Bastin ML. Ehrlichiosis presenting as severe sepsis and meningoencephalitis in an immunocompetent adult. JMM Case Rep. 2018;5(9):e005162.
26. Ta H, Reid B, Bhatia D, Levorson R. Ehrlichiosis induced aseptic meningitis and second-degree heart block in an adolescent male. Pediatr Infect Dis J. 2016;35(7):807–9.
27. Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. J Pediatr. 2015;166(5):1246–51.
28. Holman RC, Paddock CD, Curns AT, Krebs JW, McQuiston JH, Childs JE. Analysis of risk factors for fatal Rocky Mountain spotted fever: evidence for superiority of tetracyclines for therapy. J Infect Dis. 2001;184(11):1437–44.
29. Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics 2018.
30. Mead PS. Epidemiology of Lyme disease. Infect Dis Clin N Am. 2015;29(2):187–210.
31. Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease – United States, 2008–2015. MMWR Surveill Summ. 2017;66(22):1–12.
32. Nadelman RB. Erythema migrans. Infect Dis Clin N Am. 2015;29(2):211–39.
33. Steere AC, Sikand VK. The presenting manifestations of Lyme disease and the outcomes of treatment. N Engl J Med. 2003;348(24):2472–4.
34. Halperin JJ. Facial nerve palsy associated with Lyme disease. Muscle Nerve. 2003;28(4):516–7.
35. Belman AL, Reynolds L, Preston T, Postels D, Grimson R, Coyle PK. Cerebrospinal fluid findings in children with Lyme disease-associated facial nerve palsy. Arch Pediatr Adolesc Med. 1997;151(12):1224–8.

36. Sood SK. Lyme disease in children. Infect Dis Clin N Am. 2015;29(2):281–94.
37. Garro AC, Rutman M, Simonsen K, Jaeger JL, Chapin K, Lockhart G. Prospective validation of a clinical prediction model for Lyme meningitis in children. Pediatrics. 2009;123(5): e829–34.
38. Cohn KA, Thompson AD, Shah SS, et al. Validation of a clinical prediction rule to distinguish Lyme meningitis from aseptic meningitis. Pediatrics. 2012;129(1):e46–53.
39. Dumic I, Vitorovic D, Spritzer S, Sviggum E, Patel J, Ramanan P. Acute transverse myelitis – a rare clinical manifestation of Lyme neuroborreliosis. IDCases. 2019;15:e00479.
40. Halperin JJ. Neuroborreliosis and neurosyphilis. Continuum (Minneap Minn). 2018;24(5, Neuroinfectious Disease):1439–58.
41. Marques AR. Lyme neuroborreliosis. Continuum (Minneap Minn). 2015;21(6 Neuroinfectious Disease):1729–44.
42. Halperin J, Luft BJ, Volkman DJ, Dattwyler RJ. Lyme neuroborreliosis. Peripheral nervous system manifestations. Brain J Neurol. 1990;113(Pt 4):1207–21.
43. Kohler J, Kasper J, Kern U, Thoden U, Rehse-Kupper B. Borrelia encephalomyelitis. Lancet. 1986;2(8497):35.
44. Ackermann R, Gollmer E, Rehse-Kupper B. Progressive Borrelia encephalomyelitis. Chronic manifestation of erythema chronicum migrans disease of the nervous system. Dtsch Med Wochenschr. 1985;110(26):1039–42.
45. Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985–1990. A prospective study of 187 patients with Borrelia burgdorferi specific intrathecal antibody production. Brain J Neurol. 1992;115(Pt 2):399–423.
46. Garkowski A, Zajkowska J, Zajkowska A, et al. Cerebrovascular manifestations of Lyme neuroborreliosis-A systematic review of published cases. Front Neurol. 2017;8:146.
47. Back T, Grunig S, Winter Y, et al. Neuroborreliosis-associated cerebral vasculitis: long-term outcome and health-related quality of life. J Neurol. 2013;260(6):1569–75.
48. Koedel U, Fingerle V, Pfister HW. Lyme neuroborreliosis-epidemiology, diagnosis and management. Nat Rev Neurol. 2015;11(8):446–56.
49. Wormser GP, Weitzner E, McKenna D, et al. Long-term assessment of health-related quality of life in patients with culture-confirmed early Lyme disease. Clin Infect Dis. 2015;61(2):244–7.
50. Wormser GP, Weitzner E, McKenna D, Nadelman RB, Scavarda C, Nowakowski J. Long-term assessment of fatigue in patients with culture-confirmed Lyme disease. Am J Med. 2015;128(2):181–4.
51. Oliveira CR, Shapiro ED. Update on persistent symptoms associated with Lyme disease. Curr Opin Pediatr. 2015;27(1):100–4.
52. Lantos PM, Auwaerter PG, Wormser GP. A systematic review of Borrelia burgdorferi morphologic variants does not support a role in chronic Lyme disease. Clin Infect Dis. 2014;58(5):663–71.
53. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003;60(12):1923–30.
54. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008;70(13):992–1003.
55. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep. 2019;68(32):703.
56. Centers for Disease C, Prevention. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995;44(31):590–1.
57. Blanc F, Jaulhac B, Fleury M, et al. Relevance of the antibody index to diagnose Lyme neuroborreliosis among seropositive patients. Neurology. 2007;69(10):953–8.
58. Ljostad U, Skarpaas T, Mygland A. Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis. Eur J Neurol. 2007;14(8):873–6.
59. Kruger H, Kohlhepp W, Konig S. Follow-up of antibiotically treated and untreated neuroborreliosis. Acta Neurol Scand. 1990;82(1):59–67.

60. Kruger H, Reuss K, Pulz M, et al. Meningoradiculitis and encephalomyelitis due to Borrelia burgdorferi: a follow-up study of 72 patients over 27 years. J Neurol. 1989;236(6):322–8.
61. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology. 1994;44(7):1203–7.
62. Ogrinc K, Logar M, Lotric-Furlan S, Cerar D, Ruzic-Sabljic E, Strle F. Doxycycline versus ceftriaxone for the treatment of patients with chronic Lyme borreliosis. Wien Klin Wochenschr. 2006;118(21–22):696–701.
63. Drexler NA, Dahlgren FS, Heitman KN, Massung RF, Paddock CD, Behravesh CB. National surveillance of spotted fever group rickettsioses in the United States, 2008–2012. Am J Trop Med Hyg. 2016;94(1):26–34.
64. Dahlgren FS, Holman RC, Paddock CD, Callinan LS, McQuiston JH. Fatal Rocky Mountain spotted fever in the United States, 1999–2007. Am J Trop Med Hyg. 2012;86(4):713–9.
65. Razzaq S, Schutze GE. Rocky Mountain spotted fever: a physician's challenge. Pediatr Rev / Am Acad Pediatr. 2005;26(4):125–30.
66. Regan JJ, Traeger MS, Humpherys D, et al. Risk factors for fatal outcome from rocky mountain spotted fever in a highly endemic area-Arizona, 2002–2011. Clin Infect Dis. 2015;60(11):1659–66.
67. Dumler JS, Walker DH. Rocky Mountain spotted fever--changing ecology and persisting virulence. N Engl J Med. 2005;353(6):551–3.
68. Walker DH, Valbuena GA, Olano JP. Pathogenic mechanisms of diseases caused by Rickettsia. Ann N Y Acad Sci. 2003;990:1–11.
69. Bradshaw MJ, Lalor KB, Vu N, Pruthi S, Bloch KC. Child neurology: Rocky Mountain spotted fever encephalitis. Neurology. 2017;88(11):e92–5.
70. Elghetany MT, Walker DH. Hemostatic changes in Rocky Mountain spotted fever and Mediterranean spotted fever. Am J Clin Pathol. 1999;112(2):159–68.
71. Dantas-Torres F. Rocky Mountain spotted fever. Lancet Infect Dis. 2007;7(11):724–32.
72. Lacz NL, Schwartz RA, Kapila R. Rocky Mountain spotted fever. J Eur Acad Dermatol Venereol JEADV. 2006;20(4):411–7.
73. Kirk JL, Fine DP, Sexton DJ, Muchmore HG. Rocky Mountain spotted fever. A clinical review based on 48 confirmed cases, 1943–1986. Medicine (Baltimore). 1990;69(1):35–45.
74. Myers SA, Sexton DJ. Dermatologic manifestations of arthropod-borne diseases. Infect Dis Clin N Am. 1994;8(3):689–712.
75. Kirkland KB, Marcom PK, Sexton DJ, Dumler JS, Walker DH. Rocky Mountain spotted fever complicated by gangrene: report of six cases and review. Clin Infect Dis. 1993;16(5):629–34.
76. Bradshaw MJ, Carpenter Byrge K, Ivey KS, Pruthi S, Bloch KC. Meningoencephalitis due to spotted fever rickettsioses, including Rocky Mountain spotted fever. Clin Infect Dis. 2020;71(1):188–95.
77. Lillie RD. Pathology of the Eastern type of Rocky Mountain spotted fever. Public Health Rep. 1931;46:2840–59.
78. Crapp S, Harrar D, Strother M, Wushensky C, Pruthi S. Rocky Mountain spotted fever: 'starry sky' appearance with diffusion-weighted imaging in a child. Pediatr Radiol. 2012;42(4):499–502.
79. Bradshaw MJ, Venkatesan A. Emergency evaluation and management of encephalitis and myelitis in adults. Semin Neurol. 2019;39(1):82–101.
80. Kaplan JE, Schonberger LB. The sensitivity of various serologic tests in the diagnosis of Rocky Mountain spotted fever. Am J Trop Med Hyg. 1986;35(4):840–4.
81. Traeger MS, Regan JJ, Humpherys D, et al. Rocky mountain spotted fever characterization and comparison to similar illnesses in a highly endemic area-Arizona, 2002–2011. Clin Infect Dis. 2015;60(11):1650–8.
82. Sexton DJ, Kanj SS, Wilson K, et al. The use of a polymerase chain reaction as a diagnostic test for Rocky Mountain spotted fever. Am J Trop Med Hyg. 1994;50(1):59–63.
83. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis--United States: a

practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep. 2006;55(RR-4):1–27.
84. Pedati C, House J, Hancock-Allen J, et al. Notes from the field: increase in human cases of tularemia--Colorado, Nebraska, South Dakota, and Wyoming, January-September 2015. MMWR Morb Mortal Wkly Rep. 2015;64(47):1317–8.
85. Carvalho CL, Lopes de Carvalho I, Ze-Ze L, Nuncio MS, Duarte EL. Tularaemia: a challenging zoonosis. Comp Immunol Microbiol Infect Dis. 2014;37(2):85–96.
86. Mani RJ, Morton RJ, Clinkenbeard KD. Ecology of tularemia in central US endemic region. Curr Trop Med Rep. 2016;3:75–9.
87. Maurin M, Gyuranecz M. Tularaemia: clinical aspects in Europe. Lancet Infect Dis. 2016;16(1):113–24.
88. Hofinger DM, Cardona L, Mertz GJ, Davis LE. Tularemic meningitis in the United States. Arch Neurol. 2009;66(4):523–7.
89. Rastawicki W, Forminska K, Zasada AA. Development and evaluation of a latex agglutination test for the identification of Francisella tularensis subspecies pathogenic for human. Pol J Microbiol. 2018;67(2):241–4.
90. Barbaz M, Piau C, Tadie JM, et al. Rhombencephalitis caused by Francisella tularensis. J Clin Microbiol. 2013;51(10):3454–5.
91. Page J, Wittler RR. An 8-year-old boy with fever, axillary ulcerative lesion, and altered mental status. Clin Infect Dis. 2009;48(9):1266–7, 1327–1268.
92. https://www.cdc.gov/coloradotickfever/. Accessed 20 Oct 2019.
93. Romero JR, Simonsen KA. Powassan encephalitis and Colorado tick fever. Infect Dis Clin N Am. 2008;22(3):545–59, x.
94. Yendell SJ, Fischer M, Staples JE. Colorado tick fever in the United States, 2002–2012. Vector Borne Zoonotic Dis. 2015;15(5):311–6.
95. Brackney MM, Marfin AA, Staples JE, et al. Epidemiology of Colorado tick fever in Montana, Utah, and Wyoming, 1995–2003. Vector Borne Zoonotic Dis. 2010;10(4):381–5.
96. Goodpasture HC, Poland JD, Francy DB, Bowen GS, Horn KA. Colorado tick fever: clinical, epidemiologic, and laboratory aspects of 228 cases in Colorado in 1973–1974. Ann Intern Med. 1978;88(3):303–10.
97. Fraser CH, Schiff DW. Colorado tick fever encephalitis. Report of a case. Pediatrics. 1962;29:187–90.
98. Spruance SL, Bailey A. Colorado Tick Fever. A review of 115 laboratory confirmed cases. Arch Intern Med. 1973;131(2):288–93.
99. Brault AC, Savage HM, Duggal NK, Eisen RJ, Staples JE. Heartland virus epidemiology, vector association, and disease potential. Viruses. 2018;10(9):498.
100. Fill MA, Compton ML, McDonald EC, et al. Novel clinical and pathologic findings in a heartland virus-associated death. Clin Infect Dis. 2017;64(4):510–2.
101. Vannier E, Krause PJ. Human babesiosis. N Engl J Med. 2012;366(25):2397–407.
102. https://www.cdc.gov/parasites/babesiosis/resources/babesiosis_surveillance_summary_2017b.pdf. Accessed 11 Jan 2019.
103. Hatcher JC, Greenberg PD, Antique J, Jimenez-Lucho VE. Severe babesiosis in Long Island: review of 34 cases and their complications. Clin Infect Dis. 2001;32(8):1117–25.
104. Vannier EG, Diuk-Wasser MA, Ben Mamoun C, Krause PJ. Babesiosis. Infect Dis Clin N Am. 2015;29(2):357–70.
105. Usmani-Brown S, Halperin JJ, Krause PJ. Neurological manifestations of human babesiosis. Handb Clin Neurol. 2013;114:199–203.

Chapter 17
CNS Whipple's Disease

Rima El-Abassi, Michael Soliman, Nicole R. Villemarette-Pittman, and John England

Whipple's Disease (WD) was first described by George H. Whipple in 1907 [1]. Classic Whipple disease (CWD) is a systemic chronic infection by Tropheryma whipplei (T whipplei) that can involve various organ systems such as gastrointestinal tract, joints, and central nervous system (CNS) [2–4]. Central nervous system Whipple's disease (CNS- WD) can be a part of the classical WD, a recurrent phenomenon or an isolated disease. It encompasses a wide array of clinical manifestations depending on the anatomic region affected by the pathological process [5]. Diagnosis is made by polymerase chain reaction testing. It is vital to implement an aggressive mode of treatment to reduce the chances of complications like cognitive impairment, or disease recurrence, even many years later.

History

Initially thought to be a disease of lipodystrophy due to the finding of foamy macrophages with cytoplasmatic periodic acid-Schiff (PAS) reactivity in intestinal mucosa [6], the etiology was further clarified in 1961 by detecting the bacteria by electron microscopy [7, 8] 30 years later, a first specific polymerase chain reaction (PCR) assay was established targeting T whipplei 16S ribosomal RNA (rRNA) genes from duodenal lesions [9]. In 2000, the bacterium was cultured in human fibroblast cells and the genome was sequenced, followed by the development of a specific immunohistochemical staining in 2002 [10, 11] and various diagnostic PCR assays [12, 13].

R. El-Abassi (✉) · M. Soliman · N. R. Villemarette-Pittman · J. England
Department of Neurology, Louisiana State University, New Orleans, LA, USA
e-mail: relab1@lsuhsc.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*,
Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_17

Epidemiology

The overall prevalence of Whipple's disease in the USA is 3/1,000,000 and the incidence is 0.1–0.6/1,000,000 new cases in Western populations [14] (Table 17.1). T. whipplei is an environmental actinomycetes bacteria residing in soil or water that concentrates in sewage, thus endangering farmers, sewage plant workers, and other outdoor professions. Transmission is postulated to be from person to person [15–17]. The organism disseminates hematogenously as suggested by the characteristic prominent perivascular and subependymal distribution [18]. The naming of the etiologic agent, Tropheryma whipplei, comes from the Greek "trophe", nourishment, and "eryma", barrier. The name refers to nutrient malabsorption [9, 19]. Neurologic involvement is the third major manifestation of Whipple's disease (10–43%) [4, 20]. It affects males and females equally and is more common in individuals >65 years old [14]. Approximately 20–40% of patients suffer from neurological manifestations [21] and 5% of patients present with isolated CNS-WD [22]. There is a higher incidence in Caucasians as compared to the native Asian and African populations [23]. Genetic carriage is common [24, 25].

Pathophysiology

WD has occasionally been reported in families [26]. These findings are consistent with a common environmental exposure and shared genetic susceptibility. The organism is detectable in the saliva, dental plaque and feces of healthy hosts without invasive infection [27–30] and IgG antibodies are found in about 70% of healthy individuals [10].

The organism accumulates in the macrophages as intensely periodic acid-Schiff (PAS)-positive intracellular material [6, 31], that exerts no visible cytotoxic effects upon host cells, and there is a remarkable lack of inflammatory response to it. This is the foundation of the idea that WD is caused by an underlying genetic predisposition in affected individuals that leads to colonization of T. whipplei. An association between HLA alleles DRB1*13 and DQB1*06 and Whipple's disease

Table 17.1 Epidemiology

Caucasians > Native Asian and African populations
Males = Females
More common in individuals >65 years
Transmission from person to person
Endangering farmers, sewage plant workers, and other outdoor professions
Disseminates hematogenously
Genetic carriage is common
20–40% of patients suffer from neurological manifestations

was shown in a cohort of 122 European patients [32, 33]. Immunologic studies show mononuclear cells' deficiency in the expression of complement receptor type 3 (CD11b) [34] and a persistently diminished ability to degrade intracellular organisms [35, 36]. Intestinal macrophages revealed up-regulation of genes encoding IL-1 and IL-16 [37–39] contributing to increased T. whipplei replication. There is a specific defect in cell-mediated immunity [34], an impaired production of interleukin-12, a stimulator of T-cell function [34, 40], a decrease in the CD4/CD8 T-cell ratio [34] with associated low functional activity of type 1 T-helper cells (Th1), an increase in functional Th2 responses and absent or diminished antigen presentation by the MHC class II apparatus [41, 42]. Upon stimulating blood and mucosal lymphoctes with T. Whipplei antigens, there is decreased intracellular Interferon gamma (IFN γ) production [41]. These findings normalize with treatment, suggesting immune downregulation by the bacteria [42].

Clinical Presentation

The clinical picture of CNS-WD involves the entire neurologic spectrum [43]. It follows three distinct patterns: (1) neurologic involvement in untreated classic WD; (2) exclusive CNS relapse of previously treated classic WD [32], with microscopic lesions in the gastrointestinal tract; and (3) isolated neurologic symptoms, CNS-WD [44] without histologic evidence of intestinal involvement [4, 22, 45, 46] (Fig. 17.1). Isolated spinal involvement is rare in CNS-WD and spinal lesions with pachymeningitis have been rarely described [45, 47–52].

The classic, but not benchmark, triad of CNS-WD is progressive dementia, supranuclear gaze palsy, and myoclonus [53, 54].

Cognitive impairment is found in 71% of patients with neurologic signs. Cognitive decline can take the form of memory impairment and attention defects, apathy and personality changes, typical frontal lobe syndrome, confusion, or frank young-onset dementia [21]. Neurocognitive symptoms may pursue a

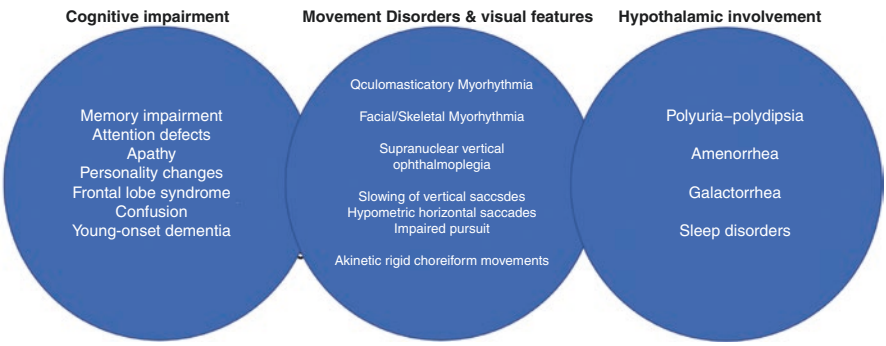


Fig. 17.1 Clinical features of CNS-WD

remitting-relapsing course. Forty-seven percent of patient with cognitive impairment due to CNS-WD also have psychiatric signs [22].

Cerebellar ataxia occurs in 20–45% of patients with neurologic signs [22, 52, 55, 56]. Progressive dementia and ataxia are more frequent in patients with isolated T. whipplei encephalitis [56]. Cerebellar involvement contributes to gaze-evoked nystagmus and esotropia [57]. Clumsy limbs are considered a manifestation of appendicular ataxia [21].

Movement disorders suggest the specific involvement of the basal ganglia. Myorhythmias are slow (1–4 Hz), rhythmic, or semirhythmic myoclonus, with repetitive, jerky movement affecting mainly cranial and limb muscles. They are produced by co-contraction of antagonist muscles when one agonist muscle contracts more intensely or for longer time than the antagonist [58]. It has an electromyographic discharge lasting 200–300 ms [59–61]. It involves either branchial (facial myorhythmia) or spinal (skeletal myorhythmia) muscles, originating from the brainstem and spinal cord [62], that disappears during sleep [58].

Oculomasticatory myorhythmias (OMM) are pendular convergent-divergent oscillations of the eyes, synchronous with involuntary rhythmic, 1 Hz contraction of the muscles of mastication, and thus jaw movements, at a rate of 1/s [63]. It constitutes complete supranuclear vertical ophthalmoplegia [64–67] with selective deficit of the vertical saccades, attributed to the involvement of the anterior-rostral [68] interstitial nucleus of the medial longitudinal fasciculus (riMLF), the anatomical substrate for vertical saccade generation [69]. CNS-WD can also present with slowing of vertical saccades, mimicking progressive supranuclear palsy [70, 71] and impaired pursuit and hypometric horizontal saccades attributed to abnormal cerebellar gaze control at the level of the paramedian pontine reticular formation [70, 71], and disinhibition of autorhythmic pacemaker nuclei [58].

Oculo-facial-skeletal myorhythmia (OFSM) constitutes pendular convergent-divergent nystagmus in association with myorhythmia that extends beyond the masticatory muscles, involving any facial, neck, or limb muscles [22]. OMM and OFSM both occur in 8–20% of CNS-WD [45, 72, 73], are considered pathognomonic for CNS-WD [67, 71, 74–76], and tend to persist during sleep [77].

Other abnormal movements include akinetic rigid forms of parkinsonism [70, 71, 78, 79] and choreiform movements [80]. Hypothalamic involvement typically presents as polyuria–polydipsia; amenorrhea and galactorrhea [43, 45] and sleep disorders, mostly hypersomnia occur in 17% of patients [56].

Differential Diagnosis

The early-onset complete supranuclear gaze palsy in CNS-WD brings progressive supranuclear palsy (PSP) in the differential picture. The age of onset is typically younger in CNS-WD [81] and has a more rapid evolution [82]. Rigidity and other

Table 17.2 Differential diagnosis for CNS-WD

Differential diagnosis	Similarities with CNS-WD	Differences from CNS-WD
Progressive supranuclear palsy (PSP)	Supranuclear gaze palsy (SGP)	Older age-onset. Insidious evolution Extrapyramidal features Vertical gaze palsy Absence of systemic features
Neurodegenerative dementias (MSA) Encephalitis	Cognitive impairment	
Cerebellar syndromes	Ataxia	Ataxia in CNS-WD occurs with other neurological and systemic signs.
Niemann-Pick C and spastic ataxia type 1	Ataxia with supranuclear gaze palsies (SGP)	
Gaucher disease	Horizontal SGP	

MSA multiple system atrophy, *SPG* supranuclear palsy

parkinsonian signs are uncommon compared with PSP. PSP symptoms rarely include early, complete horizontal gaze palsy and myoclonus [73, 83–85]. The association with systemic features in WD is also an important differentiating feature. Table 17.2 reviews the factors that should be included in a differential diagnosis.

Diagnosis

The average delay between first symptoms and diagnosis is 24–30 months for neurologic symptoms [20, 49]. Given its protean manifestations, the diagnosis of Neuro-Whipple disease should be considered in a variety of clinical situations.

As outlined in Fig. 17.2, a complete work-up requires a careful history and physical examination, a combination of DNA detection by polymerase chain reaction (PCR), Periodic-Acid-Schiff (PAS) staining, immunohistochemical staining with T whipplei antibodies, and MR imaging.

Fenollar et al. [52] proposed a diagnostic classification system for chronic Whipple's encephalitis. Patients with positive polymerase chain reaction of cerebrospinal fluid and/or brain biopsy are classified as definite isolated cerebral WD. Patients with positive staining of periodic acid–Schiff and electron microscopy of brain biopsy are regarded to have possible isolated cerebral WD.

PAS-staining and PCR are the diagnostic cornerstones [58]. T. whipplei PCR, can be performed on a variety of tissues and body fluids [5, 22, 45–48] and is the main tool for the diagnosis of localized chronic infections. It is done using broad-range primers for amplification of the 16S ribosomal ribonucleic acid (rRNA) gene or the intergenic region of the 16 s–23 s rRNA; followed by sequencing of the amplified product [12, 86–88].

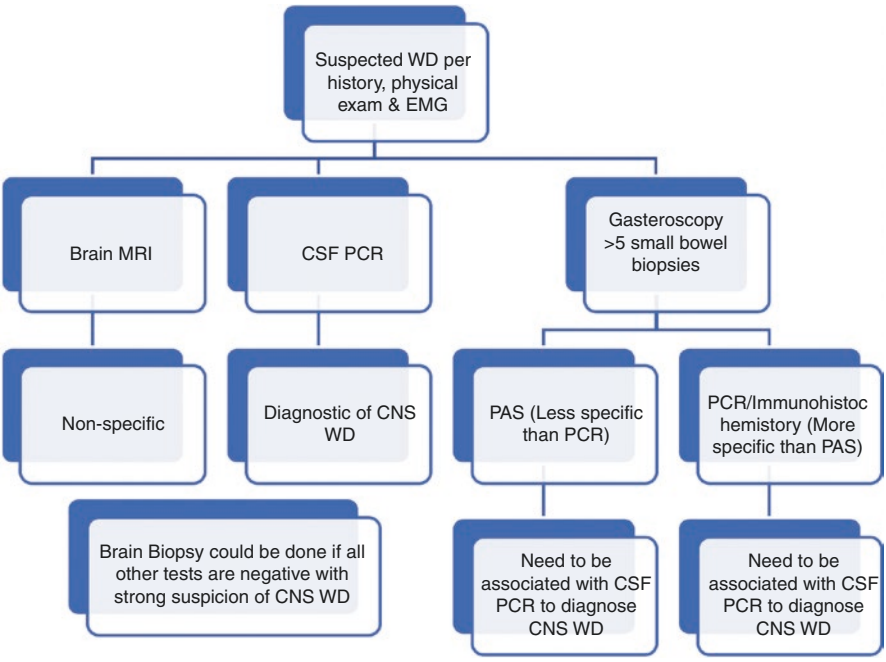


Fig. 17.2 Diagnosis of CNS-WD. CSF: Cerebrospinal fluid; PCR: Polymerase chain reaction; MRI: Magnetic resonance imaging; WD: Whipple's disease; PAS: Periodic-acid-schiff; EMG: Electromyogram

Cerebrospinal Fluid (CSF) Analysis

PCR performed on CSF confirms the diagnosis of CNS-WD [89]. CSF PCR is strongly considered during the initial diagnostic investigation in patients presenting with localized symptoms consistent with localized CNS WD [58]. CSF analysis shows elevated protein level and the presence of oligo-clonal bands. A low to moderate pleocytosis (5–100 cells/microL) is mostly made up of lymphocytes and monocytes or macrophages. Electron microscopy [90] shows a core enclosed within a plasma membrane, surrounded by a three-layered cell wall. The inner layer contains polysaccharides that stain positive with PAS [91]. PAS staining shows macrophages with rod-shaped and sickle-shaped inclusions, also called sickle particle or Sieracki cells [92–96], in about 50% of the cases [22, 45]. Normal CSF cytology does not rule out neurologic involvement in WD [22, 45].

Biopsy

Gastrointestinal tract involvement is investigated with multiple duodenal biopsies [45]. Duodenal biopsies can provide a diagnostic clue even without obvious clinical intestinal tract involvement [49]. Small bowel biopsy shows characteristic villous atrophy with distension of villi and infiltrates of foamy macrophages with PAS-positive granular cytoplasm which are filled with clumps of T whipplei, and rounded empty spaces that contain neutral fat; lipodystrophy. PCR or immunohistochemistry can identify the agent more specifically [97]. In Localized WD, duodenal PCR as an independent, specific method [5, 17, 18, 21, 32, 43, 44] showed increased sensitivity compared with PAS staining [4, 15, 49, 58, 98–100].

Searching for systemic involvement is done with lymph node biopsies, which should be analyzed with light microscopy, electron microscopy, and PCR [45].

CSF PCR is tested in CWD without clinical neurologic manifestations, to rule out central involvement [18, 52, 72].

PCR performed on urine samples is acquiring an important role of noninvasive diagnostic strategies, while T. whipplei PCR performed on saliva and stool lack specificity for determination of localized WD [13, 101, 102].

When all examinations are negative, if Whipple disease is suspected and a lesion is found on brain MRI, a stereotactic cerebral biopsy should be performed. Brain specimens demonstrate lymphocytic encephalitis with the presence of abundant perivascular foamy macrophages infiltrate with central areas of necrosis and hemorrhage.

Radiology

Radiologically, brain magnetic resonance imaging (MRI) in CNS-WD shows no pathognomonic pattern. Patients' CNS symptoms may or may not reflect the anatomic locations of the lesions, and on the other hand the anatomic abnormality may or may not correlate with the extend of neurologic clinical manifestation [103].

Panegyres et al. [43] reported that patients with primary CNS-WD can be divided into: (1) patients with focal neurological manifestations due to **solitary mass lesion;** and (2) those with multiple neurological signs and symptoms and **multiple nodular enhancing** MRI or CT lesions. Abnormal T2 signal intensity lesions are most evident on FLAIR sequences within midline structures, basilar telencephalon, thalamus, hypothalamus, quadrigeminal plate, and periaqueductal gray matter, without mass effect [93]. Less frequently, scattered lesions of high T2 signal intensity show

in a peripheral array involving the gray-white junction with or without associated vasogenic edema and mass effect [104, 105]. Nodular parenchymal lesions may show enhancement [43, 106, 107] and may have stroke-like presentations of focal tumor-like lesions [108–111]. Other radiologic findings include leptomeningeal enhancement and ring lesions [105, 112]. It was recently found that 18 FDG-PET was associated with a high diagnostic yield in case of neurological involvement, showing hypometabolism that resolves with treatment, and thus was suggested to facilitate follow-up [55, 102].

Treatment

Successful treatment with antibiotics was reported in 1952 [56] and remains the currently recommended primary treatment of CNS-WD. The two-phase treatment involves antibiotics that can infiltrate the CSF [113].

The initial phase of treatment constitutes Cephalosporins e.g. ceftriaxone, 2 g, intravenously every 12 hours for 2 weeks. The second phase of treatment consists of prophylaxis with oral trimethoprim160 mg- sulfamethoxazole 800 mg twice daily for 1–2 years [45, 56, 114] or life-long [32, 115] to decrease the risk of relapses.

Penicillin G, 2 million units every 4 hours for 2 weeks, or Meropenem can also be used for the initial phase [113]. For prophylaxis, doxycycline and hydroxychloroquine [115] or oral cefixime, 400 mg once daily [116] were also recommended for 12 months, followed by life-long doxycycline [115].

Markers of successful treatment are symptom remission. MRI focal lesions generally resolve with therapy [117]. Given the underlying genetic-based alterations of the immune system that predispose individuals to infection, a lifetime susceptibility to relapse is possible. Patients are more likely to relapse if PCR positivity persisted after clinical response [4, 113, 118].

Based on the insufficient T-cell activation and the reduced percentage of gamma interferon-positive (IFN-) CD4 T-cells [119], Human recombinant interferon gamma was tried successfully in a case of central nervous system involvement and refractory disease [2, 120].

Complications

Immune reconstitution inflammatory syndrome (IRIS) presents by recurrence of clinical symptoms [121] with no evidence of other causes (e.g., infection, manifesting tumor, allergic reaction, etc.), yet negative PCR testing [122]. It may occur in the early months of treatment [121], or years after the initial antibiotic therapy. An increased risk exists in patients with severe CNS involvement [122] and previous immunosuppressive therapy. Risk of complications may be tempered by the timely identification of high-risk patients and anticipation of recurrence of inflammatory

signs during or after antibiotic therapy. Treatment early on with glucocorticosteroids is vital and pre-existing steroid medication must not be stopped during antibiotic therapy.

Follow Up

All WD patients should be followed up clinically, as well as by means of CSF examination and T. whipple-specific PCR. The frequency of follow up should be every 12 months and should be life-long because of possible late relapse or late complications [123]. Cerebrospinal fluid should be analyzed repeatedly during follow-up, and treatment should be discontinued only when the results of PCR assay performed on cerebrospinal fluid are negative [45, 124].

Prognosis

WD is invariably fatal without treatment, but even with treatment, 2–33% of classical WD patients relapse, most often with a neurologic manifestation [125]. CNS involvement of WD carries a 25% risk of having major neurologic sequelae [54]. Severe cognitive impairment and dementia caused by T. whipplei is only rarely reversible [44]. Approximately 60% of patients do experience some improvement in their symptoms during antibiotic therapy [32].

In conclusion, Tropherema whipplei infection remains a challenging-to-diagnose infectious syndrome rarely encountered in the United States. Localized CNS-WD is prevalent and can present without any gastrointestinal signs. Latency of diagnosis and previous exposure to immunosuppressive medications are common. Diagnosis of TW infection requires a high degree of suspicion and targeted testing, utilizing both histopathology and PCR, recognizing that blood PCR is insensitive.

References

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Bull Johns Hopkins Hosp. 1907;18:382–91.
2. Schneider T, et al. Whipple's disease: new aspects of pathogenesis and treatment. Lancet Infect Dis. 2008;8(3):179–90.
3. Fenollar F, Raoult D. Whipple's disease. Curr Gastroenterol Rep. 2003;5(5):379–85.
4. Lagier JC, et al. Systemic Tropheryma whipplei: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. Medicine (Baltimore). 2010;89(5):337–45.
5. Poureisa M, et al. Magnetic resonance imaging of Whipple's disease confined to the CNS presenting with multiple intracerebral mass lesions. Acta Med Iran. 2015;53(4):250–5.

6. Black-Schaffer B. The tinctoral demonstration of a glycoprotein in Whipple's disease. Proc Soc Exp Biol Med. 1949;72(1):225–7.
7. Yardley JH, Hendrix TR. Combined electron and light microscopy in Whipple's disease. Demonstration of "bacillary bodies" in the intestine. Bull Johns Hopkins Hosp. 1961;109:80–98.
8. Chears WC Jr, Ashworth CT. Electron microscopic study of the intestinal mucosa in Whipple's disease. Demonstration of encapsulated bacilliform bodies in the lesion. Gastroenterology. 1961;41:129–38.
9. Relman DA, et al. Identification of the uncultured bacillus of Whipple's disease. N Engl J Med. 1992;327(5):293–301.
10. Raoult D, et al. Cultivation of the bacillus of Whipple's disease. N Engl J Med. 2000;342(9):620–5.
11. Baisden BL, et al. Diagnosis of Wihipple disease by immunohistochemical analysis: a sensitive and specific method for the detection of Tropheryma whipplei (the Whipple bacillus) in paraffin-embedded tissue. Am J Clin Pathol. 2002;118(5):742–8.
12. Moter A, et al. Validation of an rpoB gene PCR assay for detection of Tropheryma whipplei: 10 years' experience in a National Reference Laboratory. J Clin Microbiol. 2013;51(11):3858–61.
13. Fenollar F, et al. Value of Tropheryma whipplei quantitative polymerase chain reaction assay for the diagnosis of Whipple disease: usefulness of saliva and stool specimens for first-line screening. Clin Infect Dis. 2008;47(5):659–67.
14. Elchert JA, et al. Epidemiology of Whipple's disease in the USA between 2012 and 2017: a population-based national study. Dig Dis Sci. 2019;64(5):1305–11.
15. Raoult D, et al. Tropheryma whipplei in children with gastroenteritis. Emerg Infect Dis. 2010;16(5):776–82.
16. Keita AK, et al. Tropheryma whipplei prevalence strongly suggests human transmission in homeless shelters. Int J Infect Dis. 2013;17(1):e67–8.
17. Fenollar F, et al. Prevalence of asymptomatic Tropheryma whipplei carriage among humans and nonhuman primates. J Infect Dis. 2008;197(6):880–7.
18. Scheld WM. Whipple disease of the central nervous system. J Infect Dis. 2003;188(6): 797–800.
19. Wilson K, et al. Phylogeny of the Whipple's-disease-associated bacterium. Lancet. 1991;338(8765):474–5.
20. Durand DV, et al. Whipple disease. Clinical review of 52 cases. The SNFMI Research Group on Whipple Disease. Societe Nationale Francaise de Medecine Interne. Medicine (Baltimore). 1997;76(3):170–84.
21. Bally JF, et al. Systematic review of movement disorders and oculomotor abnormalities in Whipple's disease. Mov Disord. 2018;33(11):1700–11.
22. Louis E, et al. Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol. 1996;40(4):561–8.
23. Dobbins W. Whipple's disease. Springfield: Thomas; 1987.
24. Keita AK, et al. Looking for Tropheryma whipplei source and reservoir in rural Senegal. Am J Trop Med Hyg. 2013;88(2):339–43.
25. Keita AK, et al. High prevalence of Tropheryma whipplei in Lao kindergarten children. PLoS Negl Trop Dis. 2015;9(2):e0003538.
26. Maiwald M, et al. Environmental occurrence of the Whipple's disease bacterium (Tropheryma whippelii). Appl Environ Microbiol. 1998;64(2):760–2.
27. Ehrbar H-U, et al. PCR-positive tests for Tropheryma whippelii in patients without Whipple's disease. Lancet. 1999;353(9171):2214.
28. Street S, Donoghue HD, Neild G. Tropheryma whippelii DNA in saliva of healthy people. Lancet. 1999;354(9185):1178–9.
29. Zinkernagel A, et al. Marginal and subgingival plaque–a natural habitat of Tropheryma whipplei? Infection. 2003;31(2):86–91.

30. Maibach RC, Dutly F, Altwegg M. Detection of Tropheryma whipplei DNA in feces by PCR using a target capture method. J Clin Microbiol. 2002;40(7):2466–71.
31. Schinnerling K, et al. Regulatory T cells in patients with Whipple's disease. J Immunol. 2011;187(8):4061–7.
32. Fenollar F, Puéchal X, Raoult D. Whipple's disease. N Engl J Med. 2007;356(1):55–66.
33. Martinetti M, et al. The HLA alleles DRB1* 13 and DQB1* 06 are associated to Whipple's disease. Gastroenterology. 2009;136(7):2289–94.
34. Marth T, et al. Persistent reduction of complement receptor 3 α-chain expressing mononuclear blood cells and transient inhibitory serum factors in Whipple's disease. Clin Immunol Immunopathol. 1994;72(2):217–26.
35. Bai J, et al. Impaired monocyte function in patients successfully treated for Whipple's disease. Acta Gastroenterol Latinoam. 1996;26(2):85–9.
36. Moos V, et al. Impaired immune functions of monocytes and macrophages in Whipple's disease. Gastroenterology. 2010;138(1):210–20.
37. Desnues B, Raoult D, Mege J-L. IL-16 is critical for Tropheryma whipplei replication in Whipple's disease. J Immunol. 2005;175(7):4575–82.
38. Desnues B, et al. Whipple disease: intestinal infiltrating cells exhibit a transcriptional pattern of M2/alternatively activated macrophages. J Infect Dis. 2005;192(9):1642–6.
39. Desnues B, et al. Whipple's disease: a macrophage disease. Clin Vaccine Immunol. 2006;13(2):170–8.
40. Marth T, et al. Defects of monocyte interleukin 12 production and humoral immunity in Whipple's disease. Gastroenterology. 1997;113(2):442–8.
41. Marth T, et al. Dysregulated peripheral and mucosal Th1/Th2 response in Whipple's disease. Gastroenterology. 2002;123(5):1468–77.
42. Ectors NL, et al. Whipple's disease: a histological, immunocytochemical, and electron microscopic study of the small intestinal epithelium. J Pathol. 1994;172(1):73–9.
43. Panegyres PK, et al. Primary Whipple's disease of the brain: characterization of the clinical syndrome and molecular diagnosis. QJM. 2006;99(9):609–23.
44. Benito-León J, Sedano LF, Louis ED. Isolated central nervous system Whipple's disease causing reversible frontotemporal-like dementia. Clin Neurol Neurosurg. 2008;110(7):747–9.
45. Gerard A, et al. Neurologic presentation of Whipple disease: report of 12 cases and review of the literature. Medicine. 2002;81(6):443–57.
46. Misbah S, et al. Whipple's disease without malabsorption: new atypical features. QJM Int J Med. 1997;90(12):765–72.
47. Buckle MJ, et al. Neurologically presenting Whipple disease: case report and review of the literature. J Clin Pathol. 2008;61(10):1140–1.
48. Clarke C, et al. Cervical myelopathy caused by Whipple's disease. Neurology. 1998;50(5):1505–6.
49. Compain C, et al. Central nervous system involvement in Whipple disease: clinical study of 18 patients and long-term follow-up. Medicine. 2013;92(6):324.
50. Messori A, et al. An unusual spinal presentation of Whipple disease. Am J Neuroradiol. 2001;22(5):1004–8.
51. Schröter A, et al. Whipple's disease presenting as an isolated lesion of the cervical spinal cord. Eur J Neurol. 2005;12(4):276–9.
52. Fenollar F, et al. Progressive dementia associated with ataxia or obesity in patients with Tropheryma whipplei encephalitis. BMC Infect Dis. 2011;11(1):171.
53. Brown AP, et al. Whipple's disease presenting with isolated neurological symptoms. Case report. J Neurosurg. 1990;73(4):623–7.
54. Schnider PJ, et al. Long-term follow-up in cerebral Whipple's disease. Eur J Gastroenterol Hepatol. 1996;8(9):899–903.
55. Lagier J, et al. Weight loss, dementia and ataxia susceptible to doxycycline: a likely new case report caused by T. whipplei. Rev Med Interne. 2013;34(10):641–4.

56. Matthews BR, et al. Cerebellar ataxia and central nervous system Whipple disease. Arch Neurol. 2005;62(4):618–20.
57. Shaikh AG, Ghasia FF. Novel eye movement disorders in Whipple's disease—staircase horizontal saccades, Gaze-evoked Nystagmus, and esotropia. Front Neurol. 2017;8:321.
58. Crews NR, et al. Diagnostic approach for classic compared with localized whipple disease. In: Open forum infectious diseases. US: Oxford University Press; 2018.
59. Fénelon G, Ahdab R, Lefaucheur J. Electrophysiological assessment of a case of limb myorhythmia. Clin Neurophysiol. 2010;121(12):2180–3.
60. Jankovic J. Whipple's disease of the central nervous system in AIDS. N Engl J Med. 1986;315(16):1029–30.
61. Weeks RA, BD, Hodgson H, Cohen J. Cerebral Whipple's disease. Br Med J. 1996;312(7027):371–3.
62. Jankovic J, Pardo R. Segmental myoclonus: clinical and pharmacologic study. Arch Neurol. 1986;43(10):1025–31.
63. Selhorst JB, Schwartz MA. Cerebral manifestations of Whipple's disease. In: Mayo Clinic Proceedings. Philadelphia, PA: Elsevier; 1988.
64. Knox DL, Bayless TM, Pittman FE. Neurologic disease in patients with treated Whipple's disease. Medicine. 1976;55(6):467–76.
65. Silbert SW, Parker E, Horenstein S. Whipple's disease of the central nervous system. Acta Neuropathol. 1976;36(1):31–8.
66. Pallis CA, Lewis PD. The neurology of gastrointestinal disease. Vol. 3. Saunders Limited; London, UK; 1974.
67. Schwartz MA, et al. Oculomasticatory myorhythrma: a unique movement disorder occurring in Whipple's disease. Ann Neurol. 1986;20(6):677–83.
68. Stamboulis E, et al. Segmental myoclonus in Whipple's disease. Electromyogr Clin Neurophysiol. 1995;35(2):113–6.
69. Büttner-Ennever J, Büttner U. A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. Brain Res. 1978;151(1):31–47.
70. Knox D, et al. Cerebral ocular Whipple's disease: a 62-year odyssey from death to diagnosis. Neurology. 1995;45(4):617–25.
71. Averbuch-Heller L, et al. Whipple's disease mimicking progressive supranuclear palsy: the diagnostic value of eye movement recording. J Neurol Neurosurg Psychiatry. 1999;66(4):532–5.
72. França MC Jr, et al. Whipple's disease with neurological manifestions: case report. Arq Neuropsiquiatr. 2004;62(2A):342–6.
73. Magherini A, et al. Progressive supranuclear gaze palsy without parkinsonism: a case of neuro-Whipple. Parkinsonism Relat Disord. 2007;13(7):449–52.
74. Amarenco P, et al. Progressive supranuclear palsy as the sole manifestation of systemic Whipple's disease treated with pefloxacine. J Neurol Neurosurg Psychiatry. 1991;54(12):1121.
75. Lynch T, et al. Oculofacial-skeletal myorhythmia in Whipple's disease. Mov Disord. 1997;12(4):625–6.
76. Revilla FJ, et al. Teaching NeuroImage: oculomasticatory myorhythmia: pathognomonic phenomenology of Whipple disease. Neurology. 2008;70(6):e25.
77. Calandra-Buonaura G, et al. Oculomasticatory myorhythmia and agrypnia excitata guide the diagnosis of Whipple disease. Sleep Med. 2013;14(12):1428–30.
78. Uldry P-A, Bogousslavsky J. Partially reversible parkinsonism in Whipple's disease with antibiotherapy. Eur Neurol. 1992;32(3):151–3.
79. Clark D, Eggenberger E. Neuro-ophthalmology of movement disorders. Curr Opin Ophthalmol. 2012;23(6):491–6.
80. Süzer T, et al. Whipple's disease confined to the central nervous system: case report and review of the literature. Scand J Infect Dis. 1999;31(4):411–4.
81. Cosseddu M, et al. Natural history and predictors of survival in progressive supranuclear palsy. J Neurol Sci. 2017;382:105–7.

82. Benito-León J, et al. Isolated CNS Whipple disease: acute onset and relapsing-remitting course. Scand J Infect Dis. 2007;39(6–7):623–5.
83. Strupp M, et al. Central ocular motor disorders, including gaze palsy and nystagmus. J Neurol. 2014;261(2):542–58.
84. Defebvre L. Myoclonus and extrapyramidal diseases. Neurophysiol Clin. 2006;36(5–6):319–25.
85. Caviness JN. Myoclonus and neurodegenerative disease—what's in a name? Parkinsonism Relat Disord. 2003;9(4):185–92.
86. Edouard S, Fenollar F, Raoult D. The rise of Tropheryma whipplei: a 12-year retrospective study of PCR diagnoses in our reference center. J Clin Microbiol. 2012;50(12): 3917–20.
87. Fenollar F, et al. Use of genome selected repeated sequences increases the sensitivity of PCR detection of Tropheryma whipplei. J Clin Microbiol. 2004;42(1):401–3.
88. Fenollar F, Raoult D. Molecular techniques in Whipple's disease. Expert Rev Mol Diagn. 2001;1(3):299–309.
89. Pessa ME, et al. A case of rapidly progressive dementia: Whipple disease of CNS. Neurol Sci. 2018;39(3):591–2.
90. Saito H, et al. Whipple's disease with long-term endoscopic follow-up. Intern Med. 2018;57(12):1707–13.
91. Tábuas-Pereira M, et al. Prosopagnosia as the presenting symptom of Whipple disease. Cogn Behav Neurol. 2016;29(2):100–6.
92. De PJ, et al. Cerebral manifestations of Whipple's disease. Acta Neurol Belg. 1979;79(4):305–13.
93. Romanul F, Radvany J, Rosales R. Whipple's disease confined to the brain: a case studied clinically and pathologically. J Neurol Neurosurg Psychiatry. 1977;40(9):901–9.
94. Sieracki JC, et al. Central nervous system involvement in Whipple's disease. J Neuropathol Exp Neurol. 1960;19(1):70–5.
95. Sieracki J. Whipple's disease-observation on systemic involvement. I. Cytologic observations. AMA Arch Pathol. 1958;66(4):464–7.
96. Brown E, GF, Greenfield's neuropathology. 8th ed. London: U.H.A.; 2008. p. 1426–7.
97. Schneider T, Moos V. Tropheryma whipplei: pathogen of Whipple's disease and more. Dtsch Med Wochenschr. 2015;140(6):428–32.
98. Günther U, et al. Gastrointestinal diagnosis of classical Whipple disease: clinical, endoscopic, and histopathologic features in 191 patients. Medicine. 2015;94(15):e714.
99. Lehmann P, et al. PCR analysis is superior to histology for diagnosis of Whipple's disease mimicking seronegative rheumatic diseases. Scand J Rheumatol. 2017;46(2):138–42.
100. Flemmer MC, Flenner RW. Toward a new understanding of Whipple's disease. Curr Gastroenterol Rep. 2000;2(4):299–304.
101. Moter A, et al. Potential role for urine polymerase chain reaction in the diagnosis of Whipple's disease. Clin Infect Dis. 2019;68(7):1089–97.
102. Lagier JC, Raoult D. Whipple's disease and Tropheryma whipplei infections: when to suspect them and how to diagnose and treat them. Curr Opin Infect Dis. 2018;31(6):463–70.
103. Pauletti C, et al. An atypical case of neuro-Whipple: clinical presentation, magnetic resonance spectroscopy and follow-up. J Neurol Sci. 2010;297(1–2):97–100.
104. Niekrash R, et al. Rapidly progressive Whipple's disease of the central nervous system. J Clin Neurosci. 1995;2(2):171–6.
105. De Coene B, et al. Whipple's disease confined to the central nervous system. Neuroradiology. 1996;38(4):325–7.
106. Scholz KB, et al. MRI findings in isolated cerebral manifestation of Whipple's disease—Case report and review of the literature. Eur J Radiol Extra. 2006;59(1):1–5.
107. Schnider P, et al. MR of cerebral Whipple disease. Am J Neuroradiol. 1995;16(6):1328–9.
108. Peters G, Du Plessis D, Humphrey P. Cerebral Whipple's disease with a stroke-like presentation and cerebrovascular pathology. J Neurol Neurosurg Psychiatry. 2002;73(3):336–9.

109. Famularo G, Minisola G, De Simone C. A patient with cerebral Whipple's disease and a stroke-like syndrome. Scand J Gastroenterol. 2005;40(5):607–9.
110. Frazier JL, Quinones-Hinojosa A. Isolated Whipple disease of the brain resembling a tumour. Acta Neurochir. 2009;151(2):173.
111. Leesch W, et al. Primary cerebral Whipple disease presenting as Klüver-Bucy syndrome. Arch Neurol. 2009;66(1):130–1.
112. Wroe S, et al. Whipple's disease confined to the CNS presenting with multiple intracerebral mass lesions. J Neurol Neurosurg Psychiatry. 1991;54(11):989–92.
113. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology. 2010;138(2):478–86.
114. De Francesco V, et al. Whipple's disease: case report and review of the literature. J Gastrointestin Liver Dis. 2018;27(3):331–6.
115. Fenollar F, Lagier J-C, Raoult D. Tropheryma whipplei and Whipple's disease. J Infect. 2014;69(2):103–12.
116. Schnider P, et al. Treatment guidelines in central nervous system Whipple's disease. Ann Neurol. 1997;41(4):561–2.
117. Gaudé M, Tébib J, Puéchal X. Atypical focal forms of Whipple's disease seen by rheumatologists. Joint Bone Spine. 2015;82(1):56–9.
118. Ramzan NN, et al. Diagnosis and monitoring of Whipple disease by polymerase chain reaction. Ann Intern Med. 1997;126(7):520–7.
119. Trotta L, et al. Peripheral T-cell reactivity to heat shock protein 70 and its cofactor GrpE from Tropheryma whipplei is reduced in patients with classical Whipple's disease. Infect Immun. 2017;85(8):e00363–17.
120. Schneider T, et al. Treatment of refractory Whipple disease with interferon-γ. Ann Intern Med. 1998;129(11_Part_1):875–7.
121. Lagier JC, et al. Successful treatment of immune reconstitution inflammatory syndrome in Whipple's disease using thalidomide. J Infect. 2010;60(1):79–82.
122. Feurle GE, et al. The immune reconstitution inflammatory syndrome in Whipple disease: a cohort study. Ann Intern Med. 2010;153(11):710–7.
123. Lagier J-C, et al. Evidence of lifetime susceptibility to Tropheryma whipplei in patients with Whipple's disease. J Antimicrob Chemother. 2011;66(5):1188–9.
124. von Herbay A, et al. Whipple's disease: staging and monitoring by cytology and polymerase chain reaction analysis of cerebrospinal fluid. Gastroenterology. 1997;113(2):434–41.
125. Keinath R, et al. Antibiotic treatment and relapse in Whipple's disease: long-term follow-up of 88 patients. Gastroenterology. 1985;88(6):1867–73.

Chapter 18
Prion Diseases

Salam Nasralla, Daniel D. Rhoads, and Brian S. Appleby

The prion protein is a normal cellular protein (PrP^c) that is most abundant in the nervous system, and its function is not well understood. An abnormal conformation of this protein is the essential common pathological process of the invariably fatal group of diseases named prion diseases (a.k.a. transmissible spongiform encephalopathies, TSE) [1]. Scrapie was the first recognized prion disease, and it occurs in sheep and goats. This disease was first recognized in the eighteenth century, and only in 1936 was formally demonstrated to be transmissible [2]. Other prion diseases affect non-human mammals, including bovine spongiform encephalopathy (BSE) in cattle, camel prion disease in camel, and the current public health concern in North American cervids (e.g., deer, elk); chronic wasting disease (CWD).

S. Nasralla
Department of Neurology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

D. D. Rhoads
Department of Laboratory Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA

B. S. Appleby (✉)
Department of Neurology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, OH, USA

Department of Pathology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Department of Psychiatry, University Hospitals Cleveland Medical Center, Cleveland, OH, USA
e-mail: bsa35@case.edu

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3_18

The discovery of prion disease in humans, including the discovery of its potential transmissibility and the entity responsible for its transmissibility, was aided by prior knowledge of animal prion diseases. Human prion disease was first described as Creutzfeldt-Jakob disease (CJD). Hans Creutzfeldt first published a case of atypical dementia in 1920 that was later included in a case series published by Alfons Jakob in 1921, which proposed these cases to be a new clinical entity based upon clinical symptoms and neuropathological features of spongiform degeneration [3, 4]. However, the transmissible nature of human prion disease was not noted until the discovery of kuru, a rapidly progressive cerebellar disorder that occurred in the Fore-speaking people of Papua New Guinea [5]. Neuropathological similarities between scrapie and kuru were noted by William Hadlow in 1959 and led to the discovery of kuru's transmissibility through ritualistic endocannibalism. Kuru was successfully transmitted to chimpanzees by intracerebral inoculation in 1966 [6, 7]. Neuropathological similarities between kuru and CJD were also noted, and CJD was subsequently successfully transmitted to chimpanzees, bringing it into the category of transmissible spongiform encephalopathies [8, 9].

Although the aforementioned clinical entities could be collectively categorized based upon transmissibility and spongiform degeneration, the etiologic agent of disease remained elusive. Initially thought to be due to a "slow virus" given the extended incubation periods observed in transmission studies, accumulating evidence rejected the notion that the etiologic agent contained nucleic acid common to bacteria and viruses [10, 11]. The hypothesis that the putative agent could be a protein was first postulated by a mathematician named John Griffith in 1967 [12]. As increasing evidence towards a protein-only mechanism mounted, Stanley Prusiner coined the term "prion" in 1982 [13]. The prion paradigm describes the ability of a host encoded protein to assume a pathologic isoform that can undergo self-propagation of the pathogenic conformation without nucleic acid. Pathological prion proteins (termed prions for the rest of this chapter) were then isolated from TSEs, which were subsequently referred to as prion diseases. Many studies support the prion hypothesis in these diseases, and it is nearly universally accepted within the field [14].

Human prion diseases are categorized according to etiology; sporadic, genetic, or acquired. Sporadic prion disease is thought to be due to a spontaneous post-translational change of PrP^{c} to PrP^{Sc} and includes sporadic Creutzfeldt-Jakob disease (sCJD), sporadic fatal insomnia (sFI), and variably protease sensitive prionopathy (VPSPr). Genetic prion diseases are due to a mutation of the prion protein gene (*PRNP*) and include genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstman-Sträussler-Scheinker syndrome (GSS). Acquired prion diseases occur when prion disease is transmitted to an individual such as in kuru, iatrogenic Creutzfeldt-Jakob disease (iCJD), and variant Creutzfeldt-Jakob disease (vCJD), which is a zoonotic prion disease acquired from eating meat contaminated with BSE.

Although neuropathological examination via immunohistochemistry and Western blot are the only ways to definitively diagnosis prion disease, a confident antemortem diagnosis can often be achieved. Diagnosing prion disease can be

difficult due to the rarity of the disease and its ability to mimic many other neuropsychiatric conditions. The diagnosis is obtained by recognizing the clinical syndrome, ruling out other possible diagnoses, and employing diagnostic testing that can support the diagnosis. Electroencephalogram (EEG), brain magnetic resonance (MRI), and markers of neurodegeneration found in cerebrospinal fluid (CSF) (e.g., 14-3-3 and tau proteins) can be useful in ascertaining cases of prion disease. Additionally, a recently developed diagnostic test called real time quaking induced conversion (RT-QuIC) can detect small amounts of abnormal prion protein via misfolding amplification *in vitro*, and RT-QuIC is usually performed on CSF.

The purpose of this article is to provide an overview of human prion diseases including its epidemiology, subtypes, clinical presentation, diagnostic work-up, and infection control practices.

Epidemiology

Human prion diseases are relatively rare, but neurologists and infectious disease experts will certainly encounter cases during their career. The most common prion disease in humans is sCJD, which accounts for 85% of all prion diseases, followed by genetic prion diseases (10–15%), and acquired prion diseases (<1%). Prion disease affects an equal number of men and women. sCJD typically occurs in individuals 65 years-of-age or older and its mean duration is 4–6 months, though there is significant variability in both. Genetic prion diseases tend to have an earlier age at onset and can have longer disease durations. Acquired prion diseases, especially vCJD, typically occur in young to middle aged individuals. vCJD almost exclusively occurs in people less than 55 years of age after long incubation periods that can last 17 years or more. The incidence of sCJD is 1–2 new cases per one million individuals per year in the United States, which is similar to the worldwide incidence [15, 16]. Two hundred and thirty two cases of vCJD have been documented worldwide. Four cases of vCJD have occurred in the U.S., all of which are thought to have been acquired in other countries [17].

Types of Prion Disease

Sporadic Prion Disease

Sporadic Creutzfeldt-Jakob Disease (sCJD)

sCJD is the most common prion disease and accounts for approximately 85% of all cases. Epidemiologic studies have not consistently demonstrated any common risk factors among sCJD cases and it is believed to be due to a spontaneous post-translational modification of PrP^c. Most cases of of sCJD are characterized by rapid

neurocognitive decline with a mean illness duration of 4–6 months. Typical symptoms observed during the disease course include dementia, cerebellar dysfunction (e.g., ataxia, incoordination), myoclonus, visual changes, parkinsonism, and pyramidal symptoms (e.g., weakness, increased tone). Patients reach a stage of akinetic mutism towards the end of the illness. Most cases of sCJD will have findings suggestive of prion disease on EEG, CSF tests, and/or brain MRI.

Although typically thought of as having a relatively classic presentation and phenotype, there is a fair amount of heterogeneity in sCJD. The U.S. has documented cases of sCJD from the teenage years to as old as 104, though the mean age at onset is in the early 60's. Illness duration is typically 4–6 months, but can be as quick as a few weeks or as long as a few years. Although most cases will demonstrate the classic CJD phenotype consisting of dementia, myoclonus, and ataxia; some may present with an isolated atypical dementia or other neurologic symptom before developing other classic symptoms [18]. Much of this heterogeneity has been attributed to the codon 129 polymorphism of *PRNP* (i.e., MM, VV, or MV) and the prion protein type as determined by molecular weight on Western blot (i.e., type 1 or 2). The combination of these two variables creates six possible molecular subtypes (e.g., MM1, VV2, MV2, etc.) that differ in clinical phenotype, neuropathologic phenotype, and diagnostic tests results [19].

Sporadic Fatal Insomnia (sFI)

sFI is similar to FFI (described later in this article) clinically and neuropathologically but lacks the characteristic *PRNP* mutation observed in the latter. sFI cases are homozygous for methionine at codon 129 of *PRNP,* are associated with the type 2 prion protein, and are distinguishable from sCJD MM2 in that the thalamus undergoes severe neuronal loss [20]. sFI is rare, with only 34 cases documented in the U.S. sFI cases are characterized by a younger age at onset, longer disease duration, and the diagnostic tests typically used to diagnose prion disease are usually negative.

Variably Protease Sensitive Prionopathy (VPSPr)

VPSPr is named for its unique electrophoretic prion protein properties [21]. The distribution of the three codon 129 genotypes in VPSPr (MM-11%, MV-24%, VV-65%) contrasts with sCJD (MM-68%, MV-16%, VV-16%) [21]. Also, presence of valine at codon 129 is associated with shorter disease duration compared to sCJD in which valine is associated with a longer disease duration. As of 2018, the number of total known cases worldwide is 77 [21]. The mean age of onset is 70 years and median duration is 2 years. Patients with VPSPr usually present with nonspecific psychiatric abnormalities, cognitive decline, and speech and language deficits. Interestingly, 42% of cases have a family history of dementia, raising the possibility that genes outside of *PRNP* may be involved. It is not uncommon for diagnostic tests that are typically suggestive of prion disease to be noncontributory to the

diagnosis of VPSPr. For example, EEG demonstrated 9% diagnostic sensitivity and CSF 14-3-3 protein and total tau protein had a combined sensitivity of 21%. Diagnostic sensitivity of brain MRI is approximately 3% and preliminary data suggest that CSF RT-QuIC sensitivity is lower in VPSPr compared to sCJD. The combination of long disease duration, atypical clinical phenotype, and the low sensitivity of prion disease diagnostic tests raises the suspicion that undiagnosed cases may be misdiagnosed with other forms of dementia and the true prevalence of this disease may be unrealized.

Genetic Prion Disease (gPD)

Genetic prion disease accounts for 10–15% of human prion disease and is due to over 40 recognized mutations of *PRNP*. The majority of mutations are point mutations, but insertions and deletions of an octapeptide repeat region of the gene are also recognized. The manifestation of disease in mutation carriers (i.e., penetrance) varies by mutation and can vary between <1% and nearly 100% [22]. Genetic prion diseases are named primarily based on their neuropathologic phenotype, which closely correlates to clinical phenotype, and includes gCJD, FFI, and GSS.

Genetic Creutzfeldt-Jakob Disease (gCJD)

As suggested by its name, gCJD closely resembles sCJD. The E200K mutation is by far the most common mutation observed worldwide and within the U.S. Although the majority of gCJD cases will have a family history of prion disease, variable penetrance can account for the absence of family history in some cases. Interestingly, individuals who carry the same mutation, even within the same family, may have different ages at onset, clinical symptoms, and illness durations and some of them may not develop prion disease [23]. Consequently, genetic testing (usually performed postmortem) is encouraged to definitely determine the genetic status of prion disease cases. The majority of gCJD cases are detected by EEG, CSF analyses, and/or brain MRI. CSF RT-QuIC analyses have not been tested on all gCJD mutations, but it ranges from 0% (only one patient of V180I-129V that was tested and resulted negative) to 100% sensitive in some types (i.e, E200K). Preliminary analyses of gCJD suggests that RT-QuIC demonstrates diagnostic sensitivity close to what is observed in sCJD.

Fatal Familial Insomnia (FFI)

FFI is linked to the D178N mutation coupled with methionine at codon 129 on the mutated allele (D178N-129M) and is associated with severe neuronal loss within the thalami [20]. Clinical onset is typically between the ages of 40 to 60 and illness

duration varies from a few months to a few years. FFI is clinically characterized by sleep disturbance either symptomatically or demonstrated by subclinical sleep disturbances on polysomnography (PSG). Other typical symptoms include autonomic dysfunction (e.g., tachycardia, hypertension, hyperpyrexia, hyperhidrosis, impotence, lacrimation, and salivation). Patients typically manifest cognitive and motor symptoms later in the disease course. EEG, CSF 14-3-3 protein, CSF total tau levels, and brain MRI findings are usually not suggestive of prion disease. The diagnostic sensitivity of CSF RT-QuIC is uncertain as one study demonstrated diagnostic sensitivity of 83% and other studies have demonstrated low diagnostic sensitivity. PSG can be useful, especially since patients and families do not always report subjective sleep symptoms, and typically shows reduction of sleep spindles, loss of K complexes, loss of slow wave sleep, reduction of REM sleep, and reduction of total sleep time. Brain fluorodeoxyglucose-PET and single photon emission tomography (SPECT) typically shows early and prominent thalamic hypometabolism which can spread to other brain areas later in the disease course.

Gerstman-Sträussler-Scheinker Syndrome (GSS)

GSS is characterized neuropathologically by amyloid deposits comprised of prion proteins [24]. Several different mutations are associated with the GSS phenotype including several point mutations (e.g., P102L, A117V) and higher number octapeptide repeat insertions (OPRI). GSS typically affects young to middle aged individuals and illness durations can be quite long, spanning several years. Initial symptoms may be confined to cerebellar dysfunction (e.g., P102L) to atypical parkinsonism (e.g., A117V) that may last a few years before other symptoms develop. The sensitivity of diagnostic tests typically used to diagnose prion disease vary by mutation but are generally lower than what is observed in sCJD. The few cases that have reported CSF RT-QuIC results demonstrate that this test captures some cases, but lacks the sensitivity seen in sCJD.

Acquired Prion Disease

Kuru

Kuru, as described above, was the first human prion disease to be transmitted to non-human primates. The clinical phenotype of kuru is characterized by fatal cerebellar ataxia accompanied by tremor, choreiform, and athetoid movements. Progressive dementia is not the striking feature of kuru. Patients manifest emotional changes, inappropriate euphoria and compulsive laughter, hence its original name: “laughing death.” The extensive investigation of kuru helped elucidate the

neuropathologic characteristics and transmissible nature of prion diseases. In addition to these lessons, the anthropological study of this culture allowed researchers to estimate exposure periods with reasonable accuracy by recording time periods in which the patients partook in endocannabalistic mortuary feasts. This knowledge was then used to calculate incubation periods, which have been over 50 years in some cases. Knowledge of such prolonged incubation periods can then be translated to other acquired prion diseases such as vCJD and iCJD.

Variant Creutzfeldt-Jakob Disease (vCJD)

vCJD is prion disease in humans that is acquired through the ingestion of food contaminated with bovine spongiform encephalopathy (BSE). vCJD was first described in 1996 after detecting an unusual increase of prion disease in teenagers who did not have iCJD risk factors nor mutated genes in the setting of the BSE epidemic in the UK [25]. To date, 232 cases of vCJD have been documented worldwide, with the UK representing the majority of reported cases (http://www.eurocjd.ed.ac.uk/surveillance%20data%201.html). Because of the recognized transmission of BSE to humans, public health and agricultural measures were put into place to prevent further exposure. The mean incubation period is approximately 10–15 years; however, variability in incubation periods as seen in kuru will translate to continued cases stemming from the same initial exposure period [26]. All but one case have been homozygous for methionine at codon 129 and a heterozygous case was reported in 2018 [27]. Because vCJD can be detected in lymphoreticular tissue, several surveys of appendices and tonsils was conducted in the UK, estimating an asymptomatic carrier rate of approximately 1 in every 2000 UK citizens [28–30]. All codon 129 polymorphisms were represented in the surveyed samples that demonstrated positivity for vCJD.

Perhaps because of its zoonotic transmission, vCJD has rather unique neuropathologic and clinical phenotypes. Neuropathologic characteristics include astrogliosis, neuronal loss, and spongiform changes as well as the telltale presence of florid plaques. vCJD has primarily affected young individuals, but occasional middle age and elderly cases have been documented. Illness duration is longer than sCJD, with a median of 14 months. Initial symptoms include neuropsychiatric symptoms (depression, apathy, psychosis) and sensory symptoms that evolve to include more characteristic symptoms of prion disease like cerebellar ataxia, movement disorders, and cognitive impairment. EEG is usually not suggestive of prion disease and CSF 14-3-3 protein is typically present in 50% of vCJD cases. Brain MRI findings differ from sCJD, with vCJD cases typically demonstrating the pulvinar sign (a.k.a. hockey stick sign), which is defined as greater signal in the thalamus compared to the basal ganglia on fluid attenuated inversion recovery (FLAIR) sequences [31]. Unique to vCJD, a tonsil biopsy can be diagnostic. CSF RT-QuIC is reported to be negative in vCJD [32].

Iatrogenic Creutzfeldt-Jakob Disease (iCJD)

iCJD is human prion disease that is acquired via medical means. Recognized iCJD transmissions have occurred through cadaver derived human growth hormone (c-hGH) and gonadotropins, corneal transplants, cadaveric dura mater grafts, and neurosurgical instrumentation [33]. vCJD is unique in that secondary transmission has been demonstrated via blood transfusion. There is no epidemiological evidence suggesting that blood transfusions from sCJD or gPD patients has resulted in prion disease transmission [34]. The majority of iCJD cases in the US are due to c-hGH, with incubation periods extending up to 42 years. No cases of iCJD have been documented in cases that received c-hGH through the National Human Pituitary Program (NHPP) after 1977 due to changes in purification techniques. Corneal donors are screened for neurologic illness prior to donation, most dura mater is synthetically made, and precautions are taken when conducting neurosurgery on patients with suspected prion disease to help mitigate further cases of iCJD. The prevention of secondary transmission of vCJD is performed through blood donor screening and exclusion for those who spent time in Europe during the BSE epidemic. Because of the theoretical risk of blood transfusion transmission from gPD mutation carriers, the American Red Cross also excludes individuals with a family history of prion disease from donating blood. These precautions help limit new exposures to prion disease; however, we will likely continue to see cases of iCJD from prior exposures due to prolonged incubation periods.

Diagnosing Prion Disease

Like most medical conditions, the clinical diagnosis of prion disease entails the identification of the clinical syndrome, the use of diagnostic tests that may suggest the condition, and the appropriate exclusion of clinical mimickers [35]. The only way to definitely diagnose prion disease and to determine the type, is via neuropathologic examination. Autopsy is encouraged over biopsy in the majority of cases due to improved diagnostic tests, the potential exposure to other patients and medical staff, and the non-trivial risk of an inconclusive or false negative result.

Diagnostic criteria for probable sCJD entails combining clinical symptoms, with suggestive diagnostic tests, in the absence of alternative diagnoses (Table 18.1). Criteria for the clinical symptoms necessitate the presence of dementia plus two of the following categories: myoclonus, visual and/or cerebellar symptoms, extrapyramidal and/or pyramidal symptoms, and akinetic mutism. A clinical picture matching the above description typically requires the disease to have progressed over a certain period of time, oftentimes delaying the clinical suspicion of prion disease and subsequently its diagnosis. Most cases of sCJD do not present with the above symptoms, but may present with isolated syndromes of dementia, ataxia, or visual symptoms for weeks or months before developing other symptoms that could suggest the illness [18]. Only a non-specific neuropsychiatric syndrome is required for symptom criteria if RT-QuIC is positive.

Table 18.1 Diagnostic criteria for sporadic Creutzfeldt-Jakob disease[a]

Definite
Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils.
Probable
Neuropsychiatric disorder plus positive RT-QuIC in CSF or other tissues **OR** Rapidly progressive dementia; **and** at least two out of the following four clinical features: 1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism **AND** a positive result on at least one of the following diagnostic tests A typical EEG (periodic sharp wave complexes) during an illness of any duration A positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) **AND** without routine investigations indicating an alternative diagnosis.
Possible
Progressive dementia; **and** at least two out of the following four clinical features: 1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism **AND** the absence of a positive result for any of the four tests above that would classify a case as "probable" **AND** duration of illness less than 2 years **AND** without routine investigations indicating an alternative diagnosis

PrP prion protein, *RT-QuIC* real time quaking induced conversion, *CSF* cerebrospinal fluid, *EEG* electroencephalogram

[a]Sporadic Creutzfeldt Jakob Disease diagnostic criteria per Center for Disease Control and Prevention (https://www.cdc.gov/prions/cjd/diagnostic-criteria.html)

Electroencephalogram (EEG)

In current practice, EEG is most helpful in ruling out mimickers of sCJD such as seizure disorders, but it can also help support a diagnosis of prion disease. Although periodic sharp wave complexes (PSWC) are suggestive of prion disease (Fig. 18.1), not all cases will demonstrate them [36] and some molecular subtypes of sCJD do not demonstrate PSCW [37]. When PSWC do manifest on EEG, they are usually time-limited and typically occur about 2/3 of the way through the illness. It is also important to remember that other conditions can occasionally demonstrate PSWC, including other neurodegenerative disorders. In summary, EEG is helpful in ruling out seizure disorders and may be supportive of prion disease if PSWC are seen in the proper clinical context.

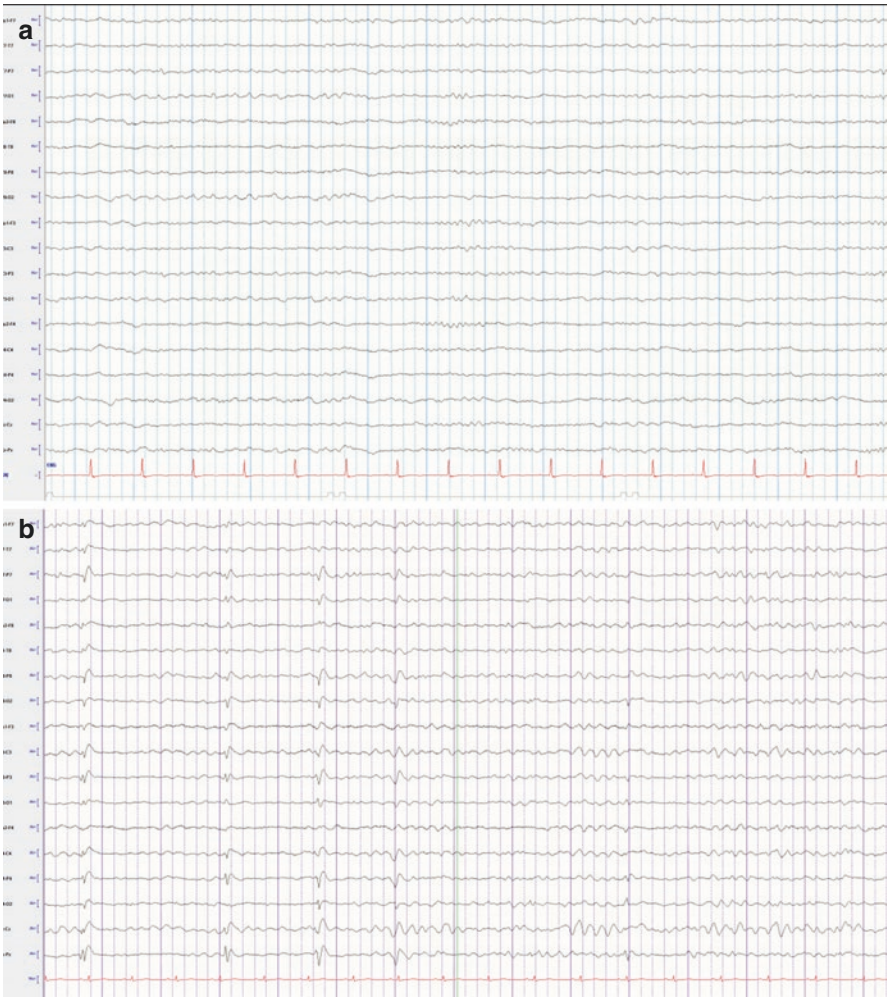


Fig. 18.1 (**a**) Bipolar electroencephalogram montage of a healthy patient in non-REM sleep. (**b**) Bipolar electroencephalogram montage of a patient who had autopsy confirmed sCJD MM1 depicting Periodic Sharp Wave Complex (PSWC); in this example they appear 4 times in the first half of the page across all electroencephalogram leads

Cerebrospinal (CSF) Protein Tests

Although the presence of several proteins can be elevated in prion disease, 14-3-3 and total tau proteins are the ones most often used to support a diagnosis of prion disease. Both proteins are markers of neuronal injury and are thus non-specific. Tau

is more specific than 14-3-3 and achieves greater specificity with higher levels [38]. Although uncommon, prion disease can be present even when 14-3-3 and total tau are found in concentrations in the normal reference range; this abnormal finding is more frequently observed in atypical subtypes of prion disease (e.g., sFI and VPSPr) and longer duration illnesses.

Brain Magnetic Resonance Imaging (MRI)

Brain MRI is important for ruling out other etiologies, but also provides high sensitivity and specificity for sCJD. Typical features are hyperintensity in the caudate/putamen and/or two or more cortical regions (excluding the frontal cortex) on diffusion weighted imaging (DWI) or FLAIR, with DWI being more sensitive to these changes (Fig. 18.2) [39]. Typically, there will also be attenuation of the signal on ADC sequences [40]. These changes appear to occur early in the disease course and sometimes are the first suggestion that a patient may have prion disease. It is unclear how imaging changes over the course of the disease. Some types of prion disease will often have normal brain MRIs (e.g., sFI and VPSPr) and there are some important brain MRI mimickers that should be appropriately considered (e.g., autoimmune encephalopathies).

Real Time Quaking Induced Conversion (RT-QuIC)

Within the last several years, RT-QuIC has proved to be an important disease-specific antemortem diagnostic test. Taking advantage of the prion paradigm and its template directed protein misfolding, RT-QuIC is an amplification assay of prions that can detect minute amounts of prions in CSF as well as other tissue [41]. Across worldwide laboratories, the specificity of CSF RT-QuIC is reported to be 99–100% and sensitivity is often reported to be between 80–95% [42]. Like the aforementioned tests, some atypical prion diseases do not demonstrate positive CSF RT-QuIC (e.g., sFI). However, its high specificity has led to a change in the diagnostic criteria for sCJD to include any individual with a neuropsychiatric disorder and a positive RT-QuIC result [43].This will undoubtedly help with earlier and more confident diagnosis as the clinician does not have to wait for the full clinical syndrome to evolve in order to make the diagnosis. Unfortunately, enough of the clinical syndrome must be present for the clinician to suspect the disease and order the test. RT-QuIC has detected prions in other tissues such as olfactory mucosa and skin, but CSF is the most widely validated and used specimen type used for clinical testing [44, 45].

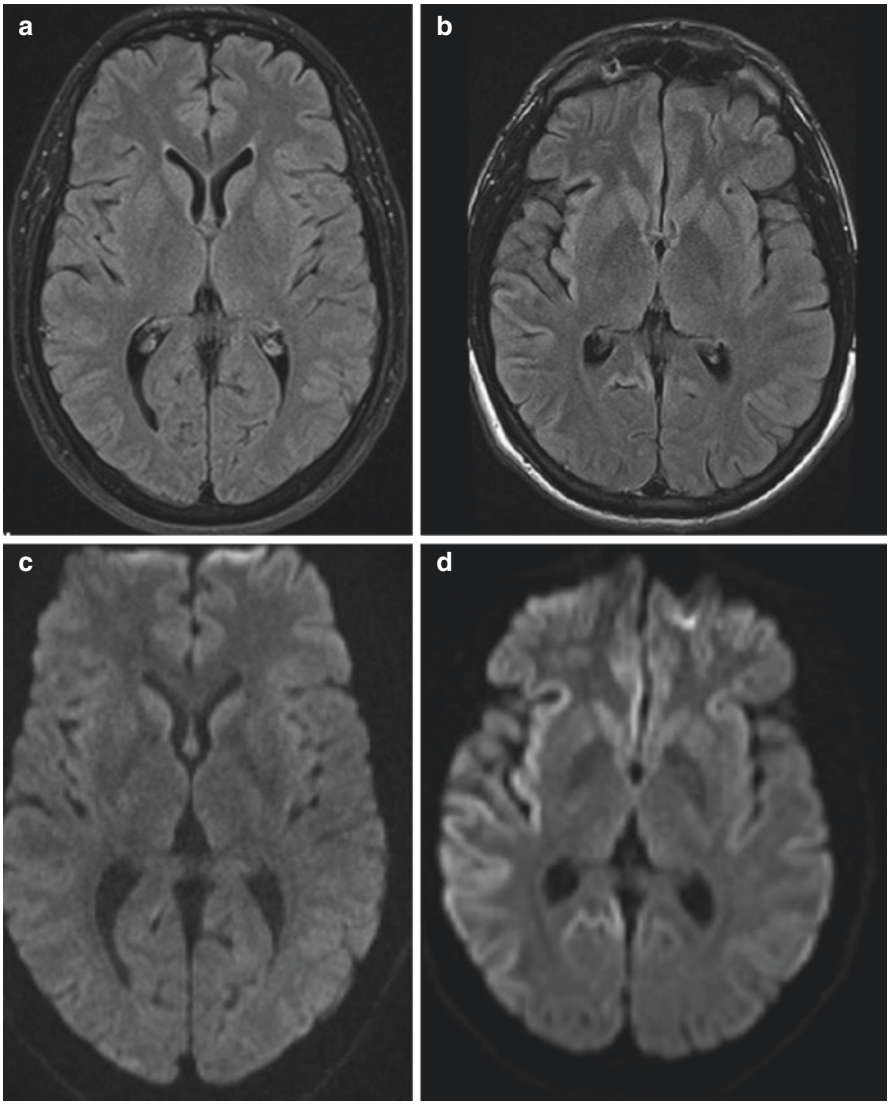


Fig. 18.2 Axial images of brain MRI. (**a**) MRI-FLAIR sequence of a healthy person. (**b**) MRI-FLAIR sequence of a patient with prion disease, this image detects cortical ribboning; hyperintensity signal mainly within right insular and temporooccipital cortices in this example. (**c**) MRI-DWI sequence of a healthy person. (**d**) MRI-DWI sequence of the same person in image **b**, this image shows diffusion restriction within the same areas of hyperintensities in FLAIR-sequence

Infection Control for Prion Diseases

Although transmission of prion disease may seem to occur easily under experimental conditions, human to human transmission is quite difficult and easily preventable by following guidelines. With the exception of vCJD, which can be secondarily

transmitted via blood products, all recognized iatrogenic transmissions of prion disease have been through the reuse of central nervous system (CNS) derived tissue from cadavers, corneal transplants, and contaminated neurosurgical instruments. Epidemiological studies have not consistently demonstrated transmission via other means suggesting that if there are unrecognized methods of transmission, they are extremely rare.

Although universal precautions are adequate for routine clinical care, special precautions are required when dealing with high infectivity tissues. Both CDC and the World Health Organization (WHO) have published guidelines for handling tissue and decontaminating instrumentation [46, 47]. Neurosurgical cases should be screened for potential symptomatic prion disease or those at risk of developing prion disease [48]. For cases in which the diagnosis is unclear, instruments can be quarantined until the diagnosis is clarified. Though proper precautions must be taken when dealing with potentially contaminated neurosurgical instruments, the fact that only four cases of iCJD from contaminated neurosurgical instruments and two from neurosurgical depth electrodes have been reported, all of which occurred in the last century, suggests that current decontamination practices are likely effective in removing the majority of infectivity.

Emerging Threats

Although the epidemic of BSE and its threat to the human food supply has been largely mitigated through public health interventions, other possible transmission risks exist, namely in the form of chronic wasting disease (CWD) [49]. CWD is a prion disease of cervids (e.g., deer, elk, moose) that primarily affects North America, but which has also been detected in South Korea, Norway, Finland, and Sweden. Unlike BSE, CWD is naturally transmitted among cervids and is excreted in saliva, urine, and feces. CWD is also the only animal prion disease that affects primarily free ranging animals, making it difficult to cull affected herds. Hence, there are already several new challenges from CWD that public health officials have not had to contend with before. There is no current evidence that CWD has been transmitted to humans and although research suggests that the risk to humans is not high, it almost certainly is not zero. The possibility that CWD may transmit to other animals and then be more apt to cross the species barrier to humans is also a possibility. These challenges require broad policy changes at the local and national levels and will require the cooperation of a litany of professionals and stakeholders. CWD is also a reminder regarding the importance of continued prion disease surveillance as much remains unknown and long incubation periods adds an extra layer of complexity to surveillance of this disease. The Centers for Disease Control and Prevention (CDC) funds the National Prion Disease Pathology Surveillance Center (NPDPSC) (www.cjdsurveillance.com) to assist in neuropathologic surveillance of prion diseases to ascertain whether CWD or other novel prion diseases are occurring in the humans. The NPDPSC offers free autopsy coordination and neuropathologic examination for cases of suspected prion disease to aid in this endeavor.

Conclusions

Human prion diseases are uncommon and universally fatal neurodegenerative conditions caused by an abnormal conformation of the prion protein. The disease can occur sporadically, develop due to a genetic mutation, or in rare instances, be acquired. Although not common, several healthcare specialties will certainly care for patients with this illness and should be knowledgeable regarding it. Prion diseases are clinically and neuropathologically heterogenous conditions. Clinical diagnosis is achieved by recognizing the clinical syndrome and the use of several diagnostic tests. The advent of RT-QuIC, which is highly specific, has greatly increased the clinical confidence of antemortem diagnosis of prion disease. However, definitive diagnosis of prion disease, as well as its subtype, is only achievable via post-mortem neuropathologic examination. Special infection control measures may be required in certain circumstances, but routine clinical care of prion disease patients can proceed as it would in a patient without prion disease. Although, the incidence of vCJD seems to be waning, there is concern that CWD could be transmissible to humans, which requires continued surveillance of these diseases.

References

1. Gill AC, Castle AR. The cellular and pathologic prion protein. Handb Clin Neurol. 2018;153:21–44.
2. Brown P, Bradley R. 1755 and all that: a historical primer of transmissible spongiform encephalopathy. BMJ. 1998;317(7174):1688–92.
3. Creutzfeldt HG. Über eine eigenartige herdförmige erkrankung des zentralnervensystems (Vorläufige mitteilung). Z Für Gesamte Neurol Psychiatr. 1920;57(1):1–18.
4. Jakob A. Über eigenartige erkrankungen des zentralnervensystems mit bemerkenswertem anatomischen befunde. Z Für Gesamte Neurol Psychiatr. 1921;64(1):147–228.
5. Gajdusek DC, Zigas V. Degenerative disease of the central nervous system in New Guinea; the endemic occurrence of kuru in the native population. N Engl J Med. 1957;257(20):974–8.
6. Asher DM, Gregori L. Human transmissible spongiform encephalopathies: historic view. Handb Clin Neurol. 2018;153:1–17.
7. Gajdusek DC, Gibbs CJ, Alpers M. Experimental transmission of a Kuru-like syndrome to chimpanzees. Nature. 1966;209(5025):794–6.
8. Gibbs CJ, Gajdusek DC, Asher DM, Alpers MP, Beck E, Daniel PM, et al. Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. Science. 1968;161(3839):388–9.
9. Klatzo I, Gajdusek DC, Zigas V. Pathology of Kuru. Lab Invest J Tech Methods Pathol. 1959;8(4):799–847.
10. Alper T, Haig DA, Clarke MC. The exceptionally small size of the scrapie agent. Biochem Biophys Res Commun. 1966;22(3):278–84.
11. Alper T, Cramp WA, Haig DA, Clarke MC. Does the agent of scrapie replicate without nucleic acid? Nature. 1967;214(5090):764–6.
12. Griffith JS. Self-replication and scrapie. Nature. 1967;215(5105):1043–4.
13. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science. 1982;216(4542):136–44.

14. Soto C, Estrada L, Castilla J. Amyloids, prions and the inherent infectious nature of misfolded protein aggregates. Trends Biochem Sci. 2006;31(3):150–5.
15. Holman RC, Belay ED, Christensen KY, Maddox RA, Minino AM, Folkema AM, et al. Human prion diseases in the United States. PLoS One. 2010;5(1):e8521.
16. Klug GMJA, Wand H, Simpson M, Boyd A, Law M, Masters CL, et al. Intensity of human prion disease surveillance predicts observed disease incidence. J Neurol Neurosurg Psychiatry. 2013;84(12):1372–7.
17. vCJD Cases Reported in the US | Variant Creutzfeldt-Jakob Disease, Classic (CJD) | Prion Disease | CDC [Internet]. 2018 [Cited 2019 Oct 13]. Available from: https://www.cdc.gov/prions/vcjd/vcjd-reported.html
18. Appleby BS, Appleby KK, Crain BJ, Onyike CU, Wallin MT, Rabins PV. Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. Arch Neurol. 2009;66(2):208–15.
19. Parchi P, Giese A, Capellari S, Brown P, Schulz-Schaeffer W, Windl O, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol. 1999;46(2):224–33.
20. Cracco L, Appleby BS, Gambetti P. Fatal familial insomnia and sporadic fatal insomnia. Handb Clin Neurol. 2018;153:271–99.
21. Notari S, Appleby BS, Gambetti P. Variably protease-sensitive prionopathy. Handb Clin Neurol. 2018;153:175–90.
22. Minikel EV, Vallabh SM, Lek M, Estrada K, Samocha KE, Sathirapongsasuti JF, et al. Quantifying prion disease penetrance using large population control cohorts. Sci Transl Med. 2016;8(322):322ra9.
23. Ladogana A, Kovacs GG. Genetic Creutzfeldt-Jakob disease. Handb Clin Neurol. 2018;153:219–42.
24. Ghetti B, Piccardo P, Zanusso G. Dominantly inherited prion protein cerebral amyloidoses – a modern view of Gerstmann-Sträussler-Scheinker. Handb Clin Neurol. 2018;153:243–69.
25. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996;347:921–5.
26. Ward H, Molesworth A, Holmes S, Sinka K. Public health: surveillance, infection prevention, and control. Handb Clin Neurol. 2018;153:473–84.
27. Bougard D, Bélondrade M, Mayran C, Bruyère-Ostells L, Lehmann S, Fournier-Wirth C, et al. Diagnosis of methionine/valine variant Creutzfeldt-Jakob disease by protein misfolding cyclic amplification. Emerg Infect Dis. 2018;24(7):1364–6.
28. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, et al. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. J Pathol. 2004;203(3):733–9.
29. Clewley JP, Kelly CM, Andrews N, Vogliqi K, Mallinson G, Kaisar M, et al. Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey. BMJ. 2009;338:b1442.
30. Gill ON, Spencer Y, Richard-Loendt A, Kelly C, Dabaghian R, Boyes L, et al. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. BMJ. 2013;347:f5675.
31. Zeidler M, Sellar RJ, Collie DA, Knight R, Stewart G, Macleod MA, et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. Lancet Lond Engl. 2000;355(9213):1412–8.
32. McGuire LI, Poleggi A, Poggiolini I, Suardi S, Grznarova K, Shi S, et al. Cerebrospinal fluid real-time quaking-induced conversion is a robust and reliable test for sporadic Creutzfeldt-Jakob disease: an international study. Ann Neurol. 2016;80(1):160–5.
33. Brown P, Brandel J-P, Sato T, Nakamura Y, MacKenzie J, Will RG, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis. 2012;18(6):901–7.
34. Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari E, et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion (Paris). 2009;49(5):977–84.

35. Geschwind MD, Murray K. Differential diagnosis with other rapid progressive dementias in human prion diseases. Handb Clin Neurol. 2018;153:371–97.
36. Steinhoff BJ, Zerr I, Glatting M, Schulz-Schaeffer W, Poser S, Kretzschmar HA. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol. 2004;56(5):702–8.
37. Collins SJ, Sanchez-Juan P, Masters CL, Klug GM, van Duijn C, Poleggi A, et al. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. Brain J Neurol. 2006;129(Pt 9):2278–87.
38. Hamlin C, Puoti G, Berri S, Sting E, Harris C, Cohen M, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2012;79(6):547–52.
39. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain J Neurol. 2009;132(Pt 10):2659–68.
40. Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology. 2011;76(20):1711–9.
41. Atarashi R, Wilham JM, Christensen L, Hughson AG, Moore RA, Johnson LM, et al. Simplified ultrasensitive prion detection by recombinant PrP conversion with shaking. Nat Methods. 2008;5(3):211–2.
42. Foutz A, Appleby BS, Hamlin C, Liu X, Yang S, Cohen Y, et al. Diagnostic and prognostic value of human prion detection in cerebrospinal fluid. Ann Neurol. 2017;81(1):79–92.
43. Diagnostic Criteria | Creutzfeldt-Jakob Disease, Classic (CJD) | Prion Disease | CDC [Internet]. [Cited 2019 Nov 17]. Available from: https://www.cdc.gov/prions/cjd/diagnostic-criteria.html
44. Bongianni M, Orrù C, Groveman BR, Sacchetto L, Fiorini M, Tonoli G, et al. Diagnosis of human prion disease using real-time quaking-induced conversion testing of olfactory mucosa and cerebrospinal fluid samples. JAMA Neurol. 2017;74(2):155–62.
45. Orrú CD, Yuan J, Appleby BS, Li B, Li Y, Winner D, et al. Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease. Sci Transl Med. 2017;9(417):eaam7785.
46. Infection Control | Creutzfeldt-Jakob Disease, Classic (CJD) | Prion Disease | CDC [Internet]. Cited 2019 Nov 17. Available from: https://www.cdc.gov/prions/cjd/infection-control.html
47. WHO | WHO infection control guidelines for transmissible spongiform encephalopathies. Report of a WHO consultation, Geneva, Switzerland, 23–26 March 1999 [Internet]. [Cited 2019 Nov 17]. Available from: https://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/
48. Karasin M. Special needs populations: perioperative care of the patient with Creutzfeldt-Jakob disease. AORN J. 2014;100(4):390–410.
49. Osterholm MT, Anderson CJ, Zabel MD, Scheftel JM, Moore KA, Appleby BS. Chronic wasting disease in cervids: implications for prion transmission to humans and other animal species. MBio. 2019;10(4):e01091–19.

Index

© Springer Nature Switzerland AG 2021

R. Hasbun et al. (eds.), *Neurological Complications of Infectious Diseases*, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-56084-3