Now in its third edition, *Ultimate Review for the Neurology Boards* is the definitive study guide for anyone preparing for the neurology board exam, RITE, or MOC exam. Compiled by nearly two dozen contributors and edited by four leading neurologists from the Cleveland Clinic, this comprehensive point form review presents the latest research, data, and knowledge on all aspects of neurology that you need to know to succeed on these exams.

The book is organized into five sections for easy access and concludes with a practice test. The first section covers basic neurosciences, including neurochemistry, clinical neuroanatomy, and genetics. The next section discusses clinical neurology, with chapters devoted to the major diseases and disorders including stroke, head trauma, dementia, epilepsy, and movement disorders, among others. In the third section, NCS, EMG, EEG, evoked potentials, and sleep neurology are covered, with images to enhance understanding of fundamental neurophysiologic techniques. After a dedicated chapter on pediatric neurology, the final section contains nine chapters on subspecialties, including neurorehabilitation, adult and child psychiatry, neurolurgy, neuro-oncology, and more.

Each chapter has been fully reviewed, revised, and updated to reflect current knowledge and practice and presents the information in an outline format, ideal for test preparation. Crucial topics and high-yield data are highlighted in bold or italic for maximal retention. With several new features, such as suggested readings and a “cheat sheet” at the end of each chapter, this third edition of *Ultimate Review for the Neurology Boards* is essential reading for anyone taking the neurology boards or MOC exam.

**THE REVISED THIRD EDITION FEATURES:**

- A completely revised and expanded practice test with all new questions
- “NB” (nota bene) items, which highlight key points to remember for the exams
- A “Cheat Sheet” in each chapter, with quick pearls, mnemonics, and definitions
- Suggestions for further reading at the end of each chapter
Ultimate Review for the Neurology Boards
Ultimate Review for the Neurology Boards

Third Edition

EDITORS

Alexander D. Rae-Grant, MD
Staff, Mellen Center for Multiple Sclerosis
Director, Center for Continuing Education
Jane and Lee Seidman Chair for Advanced Neurological Education
Cleveland Clinic
Cleveland, Ohio

Seby John, MD
Cerebrovascular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

John A. Morren, MD/MBBS(Hons)
Clinical Assistant Professor of Medicine (Neurology)
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Staff, Neuromuscular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Hubert H. Fernandez, MD
Professor of Medicine (Neurology)
Cleveland Clinic Lerner College of Medicine
James and Constance Brown Endowed Chair in Movement Disorders
Center for Neurological Restoration
Cleveland Clinic
Cleveland, Ohio
Contents

Contributors vii
Preface ix
Acknowledgments xi

INTRODUCTION: PREPARING FOR YOUR BOARDS
I. How to Use This Book xiii
II. Preparing for Your Board Examination xiv

BASIC NEUROSCIENCES
1. Neurochemistry/Pharmacology 1
2. Neurogenetics 23
3. Neurohistology, Embryology, and Developmental Disorders 51
4. Clinical Neuroanatomy 61

CLINICAL NEUROLOGY
5. Stroke 115
6. Head Trauma 139
7. Neurocritical Care 147
8. Dementia 167
9. Headache Syndromes 179
10. Neuromuscular Disorders 185
11. Epilepsy and Related Disorders 249
12. Movement Disorders 301
13. Demyelinating Disorders 327
14. Infections of the Nervous System 337
15. Neurotoxicology and Nutritional Disorders 375
16. Sleep and Sleep Disorders 391

© Demos Medical Publishing
CONTENTS

NEUROPHYSIOLOGY

17. Nerve Conduction Studies (NCS) and Electromyography (EMG) 401
18. Electroencephalography (EEG) 415
19. Evoked Potentials 429
20. Sleep Neurology 449

PEDIATRIC NEUROLOGY

21. Pediatric Neurology 461

SUBSPECIALTIES

22. Neurourology 493
23. Neuro-ophthalmology 499
24. Neuro-otology 525
25. Neurorehabilitation 531
26. Neuroendocrinology 535
27. Neuro-oncology and Transplant Neurology 541
28. Adult Psychiatry 561
29. Child Psychiatry 595
30. Neurobehavior and Neuropsychology 607

50 Practice Questions With Answers 621
Index 639
Contributors

Russell Cerejo, MD
Fellow, Cerebrovascular Fellow
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 5: Stroke

Marisa Clifton, MD
Fellow, Female Pelvic Medicine and Reconstructive Surgery
Glickman Urological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 22: Neurourology

Mita Deoras, MD
Fellow, Sleep Disorders Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 16: Sleep and Sleep Disorders

Rachel Donaldson, DO
Fellow, Neuromuscular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 3: Neurohistology, Embryology, and Developmental Disorders

Richard Drake, PhD
Director of Anatomy, Professor of Surgery
Lerner College of Medicine
Cleveland Clinic
Cleveland, Ohio

Chapter 4: Clinical Neuroanatomy

Camilo Garcia, MD
Epilepsy Center
Neurological Institute
Cleveland Clinic Florida
Weston, Florida

Chapter 18: Electroencephalography (EEG)

Joao Gomes, MD
Attending, Vascular Neurology and Neurocritical Care
Summa Health
Akron, Ohio

Chapter 6: Head Trauma
Chapter 7: Neurocritical Care

Pravin George, DO
Fellow, Neurosciences Critical Care Unit
Johns Hopkins University
Baltimore, Maryland

Chapter 7: Neurocritical Care

Gary Hsich, MD
Center for Pediatric Neurology
Department of Neurology
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 21: Pediatric Neurology

Ahmed Itrat, MD
Fellow, Cerebrovascular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 27: Neuro-oncology and Transplant Neurology

M. Cecilia Lansang, MD
Associate Professor of Medicine, Cleveland Clinic
Lerner College of Medicine
Department of Endocrinology
Cleveland Clinic
Cleveland, Ohio

Chapter 26: Neuroendocrinology

Lisa Lystad, MD
Division of Neuro-ophthalmology
Cole Eye Institute
Cleveland Clinic
Cleveland, Ohio

Chapter 23: Neuro-ophthalmology
CONTRIBUTORS

Jennifer M. McBride, PhD
Director of Histology, Associate Professor of Surgery
Lerner College of Medicine
Cleveland Clinic
Cleveland, Ohio

**Chapter 4: Clinical Neuroanatomy**

Jhanvi Menon, MD
Fellow, Neuromuscular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 15: Neurotoxicology and Nutritional Disorders**

Courtenay K. Moore, MD
Associate Professor of Surgery, Cleveland Clinic
Lerner College of Medicine
Fellowship Director, Female Pelvic Medicine and Reconstructive Surgery
Glickman Urological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 22: Neuurology**

John A. Morren, MD/MBBS(Hons)
Clinical Assistant Professor of Medicine (Neurology)
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Staff, Neuromuscular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 17: Nerve Conduction Studies (NCS) and Electromyography (EMG)**

Oluwadamilola (Lara) Ojo, MD
Fellow, Center for Neurological Restoration
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 12: Movement Disorders**

Shnehal Patel, MD, MPH
Fellow, Center for Neurological Restoration
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 25: Neurorehabilitation**

Gregory Pontone, MD
Assistant Professor
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
Baltimore, Maryland

**Chapter 28: Adult Psychiatry**

Alexander D. Rae-Grant, MD
Staff, Mellen Center for Multiple Sclerosis
Director, Center for Continuing Education
Jane and Lee Seidman Chair for Advanced Neurological Education
Cleveland Clinic
Cleveland, Ohio

**Chapter 8: Dementia**

**Chapter 11: Epilepsy and Related Disorders**

**Chapter 13: Demyelinating Disorders**

Ian Rossman, MD, PhD
Fellow, Neuroimmunology; Pediatric Neurologist
Mellen Center for Multiple Sclerosis; Center for Pediatric Neuroscience
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 2: Neurogenetics**

Aasef Shaik, MD, PhD
Fellow, Center for Neurological Restoration
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 1: Neurochemistry/Pharmacology**

Lakshmi Shankar, MD
Fellow, Cerebrovascular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 14: Infections of the Nervous System**

Qingshan Teng, MD, MS
Fellow, Neuromuscular Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Chapter 9: Headache Syndromes**
Preface

Ultimate Review for the Neurology Boards, Third Edition, continues the tradition of providing a brief but comprehensive source for study or simply review. The authors and editors have tried hard to include the most up-to-date material while keeping the verbiage to a minimum. We have followed a point form outline style where possible, also including tables and lists where long paragraphs would be problematic. A brief Cheat Sheet at the end of most chapters provides a simple quick study section for key facts or potential “board question” information, often those tricky eponyms that we all learn and rapidly forget. We have included some suggested readings for those who want to dive deeper into a review, but have not exhaustively referenced the chapters for the sake of space and clarity. Finally, there are 50 all-new questions with answers and explanations at the end of the book for self-assessment.

The editors hope this text will provide a useful tool to students of neurology at multiple levels, and will help in review for whatever neurological examination looms in the future for the reader.

Alexander D. Rae-Grant
Seby John
John A. Morren
Hubert H. Fernandez
Acknowledgments

The editors would like to acknowledge the support of Christine Moore, our editorial assistant, who valiantly assisted in organizing authors, managing editors, modifying manuscripts, and generally making the entire contraption function.

Thanks go to our authors, who carefully reviewed and updated the chapters to reflect recent changes in understanding of disease and approaches to treatment within the bounds of the Ultimate review format.

We would like to acknowledge the support of the leadership of the Neurological Institute at the Cleveland Clinic for encouraging our authors and editors to contribute to clinical pedagogy.

We would also like to thank our editor, Beth Barry, at Demos for her assistance and support during the editing of this third edition of Ultimate Review for the Neurology Boards.

The editors would also like to thank their loving wives (Mary Bruce, Ritika, Divya, and Cecilía) and their wonderful children (Michael, Tucker, George, Sasha, Jordan, and Annella Marie) for their unconditional support and understanding during this process.

Alexander D. Rae-Grant
Seby John
John A. Morren
Hubert H. Fernandez
INTRODUCTION

Preparing for Your Boards

I. How to Use This Book

Neurology covers a broad spectrum of disease processes and complex neuroanatomy, neurophysiology, and neuropathology. Moreover, your certification examination will also include psychiatry and other neurologic subspecialties such as neuro-ophthalmology, neuro-otology, and neuroendocrinology, to name a few. Covering all of the possible topics for these boards is not only impossible, it is impractical. Although this book is entitled Ultimate Review for the Neurology Boards, it is not intended to be your single source of study material in preparing for your examination. Rather, it presumes that throughout your residency training, or at the very least, several months before your board examination date, you will have already read primary references and textbooks (and, therefore, carry a considerable fund of knowledge) on the specific broad categories of neurology. Because you cannot possibly retain all the information you have assimilated, we offer this book as a convenient way of tying it all together. The point-form information will help you recall specific facts, associations, and clues that may help with answering questions correctly.

Ultimate Review for the Neurology Boards contains detailed chapters on subjects included on the neurology board examination.

For maximal retention within the shortest amount of time, we have used an expanded outline format in this manual. The main headings and subtopics are in bold. A few phrases or a short paragraph is spent on subtopics that we think are of particular importance. Crucial or essential data within the outlines are italicized or in bold. Thus, we present three levels of learning in each chapter. We suggest that you first read the entire chapter, including the brief sentences on each subtopic. After the first reading, you should go back a second time, focusing only on the headings and subtopics in bold and the italicized words within the outline. If you need to go back a third time to test yourself, or, alternatively, if you feel you already have a solid fund of knowledge on a certain topic, you can just concentrate on the backbone outline in bold to make sure you have, indeed, retained everything.

Whenever appropriate, illustrations are liberally sprinkled throughout the text to tap into your “visual memory.” Quick pearls (such as mnemonics to remember long lists and confusing terminology, tables to organize a complex body of information) and high-yield topics are preceded with this symbol “NB:” (for nota bene, Latin for “note well”), to make sure you do not miss them. We have added a few suggested readings where pertinent to help you extend your learning both for the exams and for your education.

Some chapters overlap. For example, some diseases discussed in the chapter on pediatric neurology and the chapter on neurogenetics can also be found in the individual chapters of the Clinical Neurology section. This overlap is intended to maximize memory retention through repetition.

We have included 50 questions at the end of the book to help you practice for the tests. One of the best preparation methods for taking exams is practicing the exam situation over and over. We hope these questions will give you a chance to try out your hand at answering questions.

Good luck, and we hope you pass your boards in one attempt!
INTRODUCTION

II. Preparing for Your Board Examination

Although most residents initially feel that after a busy residency training it is better to “take a break” and postpone their certification examination, we believe that, in general, it is best to take your examination right after residency, when “active” and “passive” learning are at their peak. There will never be “a perfect time” (or “enough time”) to review for your boards. The board examination is a present-day reality that you will need to prepare for whether you are exhausted, in private practice, expecting your first child, renovating your newly purchased 80-year-old house, or burning candles in your research laboratory. You just need to squeeze in the time to study. Luckily, all the others taking these tests are in the same boat, so you are not alone!

Here are a few pointers to help you prepare for the board examination. All or some of them may be applicable to you:

A. Board preparation starts from day 1 of your residency training. Although most residency programs are clinically oriented and have a case-based structure of learning, here are some suggestions as to how you can create an “active” learning process out of your clinical training, rather than just passively learning from your patients and being content with acquiring clinical skills.

1. Imagine you are on your sixth month of a boring ward rotation carrying eight patients on your service. The following table contains the diagnoses of your patients in the neurology ward and the reading initiative we recommend. The point here is to use your patient caseload to suggest topic areas for review. Our experience is that case-based learning “sticks” better than starting on page one of any textbook.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>DIAGNOSIS</th>
<th>READING INITIATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thalamic lacunar stroke</td>
<td>Master the anatomy of the thalamus.</td>
</tr>
<tr>
<td>2</td>
<td>Embolic stroke</td>
<td>Become familiar with the literature on the use of heparin versus aspirin.</td>
</tr>
<tr>
<td>3</td>
<td>Guillain-Barré syndrome</td>
<td>Master the differential diagnosis of axonal versus demyelinating polyneuropathy.</td>
</tr>
<tr>
<td>4</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Master the differential diagnosis of motor neuron diseases.</td>
</tr>
<tr>
<td>5</td>
<td>25-year-old with stroke, unclear etiology</td>
<td>Master the data on stroke risk factors.</td>
</tr>
<tr>
<td>6</td>
<td>Seizure breakthrough for overnight observation</td>
<td>Know all the mechanisms of action of antiepileptic agents.</td>
</tr>
<tr>
<td>7</td>
<td>Hemorrhagic stroke</td>
<td>Know and be able to differentiate the MRI picture of a hyperacute, acute, subacute, and chronic bleed.</td>
</tr>
<tr>
<td>8</td>
<td>Glioblastoma</td>
<td>Know the pathology of all glial tumors.</td>
</tr>
</tbody>
</table>

2. Always carry a small notebook that fits in your coat pocket so you can write down all the questions and observations that may arise in the course of your day. If possible, do not sleep without answering those questions. Likewise, jot down all the new information you have learned. Read through these notes one more time before you call it a night.

3. Follow your grand rounds schedule. Read the topic(s) beforehand. This will help you in two ways: (a) the talk itself will serve as reinforcement because you already read about it; and (b) you can ask more intelligent questions that will, at the very least, impress your colleagues and mentors, if not make you learn and appreciate neurology even more.
INTRODUCTION

4. For the driven resident: have a monthly schedule of books or book chapters to read. Maximize your reading on your light or elective rotations. On the average, a "good" resident reads 25 to 50 pages per day (from journals, notes, books, etc.). If you read more than 50 pages per day, you are driven and will be rewarded with an almost effortless board review period. If you read less than 10 pages per day, or, even worse, are an occasional reader, you are relying on passive learning and will need to make up a lot of lost time (and knowledge) during your board review.

B. Take your Residency In-Service Training Examination (RITE)/in-service examination seriously. If possible, prepare for it weeks in advance. People who do well every year are the ones who pass their written board examination on the first attempt.

C. Know all board examination requirements several months before you finish your residency training. Know all the deadlines. READ THE INSTRUCTIONS CAREFULLY! Check the name on your identification and the name on your admission slip to make sure they are identical. Contact the American Board of Psychiatry and Neurology (ABPN) if they are not. Ideally, you should be distracted as little as possible when your examination date approaches.

D. Start your formal board review midway (that is, January 2) of your senior year. Make a general, realistic schedule. Do not make it too ambitious or too detailed. Otherwise, you will find yourself frustrated and always catching up to your schedule. As we mentioned, there will never be a perfect time to study for your boards—you need to create your own time. Consider working with a study group, which will provide peer support and pressure to continue studying.

E. In general, start with topics you know the most about (and, therefore, are least likely to forget), such as clinical neurology, and end with topics you know the least about (and, thus, are more likely to forget in a short amount of time), such as neurogenetics, metabolic disorders, neuroanatomy, neurochemistry, and so forth.

F. Use your book allowance wisely. Read and underline books during residency that fit your taste and that you are likely to use for your board review. Underlined books are less overwhelming, provide a sense of security that you have already been through the material (even if you have forgotten its contents), make review time more efficient, and significantly reinforce learning and retention.

G. End your formal review at least 2 weeks before the date of your written boards. Ear-mark 1 week for the psychiatry portion (do not forget to read on child psychiatry topics) and 1 week for recapping high-yield topics, reviewing questions and answers, looking at radiology and pathology pictures, and reading the answers to past RITE/in-service examinations (they do repeat!).

H. Arrive at your examination site city at least 24 hours before the exam. You do not want to realize on the day of your examination that your hotel reservation was inadvertently misplaced or that your flight was canceled because of a snow storm. Make sure your cell phone is fully charged and that you have your driver's license with you. DO AS MUCH AS YOU CAN BEFOREHAND SO YOU DON’T HAVE TO WORRY ABOUT DETAILS.

I. You might consider bringing ear plugs, an extra sweater, and a reliable watch. When one of us took our boards in the basement of a hospital, there was a general announce- ment through the public-address system every 30 minutes. We have heard different stories: the heater was not working, a dog convention was going on in the next room, and so forth. It is best to be prepared.

J. If this is the second or third time you are taking the boards, consider the benefits of a small study group or having a study partner. You will be amazed that two or three peo- ple assigned the same topic to read will emphasize different items. It could very well be that you are underlining the wrong words and need someone to give you a different perspective. At the very least, a study group will keep you on pace with your schedule.
I. Bacterial Meningitis

1. Acute bacterial infection of the leptomeninges, subarachnoid space, and structures passing through the subarachnoid space

2. Routes of infection
   a. Nasopharynx (most common)
   b. Open trauma/surgical procedure
   c. Sinus infection
   d. Communicating congenital defect

3. Epidemiology
   a. More common in winter
   b. Annual incidence: 1 to 2 in 100,000 annually
   c. Immunization against *Haemophilus influenzae* with polyvalent pneumococcal and meningococcal vaccines has produced a significant reduction in the incidence in the United States.

4. Etiology

<table>
<thead>
<tr>
<th>NEONATE (&lt;1 MO)</th>
<th>INFANT TO YOUNG CHILD (1 MO–5 YRS)</th>
<th>ADULT (15–60 Y/O)</th>
<th>ELDERLY (&gt;60 Y/O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B Streptococcus</td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Escherichia coli, other enteric gram-negative bacilli</td>
<td><em>Neisseria meningitidis</em></td>
<td><em>Neisseria meningitidis</em></td>
<td><em>Neisseria meningitides</em></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td><em>Haemophilus influenzae</em> type b</td>
<td></td>
<td><em>Listeria monocytogenes</em></td>
</tr>
</tbody>
</table>

5. Clinical: presents in hours to days with rapid progression. Most patients will have at least two of the tetrad of fever, neck stiffness, headache, and altered mentation.
   a. Fever—85% of cases
   b. Meningismus (neck stiffness) present in 70% of cases; Kernig’s and Brudzinski’s signs may be present.
   c. Diminished level of awareness
   d. Headache +/- nausea, vomiting
   e. Seizures—poor prognosis
   f. Focal neurologic deficits
5. Clinical (cont’d)
   g. Petechial rash (*N. meningitidis*)
   h. Infant: lethargy, seizures, bulging fontanel
   i. Complications
      i. Cerebral edema
      ii. Hydrocephalus
      iii. Stroke due to infectious vasculitis
      iv. Sinus thrombosis
      v. Cranial nerve (CN) palsies
      vi. Disseminated intravascular coagulation (with *N. meningitidis*)
      vii. Syndrome of inappropriate secretion of antidiuretic hormone
      viii. Abscess/subdural empyema
      ix. Respiratory failure
   j. Prognosis: mortality rate of 10% to 15%, highest in pneumococcal meningitis, increased in immunocompromised host

6. Diagnostic testing
   a. CT brain: no diagnostic utility in meningitis. Only used to rule out other intracranial processes prior to lumbar puncture. Indications for undergoing CT imaging prior to lumbar puncture: adult patients who are >60 years of age; immunocompromised state; presentation with focal neurological deficits, new-onset seizures, papilledema, abnormal mentation, or history of central nervous system (CNS) disease.
   b. Lumbar puncture
      i. Initial cerebrospinal fluid (CSF)
         (A) Elevated opening pressure
         (B) White blood cell count (WBC): 100 to 10,000 cells/mL, predominantly polymorphonuclear cells
         (C) Glucose: <20 mg/dL or <40% of serum glucose
         (D) Protein usually elevated, >100 mg/dL
      ii. Gram stain: yield low to 20% if treated with antibiotics
      iii. Culture: within 48 to 72 hours after institution of antibiotic therapy, the CSF culture is usually negative; blood cultures may be positive in 50% of cases.

<table>
<thead>
<tr>
<th>CSF Meningitis</th>
<th>Appearance</th>
<th>Opening Pressure</th>
<th>Glucose</th>
<th>Protein</th>
<th>WBC</th>
<th>Cell Type</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Cloudy, purulent, or clear</td>
<td>Elevated</td>
<td>Low</td>
<td>Elevated</td>
<td>&gt;100 cells</td>
<td>Neutrophils</td>
<td>Red blood cells (RBCs) or xanthochromia in herpes simplex virus (HSV)</td>
</tr>
<tr>
<td>Viral</td>
<td>Clear</td>
<td>Normal or elevated</td>
<td>Normal</td>
<td>Elevated</td>
<td>10-1,000</td>
<td>Lymphocytes</td>
<td>(continued)</td>
</tr>
</tbody>
</table>
7. Treatment
   a. Supportive care
   b. Antibiotics
      i. Always administer immediately if cannot readily perform spinal tap; administration may produce sterile cultures but associated changes in CSF (if necessary, may need to follow CSF parameters).
      ii. Empiric treatment
         (A) Typical empiric treatment
            (1) Ceftriaxone: 2 g q12h
            (2) Vancomycin: 30 to 45 mg/kg/day, adjusted to renal function
               (a) If Listeria suspected (in those <3 months old or >60 years old (y/o); immunosuppressed, alcoholic), add ampicillin 2 g IV q 4 hours.
         (B) Prophylaxis with rifampin for contacts if meningococcal or Hemophilus influenza meningitis
      iii. Antibiotics for specific types of bacterial meningitis

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>ANTIBIOTIC</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Ceftriaxone and vancomycin</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>Ampicillin</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Ceftriaxone or cefotaxime</td>
<td>7 days</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Ampicillin</td>
<td>21 days</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Ceftriaxone or cefepime</td>
<td>7 days</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Ceftazidime or cefepime</td>
<td>21 days</td>
</tr>
</tbody>
</table>

c. Role of corticosteroids: a large randomized trial showed the beneficial effects of 0.15 mg/kg IV q 6 hours for 4 days, in conjunction with antibiotics, for suspected or proven meningitis due to S. pneumoniae; in kids: dexamethasone, 0.15 mg/kg/day, q6h for 4 to 7 days, should be used in conjunction with antibiotics for suspected or proven H. influenzae type B to reduce hearing loss.

d. Droplet precautions need to be undertaken until organism is identified.

8. Recurrent meningitis
   a. Evaluate for cranial or spinal defect permitting reentry
   b. Evaluate for immune deficiency (i.e., HIV)
   c. Differential diagnosis
      i. Behcet’s syndrome
      ii. Sarcoidosis
      iii. Mollaret’s meningitis
II. Viral Infections of the Nervous System

A. General

1. A wide range of neurological manifestations, including meningitis, encephalitis, cerebellitis, CN involvement, myelitis, ganglionitis, and polyradiculitis
2. Most viral infections are mild or asymptomatic.
3. Viral meningitis is more common than bacterial meningitis.
4. Etiologies
   a. Enteroviruses cause 90% of viral meningitis.
   b. Herpesviruses and arboviruses are the most common causes of encephalitis.
5. Clinical features
   a. Malaise, anorexia, myalgia, low-grade fever, vomiting, or headache
   b. Physical examination reveals photophobia, somnolence, or irritability, and meningeal irritation.
   c. Systemic features to assess include rash, pharyngitis, lymphadenopathy, arthritis, parotid gland enlargement, and hepatosplenomegaly.
   d. Seizures and altered mentation in encephalitis
   e. Transverse myelitis with flaccid weakness, reduced/absent reflexes, sensory loss, and bladder dysfunction
   f. Other neurological manifestations include CN involvement, extrapyramidal symptoms, cerebellitis, acute inflammatory demyelinating polyneuropathy (AIDP), and acute flaccid paralysis.
   g. Reye’s syndrome
      i. Seen in infection with varicella zoster virus (VZV; chicken pox) and influenza viruses
      ii. Develops between ages 2 and 15 years
      iii. Strong correlation with aspirin use
      iv. Clinical
         (A) \(<72 \text{ hours after viral illness}
         (B) Begins with continuous vomiting followed by increasing lethargy, hypoglycemia, and hyperammonemia with liver failure (and dysfunction of clotting factors)
         (C) Death and neurologic sequelae are related to increased intracranial pressure (ICP)
      v. Treatment
         (A) Supportive care, with strict control of electrolytes and treatment of clotting dysfunction
         (B) Observation/treatment of increased ICP
      vi. Prognosis depends on severity of increased ICP; mortality is 10% to 30%.
6. Diagnostic procedures
   a. Serology—elevated virus-specific antibodies
   b. Lumbar puncture for CSF
      i. Lymphocytic pleocytosis (10–1,000/mm³), mildly elevated protein, and normal glucose and normal opening pressure
      ii. Polymerase chain reaction (PCR) available for HSV, HIV, cytomegalovirus (CMV), enteroviruses, adenoviruses, Epstein–Barr virus (EBV), VZV, and flaviviruses
c. Neuroimaging  
   i. CT: may be normal in encephalitis  
   ii. MRI  
      (A) More sensitive than CT  
      (B) T2 prolongation or enhancement of cortex in encephalitis; T2 prolongation or cord swelling in myelitis  
      (C) Distinguish viral encephalitis from acute disseminated encephalomyelitis  

d. Electroencephalography (EEG)  
   i. Viral meningitis: normal or nonspecific abnormalities  
   ii. Encephalitis: slowing of background rhythms and focal or diffuse epileptiform discharges  
      (A) HSV-1 encephalitis often presents with temporal slowing or periodic lateralizing epileptiform discharges.

7. Specific antiviral treatment

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>Acyclovir, valacyclovir, famciclovir</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir, foscarnet, cidofovir</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>Isoprinosine</td>
</tr>
<tr>
<td>HIV</td>
<td>Highly active antiretroviral therapy regimen (see Section II.B.9)</td>
</tr>
</tbody>
</table>

B. Specific viral infections of the nervous system

1. Herpes viruses

   a. Herpes simplex virus 1 and herpes simplex virus 2
      i. HSV-1: causes 90% to 95% of HSV encephalitis  
         (A) Usually adolescent/adult  
         (B) Transmitted via oral mucosa  
         (C) Most common nonepidemic encephalitis and fatal sporadic encephalitis in the United States  
         (D) Remains latent in the trigeminal ganglia with reactivation and retrograde transmission to the central nervous system (CNS) in two-thirds of cases  
         (E) Exhibits propensity for the orbitofrontal cortex and temporal lobes  
      ii. HSV-2  
         (A) Usually neonate  
         (B) Transmitted sexually or via birth canal to infant  
         (C) Involves the brain diffusely via hematogenous transmission  
         (D) Causes 70% of neonatal HSV infections  
         (E) Common cause of aseptic meningitis in adult women; may not have concurrent genital herpetic lesions  
   iii. Clinical features  
      (A) HSV encephalitis
(A) HSV encephalitis (cont’d)
   (1) Prodrome of headache, fever, malaise, or vomiting followed by confusion, personality and behavioral changes, focal or generalized seizures, short-term memory dysfunction, and focal deficits, including weakness and aphasia
   (2) Two presentations
      (a) Can be rapidly progressive, with coma and death within 2 weeks
      (b) Indolent, with hallucinations, headache, memory loss, and behavioral disturbances

(B) Other manifestations
   (1) Bell’s palsy
   (2) Acute myelitis
   (3) Rhombencephalitis/brainstem encephalitis
   (4) Aseptic meningitis
   (5) Mollaret’s meningitis—recurrent episodes of benign lymphocytic meningitis, common in women; most are caused by HSV-2 infection.

iv. Diagnosis
   (A) CSF
      (1) Lymphocytic pleocytosis, moderately elevated opening pressure and protein content with normal glucose. Elevated RBC count and xanthochromia may be seen due to hemorrhagic necrosis.
      (2) HSV PCR: 99% sensitive and 95% specific. False negatives can occur in the first 72 hours of the illness.
   (B) Neuroimaging
      (1) MRI brain: restricted diffusion and hyperintensities on T2-weighted sequences in frontal regions, mesial temporal lobe, insular cortex, and cingulate gyrus, with or without gadolinium enhancement. Hemorrhagic changes may be seen. Negative MRI does not rule out HSV encephalitis.
   (C) EEG: slowing, periodic lateralizing epileptiform discharges (PLEDs), or frank epileptiform discharges
   (D) Pathology
      (1) Hemorrhagic encephalitis with neuronal destruction
      (2) Predilection for frontal and temporal regions
      (3) Cowdry A inclusions
         (a) Intranuclear, solitary large viral inclusions with halo due to margination of chromatin
         (b) Seen in HSV, VZV, CMV, and subacute sclerosing panencephalitis

v. Treatment
   (A) HSV-1 encephalitis: acyclovir, 10 mg/kg q8h for minimum of 14 to 21 days
   (B) HSV-2 in neonates: acyclovir, 20 mg/kg q8h for 21 days

vi. Prognosis
   (A) Mortality of untreated cases is 70%; mortality for acyclovir-treated neonates is 15%.
   (B) Survivors usually have permanent neurologic complications.
b. Varicella zoster virus
   i. Primary VZV infection—*chicken pox*
      (A) Peak incidence between ages 5 and 9
      (B) Respiratory transmission; typically causes no neurological symptoms.
      (C) Postinfectious encephalitis or cerebellitis can occur. In immunocompromised individuals it can cause meningitis or encephalitis.
      (D) Reye's syndrome can be seen in children who receive aspirin.
   ii. Reactivation of VZV: after primary VZV infection, the virus persists in a latent state in the dorsal root ganglia
      (A) *Shingles (herpes zoster)*
         (1) Virus reactivates and migrates via axon to the skin, producing shingles, erythematous, maculopapular rash that progresses to vesicles associated with radicular pain in a dermatomal distribution
         (2) More common among the elderly or immunocompromised
         (3) T5 to T10 dermatomes most commonly affected; can be disseminated in immunocompromised individuals
         (4) Treatment is acyclovir 800 mg oral 5 times a day for 7 days. Early initiation of treatment reduces pain associated with acute zoster.
         (5) Post-herpetic neuralgia can occur, especially in elderly. Gabapentin, pregabalin, and other anticonvulsants, antidepressants, and topical agents are used for treatment of neuralgic pain.
         (6) Live attenuated varicella vaccine has been approved for adults >50 years of age to prevent shingles and post-herpetic neuralgia.
      (B) *Zoster ophthalmicus*: due to involvement of first division of trigeminal ganglion; can be associated with VZV vasculopathy/vasculitis
      (C) *Ramsay-Hunt syndrome*: lower CN VII palsy with associated vesicular eruption in the auditory canal
      (D) Meningitis and myelitis can occur
      (E) Encephalitis is associated with large-vessel vasculitis and can cause focal infarctions. It is usually associated with ipsilateral zoster ophthalmicus. In immunocompromised individuals, small- and medium-sized vessels are involved, causing deep infarctions.
      (F) AIDP and brachial plexus neuritis
   iii. Diagnosis
      (A) Isolation of VZV from the oropharynx or skin lesions
      (B) VZV-specific antibodies in the CSF
      (C) PCR studies of CSF or vesicular fluid
   iv. Treatment
      (A) Patients with CNS involvement are treated with IV acyclovir 10 mg/kg q 8 hours for 7 to 14 days with pulse steroids for 3 to 5 days.
      (B) Supportive care

c. Epstein-Barr virus
   i. Fifty percent of children under age 5 and 90% of adults have had EBV infection.
   ii. Acute illness is usually asymptomatic; can present as nonspecific febrile illness or infectious mononucleosis.
c. Epstein-Barr virus (cont’d)

iii. Neurologic complications in <1%

(A) Aseptic meningitis—most common acute neurologic complication
(B) Encephalitis
(C) Optic neuropathy
(D) Other cranial neuropathy
(E) Cerebellitis
(F) Acute transverse myelitis
(G) AIDP
(H) Small-fiber sensory or autonomic neuropathy
(I) Primary CNS lymphoma in immunocompromised patients

iv. Diagnostic testing

(A) In meningoencephalitis, brain MRI may be normal or show T2 prolongation involving the basal ganglia, thalamus, white matter, or cerebral cortex.

(B) Diagnosis of EBV infection is usually established serologically but can also be detected in the CSF by PCR.

v. Treatment

(A) Supportive care

(B) No controlled treatment trials available

d. Cytomegalovirus

i. Most adults are seropositive for CMV and are asymptomatic.

ii. Can cause acute and latent or persistent infection

iii. Acquired by body fluid transmission, blood transfusion, organ transplant, etc.

iv. Common in immunocompromised host, including HIV-infected patients and post-transplantation (>40%–90% of transplant recipients)

v. Clinical manifestations:

(A) Congenital CMV infection

(1) Most common congenital infection
(2) Infection occurs in the first trimester. Infection can also occur perinatally during passage through infected birth canal or breastfeeding.
(3) Ranges from asymptomatic infection in 90% to disseminated disease.
(4) Systemic: jaundice, petechial rash, hepatosplenomegaly, or intrauterine growth retardation
(5) Neurologic: encephalitis, retinitis and optic atrophy, microcephaly, microgyria, seizures, abnormal tone, sensorineural hearing loss (CMV infection is the most common cause of congenital deafness).
(6) May have disorders of neuronal migration (cortical dysplasia, lissencephaly) or absence of the corpus callosum
(7) Neuroimaging: intracranial calcification in 50% of infected infants (worse prognosis)

(a) CT: calcification in the periventricular regions, also + in basal ganglia (BG), cortical, and subcortical regions

(b) MRI: disruption of gyral pattern and delayed myelination
(B) Postnatal CMV infection

(1) Immunocompetent: mononucleosis syndrome, aseptic meningitis

(2) Immunocompromised:

(a) Encephalitis (when CD4 < 50 in HIV patients), meningitis, ventriculitis, ependymitis

(b) Retinitis

(i) Occurs in 5% to 10% of persons with AIDS.

(ii) Unilateral vision loss followed by bilateral vision loss if untreated

(iii) Ganciclovir, foscarnet, and cidofovir may reduce extent of vision loss.

(c) Acute myelitis

(d) AIDP

(i) Before onset, 10% to 20% of patients are CMV positive.

(ii) More commonly also have cranial neuropathies and sensorineural hearing loss

vi. Diagnosis

(A) CMV-specific immunoglobulin M (IgM): strongly supports infection, but CMV IgG not useful because of the high prevalence of CMV in the general population

(B) CSF CMV PCR

(C) CMV DNA can be isolated from urine, saliva, and CSF in newborns

(D) Pathology: microglial nodules, especially periventricular, on cortical biopsy/autopsy

vii. Treatment in immunocompromised host

(A) Initial antiviral dose: ganciclovir, 5 mg/kg q12h for > 2 to 4 weeks

(B) Maintenance therapy: ganciclovir, 5 mg/kg/day for 5 days per week for 4 weeks

(C) Foscarnet for ganciclovir-resistant CMV

2. Arthropod-borne infections—transmitted by mosquitoes and ticks

**Vectors and animal hosts**

<table>
<thead>
<tr>
<th>ENCEPHALITIS</th>
<th>VECTOR</th>
<th>ANIMAL HOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western equine encephalitis</td>
<td>Culex</td>
<td>Birds</td>
</tr>
<tr>
<td>Eastern equine encephalitis</td>
<td>Culex</td>
<td>Birds</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Culex</td>
<td>Rodents, equine</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Culex</td>
<td>Birds</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Culex</td>
<td>Birds</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Culex</td>
<td>Birds</td>
</tr>
<tr>
<td>California encephalitis</td>
<td>Aedes</td>
<td>Rodents</td>
</tr>
<tr>
<td>Powassan</td>
<td>Tick—Ixodes</td>
<td>Rodents</td>
</tr>
<tr>
<td>Colorado tick fever</td>
<td>Tick—Dermacentor</td>
<td>Rodents</td>
</tr>
</tbody>
</table>
2. Arthropod-borne infections (cont’d)

Geographical locations and seasonal occurrence

<table>
<thead>
<tr>
<th>ENCEPHALITIS</th>
<th>GEOGRAPHICAL DISTRIBUTION</th>
<th>SEASON/MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western encephalitis</td>
<td>Western United States and Canada</td>
<td>June to August</td>
</tr>
<tr>
<td>Eastern encephalitis</td>
<td>Atlantic and Gulf coasts, Great Lakes region</td>
<td>June to September</td>
</tr>
<tr>
<td>Venezuelan encephalitis</td>
<td>Texas and Florida</td>
<td>May to September</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Central states, Ohio/Mississippi River valley</td>
<td>June to August</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>United States</td>
<td>June to October</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Asia and Western Pacific</td>
<td>Summer and fall</td>
</tr>
<tr>
<td>California encephalitis</td>
<td>Midwestern and northeastern United States, southern Canada</td>
<td>June to September</td>
</tr>
<tr>
<td>Powassan</td>
<td>North-central United States, eastern Canada</td>
<td>Spring, summer</td>
</tr>
<tr>
<td>Colorado tick fever</td>
<td>United States and Canadian Rocky Mountains</td>
<td>March to September</td>
</tr>
</tbody>
</table>

a. Transmitted by mosquitoes

i. Alphaviruses

   (A) Clinical: headache, myalgias, malaise, vomiting, stiff neck, fever, irritability, coma, or seizure

   (B) Diagnosis: detection of virus-specific antibodies in serum and CSF

   (C) Treatment: supportive care

   (1) Western equine encephalitis (EE) virus

      (a) Mortality: 5% to 15%

      (b) Most survivors recover completely.

   (2) Eastern EE virus

      (a) In human infections, 4% to 5% lead to encephalitis.

      (b) Highest mortality rate of 50% to 70%

      (c) Complications: most survivors have neurological deficits.

   (3) Venezuelan EE virus

      (a) Infection rarely causes encephalitis

      (b) Prognosis is usually good, with low mortality rate (0.4%) and rarely with significant neurological deficits.

ii. Flaviviruses

   (A) St. Louis encephalitis virus

      (1) Clinical infection in less than 1%

      (a) Encephalitis (60%)

      (b) Aseptic meningitis (15%)

      (c) Influenza-like illness

      (d) Nonconvulsive status epilepticus may occur more frequently than with other arbovirus infections.
Almost 90% of elderly patients develop encephalitis and have a higher risk of fatal disease.

Diagnosis, St. Louis encephalitis: virus-specific IgM in serum or CSF or PCR

Prognosis: mortality rate is 5% to 15%; 10% of survivors have persistent neurologic dysfunction.

West Nile virus

Human-to-human transmission can occur via organ transplantation, blood transfusion, and other body fluid transmission, including breastfeeding.

Clinical

(a) Usually asymptomatic; less than 1% develop neurological symptoms.
(b) Elderly, immunocompromised, and patients with other medical illnesses are at greatest risk for neurological complications.
(c) Prodrome of fever, malaise, headache, nausea, and vomiting followed by neurological symptoms that can include meningitis, encephalitis (60% of symptomatic cases), myelitis, a polio-like syndrome of acute flaccid paralysis, or extrapyramidal symptoms.

Diagnosis: virus-specific IgM and IgG antibodies in serum and CSF, or CSF PCR. PCR is less sensitive than serology but more specific; useful in immunocompromised patients with weak serological response.

Imaging: in encephalitis, MRI brain fluid attenuation inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) show changes in basal ganglia, thalamus, brainstem, and cerebellum. Spinal MRI shows T2 changes in myelitis.

Electrodiagnostic studies: nerve conduction study and electromyography can demonstrate injury to lower motor neurons in patients with flaccid paralysis.

Prognosis: mortality rate is 5% to 10%; 30% to 40% of survivors have persistent neurologic dysfunction.

Japanese encephalitis virus

Most common arboviral encephalitis worldwide.

Vaccination has reduced incidence.

Most common encephalitis in eastern Asia.

Affects approximately 50,000 persons annually.

Clinical: less than 1% have clinical illness. Headache; fever; anorexia; malaise; convulsions; extrapyramidal, subcortical, or cerebellar signs; coma; symptoms/signs similar to AIDP have been reported.

Diagnosis: virus-specific IgM serology or CSF.

MRI: abnormalities within thalamus, brainstem, basal ganglia, and cerebellum.

Treatment: supportive care only.

Prognosis: mortality rate of 20% to 40% among those with encephalitis; 30% of survivors have persistent neurologic dysfunction.

Bunyaviruses

California (La Crosse) encephalitis virus
348 CLINICAL NEUROLOGY

(A) California (La Crosse) encephalitis virus (cont’d)
(1) Clinical: fever, vomiting, headache, and abdominal pain, with CNS signs 2 to 4 days later; neurological illness occurs mostly in children under age 16; 50% have seizures, including status epilepticus; 20% have focal neurological signs; 10% have aseptic meningitis.
(2) Diagnosis: >4 times increase in virus-specific serology or CSF
(3) Treatment: supportive care only
(4) Prognosis: mortality rate is <1%; rate of CNS sequelae is low.

b. Transmitted by ticks
i. Flavivirus
(A) Powassan encephalitis virus
(1) Rare cause of human encephalitis in United States
(2) Clinical: fever, headache, vomiting, and somnolence followed by cognitive dysfunction, ophthalmoplegia, diffuse or focal weakness, ataxia, and seizures
(3) Diagnosis: virus-specific IgM in CSF or serum and elevations of the virus-specific IgG in convalescent sera
(4) Treatment: supportive care
(5) Prognosis: mortality rate is 10% to 15%; neurological sequelae in 35%.

ii. Orbivirus
(A) Colorado tick fever virus
(1) Clinical: fever, headache, myalgia, anorexia, nausea, and rash (similar to symptoms of Rocky Mountain spotted fever), followed by aseptic meningitis
(2) Treatment: supportive care only
(3) Prognosis: mortality rare

3. Rabies
a. Reservoirs: skunks (most common), dogs, raccoons, and bats
b. Worldwide, 50,000 to 60,000 die annually (but only 1 to 2 per year in United States)
c. Pathogenesis: virus enters peripheral nerves followed by axonal transport of the virus to the cell bodies of neurons, where the virus replicates and disseminates through the CNS.
d. Clinical features
i. Incubation: 1 week to years (shortest after infection to the head and neck), usually 1 to 3 months
ii. Prodrome: headache, malaise, sore throat, nausea/vomiting, and/or abdominal pain
iii. Furious = agitated encephalitis
(A) 80% of human rabies cases
(B) Confusion, anxiety, agitation, hallucinations, dysphagia, hydrophobia, hypersalivation, autonomic hyperactivity, and seizures
(C) Death secondary to muscle spasms involving diaphragm or accessory respiratory muscles that lead to respiratory arrest or coma
iv. Dumb = paralytic encephalitis
(A) Similar course as AIDP; more common with bat virus strains
(B) The most frequent initial symptoms are pain and paresthesias at the site of infection followed by flaccid paralysis of the same extremity and progress to quadriplegia.
(C) Death secondary to respiratory arrest and coma
e. Diagnosis
   i. Neuroimaging: can be normal or show T2 hyperintensities
   ii. Diagnosis confirmed by
      (A) Isolating the rabies virus from saliva
      (B) Pathology
         (1) Negri bodies: eosinophilic intranuclear inclusions in hippocampus and cerebellar Purkinje cells
         (2) Babes nodules: focal microglial nodules
      (C) Serologic responses
      (D) Rabies virus antigen by immunofluorescent staining of full-thickness skin biopsy specimens from the neck
      (E) Rabies virus-specific antibodies can be detected in serum or CSF by day 15.
      (F) PCR in saliva or brain tissues by day 5

f. Treatment
   i. Postexposure prophylaxis
      (A) Begin with cleaning of the wound with soap and water.
      (B) If animal suspected of having rabies, immediately vaccinate with human diploid cell rabies vaccine and consult local public health officials.
   ii. Symptomatic
      (A) Supportive care only
      (B) Place in isolation because rabies virus is present in body fluids.

g. Prognosis: 100% mortality, usually within 2 weeks of onset of symptoms

4. Progressive multifocal leukoencephalopathy (PML)
a. Caused by the John Cunningham (JC) virus
b. Infection is acquired in childhood. About 55% to 85% of adult population is seropositive.
c. Opportunistic CNS infection due to reactivation of latent JC virus in tonsil, bone marrow, and spleen
d. Seen in immunodeficiency (5% of AIDS patients have PML when CD4 <200 cells/microliter), hematologic malignancies, and organ transplantation
e. Seen in patients on immunomodulatory therapy with natalizumab, rituximab, and efalizumab
f. Pathogenesis: reactivation of virus, dissemination to CNS, and infection of oligodendrocytes (demyelination) and astrocytes (neuronal dysfunction)
g. Clinical
   i. Cognitive decline, visual field deficits, cranial neuropathies, sensory deficits, motor deficits, speech disturbances, and ataxia progressing to dementia; headaches, extrapyramidal syndromes, and seizures are rare.
h. Diagnosis
   i. Confirmed by detecting JC virus particles or antigens in brain tissue, isolating the virus from brain, or PCR
   ii. MRI brain: confluent multifocal white-matter lesions with T2 prolongation, typically within cerebral subcortical white matter and brainstem
   iii. Pathology: oligodendrocytes contain eosinophilic intranuclear inclusions; bizarre astrocytes.
4. Progressive multifocal leukoencephalopathy (PML) (cont’d)
   i. Treatment: supportive care; PML lesions may stabilize with improvement of CD4 count with highly active antiretroviral therapy (HAART).
   j. Prognosis: 80% mortality within 9 months

5. Picornaviruses
   a. Enteroviruses
      i. Non-polio enteroviruses (coxsackie, echovirus, human enterovirus 68-71) are the most common cause of aseptic viral meningitis.
      ii. Transmission is primarily feco-oral; sometimes through respiratory droplets.
      iii. Usually occur in late summer and fall

   (A) Polioviruses
      (1) Clinical
         (a) Usually limited symptoms or asymptomatic
         (b) Neurologic manifestations
            (i) Aseptic meningitis (8%)
            (ii) Paralytic poliomyelitis (1%)
               [1] Usually due to poliovirus type 1
               [2] Prodrome of fever, headache, vomiting, myalgia, and meningeal signs
               [3] Acute flaccid paralysis appears within 1 to 2 days due to involvement of alpha motor neurons in the spinal cord.
            (iii) Bulbar poliomyelitis
               [1] Involves the motor CNs of the medulla or pons (usually CNs IX, X, and XI) with dysphagia, dysphonia, and upper airway compromise
            (iv) Polioencephalitis
      (2) Diagnosis
         (a) Confirmation of poliovirus requires isolation from feces, CSF, or throat.
         (b) Detected in feces or CSF with PCR
      (3) Prophylactic
         (a) Salk vaccine
            (i) Inactivated poliovirus vaccine
         (b) Sabin vaccine
            (i) Attenuated, live-virus oral vaccine
            (ii) No longer distributed in the United States
      (4) Acute treatment
         (a) Supportive care
         (b) Immunocompromised: IV immunoglobulin
      (5) Prognosis
         (a) Mortality high (50%)
         (b) Paralytic poliomyelitis: patients frequently recover but may have residual fatigue, myalgia, arthralgia, and muscle weakness and atrophy. Post–polio syndrome is a late complication in 25% of patients due to exacerbation of motor weakness 30 to 40 years after infection.
INFECTIONS OF THE NERVOUS SYSTEM

(B) Non-polio enteroviruses—coxsackievirus and echovirus

(1) Clinical features
   (a) Range from mild febrile illnesses to severe disseminated multiple organ infections. Coxsackievirus B has more complications with involvement of the heart, liver, and CNS.
   (b) Commonly includes pharyngitis, herpangina, pleurodynia, gastroenteritis, neonatal sepsis, or hand-foot-and-mouth disease
   (c) CNS: aseptic meningitis, encephalitis, poliomyelitis-like illnesses, Guillain-Barré syndrome, acute cerebellar ataxia, or opsoclonus-myoclonus
   (d) Echovirus may also produce disseminated intravascular coagulation; 10% present with maculopapular or petechial rash.

(2) Diagnosis
   (a) Isolated from feces, CSF, or throat washings
   (b) Feces, serum, or CSF PCR

(3) Treatment: supportive care only

6. Measles virus—paramyxovirus
   a. Spreads via respiratory droplets
   b. Measles vaccination has been linked with acute encephalopathy and permanent neurologic deficits.
   c. Clinical (CNS involvement)
      i. Acute encephalitis
         (A) Rare
         (B) Begins 2 to 5 days after the rash appears
      ii. Postviral encephalomyelitis
         (A) 1/1,000 cases of measles
         (B) Seen within 2 weeks after rash appears
         (C) Usually <10 y/o
         (D) Headache, irritability, seizures, somnolence, or coma; occasionally paralysis, ataxia, choreoathetosis, or incontinence
         (E) Treatment: supportive care
         (F) Prognosis: mortality = 10% to 15%; neurologic sequelae = 20% to 60%
      iii. Measles inclusion body encephalitis
         (A) Rapidly progressive neurodegeneration
         (B) Develops 1 to 6 months after infection
         (C) Patients usually have deficiency of cell-mediated immunity or are immunocompromised.
         (D) Begins insidiously with dementia, myoclonus, and seizures followed by coma and often death
         (E) Treatment: supportive care, reduction in immunosuppression, passive immunoglobulin therapy
      iv. Subacute sclerosing panencephalitis
         (A) Persistent measles infection in the brain
         (B) Rare late complication 2 to 12 years after infection
         (C) Pathogenesis: defective measles virus maturation in the brain
         (D) Affects young (50% have had measles before 2 y/o); more common in boys
iv. *Subacute sclerosing panencephalitis (cont’d)*

(E) Clinical features

1. Stage 1: behavior and personality changes followed by myoclonus (usually focal)
2. Stage 2: persistent mental status changes with generalization of myoclonus, followed by ataxia, language difficulties, apraxias, and spasticity and chorioretinitis
3. Stage 3: vision loss, worsening myoclonus, ballistic movements, quadriplegia, akinetic mutism
4. Stage 4: coma or persistent vegetative state

(F) Diagnosis

1. Virus-specific IgG in CSF and serum
2. EEG: *bilateral synchronous high-amplitude spike or slow-wave bursts that correlate with myoclonus; EEG progresses to burst-suppression pattern.*
3. Pathology
   a. Patchy demyelination
   b. Intranuclear eosinophilic inclusions

(G) Treatment: supportive care and treatment of clinical symptoms

(H) Prognosis: usually death within 1 to 3 years

7. *Mumps virus—paramyxovirus*
   a. Respiratory spread
   b. Mild illness, parotitis, orchitis
   c. Common cause of aseptic meningitis and encephalitis in unimmunized populations
   d. Immunization with live attenuated vaccine

8. *Rubella virus*
   a. Mild illness in childhood and adults; can cause postviral encephalomyelitis
   b. **Congenital rubella syndrome**
      i. Serious if infection acquired in first trimester
      ii. CNS involvement in 80%
   c. Clinical features
      i. Infants: lethargy, irritability, bulging fontanelle
      ii. Sequelae: mental retardation, cataracts, sensorineural hearing loss, abnormal tone and posture, congenital heart disease
      iii. Progressive rubella panencephalitis: follows congenital or childhood rubella, with neurological deterioration progressing to death in the second decade of life
   d. Diagnosis: prenatal diagnosis possible via amniotic fluid or rubella-specific IgM in fetal blood
   e. Vaccination: with live attenuated virus (measles, mumps, and rubella [MMR] vaccine)

9. *Retroviruses*
   a. Contain an RNA-dependent DNA polymerase (reverse transcriptase) and replicate through a DNA intermediary
   b. **Lentiviruses (HIV-1 or HIV and HIV-2)**
      i. HIV: worldwide about 35 million people were living with HIV/AIDS as of 2013; the incidence of AIDS-defining illness has decreased in countries with access to HAART.
ii. HIV infection of nervous system occurs within 2 weeks of acquiring infection. Clinical manifestations occur based on stage of infection.

(A) Early (CD4 >500/mm³)
   (1) Asymptomatic CSF abnormalities
   (2) Neurological manifestations occur in 10%.
   (3) Seroconversion syndromes: meningitis, meningoencephalitis, seizures, myelopathy, inflammatory demyelinating peripheral neuropathies and cranial neuropathies

(B) Midstage (CD4 200–500/mm³)
   (1) Primary HIV-related disorders: cognitive deficits, meningitis, mononeuritis multiplex, distal sensory polyneuropathy, autonomic neuropathy, inflammatory myopathies
   (2) Opportunistic infections: shingles

(C) Advanced (CD4 <200/mm³)
   (1) Dementia, vacuolar myelopathy, distal symmetrical polyneuropathy, autonomic neuropathy, myopathies
   (2) Opportunistic infections: cryptococcal meningitis, cerebral toxoplasmosis, PML, primary CNS lymphoma

iii. Neurological manifestations of HIV

(A) Aseptic meningitis

(B) HIV-associated neurocognitive disorder (HAND) or AIDS-dementia complex (ADC) or HIV encephalitis
   (1) Most common complication
   (2) Occurs in 20% to 75% of patients with advanced HIV.
   (3) Short-term memory deficit, decreased concentration, bradykinesia, incoordination, gait disturbance, apathy, personality changes
   (4) Can be prevented by early treatment of HIV with HAART

(C) Stroke

(D) Cranial neuropathies

(E) HIV-associated vacuolar myelopathy
   (1) 20% of AIDS patients
   (2) Subacute onset of spastic paraparesis and posterior column involvement
   (3) Spongiform changes with vacuolization of myelin sheath

(F) Acute inflammatory demyelinating polyradiculopathy and chronic inflammatory demyelinating polyradiculopathy: treated with IVIg

(G) HIV-associated lumbosacral polyradiculomyelitis

(H) Distal sensory polyneuropathy: predominantly axonal; due to effects of virus and cytokine upregulation

(I) Mononeuritis multiplex: superimposed infection, lymphomatous infiltration or vasculitis

(J) HIV-associated myopathy: polymyositis

iv. Opportunistic infections and malignancies of the nervous system

(A) Most opportunistic infections are due to reactivation of latent infection.

(B) Reduced incidence since the institution of HAART

(C) Usually CD4 <100/mm³
iv. Opportunistic infections and malignancies of the nervous system (cont’d)

(D) Treatment involves induction phase followed by maintenance therapy and/or secondary prophylaxis to prevent relapse.

(1) Toxoplasma meningoencephalitis
   (a) Affects 5% to 15% of AIDS patients pre-HAART.
   (b) Most common focal infection
   (c) Primary prophylaxis with trimethoprim/sulfamethoxazole, atovaquone, or dapsone
   (d) See other features in Section IX.

(2) Cryptococcal meningitis
   (a) Affects 10% of AIDS patients pre-HAART.
   (b) Primary prophylaxis with fluconazole
   (c) See other features in Section VII.

(3) Progressive multifocal leukoencephalopathy
   (a) AIDS patients: 5% have PML when CD4 < 200 cells/microliter

(4) CMV encephalitis and ventriculoencephalitis
   (a) Usually only when CD4 < 50 cells/microliter
   (b) 2% of all neurological complications pre-HAART
   (c) Death within weeks to months
   (d) Prophylaxis with ganciclovir, foscarnet, or cidofovir if prior CMV retinitis

(5) CMV polyradiculomyelitis
   (a) Presents with lower extremity pain, weakness, sensory symptoms, areflexia, and sphincter dysfunction
   (b) Evolves over days

(6) Neurosyphilis
   (a) Recent increase in incidence due to HIV

(7) CNS tuberculosis

(8) Other causes of meningitis and meningoencephalitis: *Salmonella typhi*, *Pneumococcus pneumonia*, *Nocardia*, *Listeria*, *Bartonella*, *Histoplasma*, *Coccidioides*, *Candida*, *Blastomyces*, varicella zoster, *Trypanosoma*, and *Acanthamoeba*

(9) Primary CNS lymphomas (PCNSLs)
   (a) 5% of AIDS patients
   (b) Second most common focal CNS lesion in AIDS
   (c) B-cell type
   (d) Associated with Epstein–Barr virus
   (e) Clinical: focal neurological symptoms over weeks to months
   (f) Diagnosis:
      (i) CSF PCR for EBV, monoclonal B lymphocytes in CSF flow cytometry
      (ii) Imaging characteristics: can be solitary, usually uniform contrast enhancement with surrounding edema and mass effect; more likely to “cross the midline” and involve periventricular and deep white matter (as opposed to toxoplasmosis, in which lesions tend to be multiple, with heterogeneous or ring enhancement); Single-photon emission computed tomography (SPECT) and PET also with greater uptake than toxoplasmosis
(iii) Brain biopsy for definitive diagnosis

(g) Treatment:
(i) Steroids “melt” away lesions, but without long-term improvement in prognosis, should be given after biopsy. Treatment improves edema and mass effect.

(ii) Palliative radiation therapy

(iii) Use of HAART improves overall prognosis.

v. Diagnosis:
(A) HIV Ag/Ab combination immunoassay; if positive, followed by antibody differentiation tests, HIV nucleic acid tests, Western blot, or immunofluorescence assay
(B) CD4 count and viral load to monitor response to therapy

vi. Treatment:
(A) HAART protocol: two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a nonnucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir)

(B) Neurological complications of HAART

1. Nucleoside analog–associated toxic neuropathy
   (a) Major dose-limiting complication of didanosine, zalcitabine, and stavudine
   (b) Painful polyneuropathy similar to distal symmetric polyneuropathy
   (c) Seen in weeks following initiation of therapy, distal sensory polyneuropathy (DSPN) progresses over months
   (d) Stopping the offending agent stops progression or causes regression of symptoms.
   (e) Preexisting DSPN increases risk.

2. Zidovudine myopathy
   (a) Proximal muscle weakness and myalgia similar to HIV myopathy
   (b) Due to mitochondrial toxicity from zidovudine
   (c) Develops after about 6 months of therapy
   (d) Symptoms improve with discontinuing medication.

Summary of Neurologic Complications of HIV

<table>
<thead>
<tr>
<th>MUSCLE</th>
<th>HIV myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zidovudine myopathy</td>
</tr>
<tr>
<td>NERVE AND NERVE ROOTS</td>
<td>HIV distal sensory polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral drug toxic polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>CMV polyradiculopathy</td>
</tr>
<tr>
<td></td>
<td>CIDP</td>
</tr>
<tr>
<td></td>
<td>HIV or HZV cranial neuropathy</td>
</tr>
<tr>
<td></td>
<td>HIV or CMV mononeuropathy multiplex</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>HIV vacuolar myelopathy</td>
</tr>
<tr>
<td></td>
<td>Myelitis due to VZV, HSV, CMV, Toxoplasma</td>
</tr>
</tbody>
</table>

(continued)
### Summary of Neurologic Complications of HIV (cont’d)

| MENINGES                                      | HIV meningitis                  |
|                                               | Neurosyphilis                    |
|                                               | Tuberculous meningitis          |
|                                               | Cryptococcal meningitis         |
| **BRAIN—FOCAL**                               | Bacterial abscess from atypical organisms |
|                                               | HIV-associated stroke           |
|                                               | Toxoplasmic encephalitis        |
|                                               | Primary CNC lymphoma            |
|                                               | PML                            |
| **BRAIN—DIFFUSE**                             | HIV-associated dementia         |
|                                               | Postinfectious encephalomyelitis|
|                                               | CMV encephalitis                |
|                                               | VZV encephalitis                |

9. **Retroviruses (cont’d)**
   
   c. **Oncoviruses**
   
   i. **Human T-cell leukemia virus type 1**
   
   (A) Clinical features
   
   (1) Neurological: progressive myelopathy of lower thoracic segments (only 0.25% of human T-cell leukemia virus type 1 infections)
   
   (a) Progressive spastic paraparesis
   
   (b) Urinary incontinence
   
   (c) Variable sensory loss
   
   (2) Nonneurological: uveitis, infective dermatitis, T-cell lymphoma and leukemia
   
   (3) Female-to-male ratio of 3:1
   
   (B) Diagnosis
   
   (1) Human T-cell leukemia virus type 1–specific IgG in serum or CSF
   
   (2) PCR (666)
   
   (C) Transmission via contact with body fluids, sexual transmission, IV drug use, and vertical transmission
   
   (D) Treatment: symptomatic treatment; corticosteroids may produce some improvement.

### III. Encephalitis

A. **Viral encephalitis** (See Section II for specific infections.)

B. **Encephalitis due to Rickettsial disease**

   1. Infection acquired by the bite or inoculation of infected vector feces into the skin or mucous membranes
   
   2. Clinical: initial fever, headache, and malaise followed by rash and neurological symptoms
   
   3. Diagnosis: serology, PCR and immunohistochemical analysis may be helpful.
4. Treatment: immediate empiric treatment with doxycycline

<table>
<thead>
<tr>
<th>Rickettsial Disease</th>
<th>Organism</th>
<th>Vector</th>
<th>Animal Reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemic typhus</td>
<td><em>Rickettsia prowazekii</em></td>
<td>Body louse, tick</td>
<td>Humans</td>
</tr>
<tr>
<td>Endemic typhus</td>
<td><em>Rickettsia typhi</em></td>
<td>Flea</td>
<td>Rodents</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td>Wood tick, <em>D. andersoni</em></td>
<td>Rodents</td>
</tr>
</tbody>
</table>

a. *Typhus group*: epidemic typhus, endemic typhus
   i. Neurological symptoms: agitated delirium associated with pyramidal tract signs and neck stiffness followed by seizures and brainstem dysfunction
   ii. May die in week 2 due to peripheral vascular collapse

b. *Spotted fever group*: Rocky Mountain spotted fever
   i. Neurologic: headache with agitation followed by progressive lethargy, stupor, and coma; may also develop transverse myelitis, sensory neuropathy, or AIDP-like syndromes
   ii. Other systems: thrombocytopenia, hyponatremia, increased liver function tests and creatinine, myocarditis

c. *Other Rickettsial diseases—Q fever*
   i. Caused by *Coxiella burnetii*
   ii. Spreads from animals to humans by inhalation of the infected dust or by handling infected animals; primarily an occupational disease, mainly affecting shepherds and farmers
   iii. Neurologic: rare but may cause severe encephalitis similar to HSV; optic neuritis, CN palsies, AIDP, and *aseptic* meningitis
   iv. Other systems: lungs, liver (hepatitis), heart (myocarditis or endocarditis)

IV. Abscess

A. Brain abscess

1. Pathophysiology
   a. Source of infection
      i. Direct extension of sinusitis (40%); otitis, facial infection, or dental infection (5%)
      ii. Generalized septicemia (30%): usually multiple abscesses; seen in pulmonary infections, bacterial endocarditis
      iii. Cryptogenic (20%–25%)
      iv. Penetrating trauma, post-craniotomy
      v. Meningitis
   c. Initial cerebritis followed by central necrosis with surrounding vasogenic edema followed by capsule formation

2. Clinical features
   a. Onset of subacute cases within 1 month of initial manifestation
   b. Fever, headaches, neck stiffness, focal neurological signs (two-thirds of cases), seizures (one-third of cases), altered mentation

© Demos Medical Publishing
CLINICAL NEUROLOGY

2. Clinical features (cont’d)
   c. Complications usually arise from increased ICP or abscess rupture, particularly into the ventricles, causing an empyema
   d. Immunocompromised patients and patients with congenital heart disease more susceptible

3. Diagnostic procedures
   a. CT/MRI: ring-enhancing lesion with surrounding edema
   b. Lumbar puncture not done due to risk of herniation and/or rupture of abscess

4. Treatment
   a. Antibiotics: third-generation cephalosporin with metronidazole and vancomycin if *Staphylococcus* suspected
   b. CT-guided stereotactic aspiration or surgical excision

5. Other types of brain abscess—*toxoplasmosis, candida, and aspergillus*

B. Cranial epidural abscess
   1. Source of infection: local spread from cranial infection or after trauma or surgery
   2. Common organisms: *S. aureus*, aerobes, anaerobes, and gram-negative bacteria
   3. Clinical: fever, headache, unilateral focal neurological signs and symptoms
   4. Diagnosis: epidural collection on CT and MRI; increased T1 and T2 signal and dural enhancement
   5. Treatment: surgical drainage and antibiotics

C. Subdural empyema
   1. Source of infection: local spread from cranial infection
   2. Common organisms: microaerophilic, aerobic, and anaerobic streptococci
   3. Clinical: fever, headache, unilateral signs, encephalopathy due to raised ICP, seizures
   4. Diagnosis: crescent-shaped collection on CT and MRI; increased T1 and T2 signal
   5. Treatment: surgical drainage and antibiotics

D. Spinal epidural abscess
   1. Source of infection: local spread from cranial infection or after trauma or surgery
   2. Common organisms: *S. aureus*, aerobes, anaerobes, and gram-negative bacteria
   3. Clinical: fever, headache, unilateral focal neurological signs and symptoms
   4. Diagnosis: epidural collection on CT and MRI; increased T1 and T2 signal with marked dural enhancement
   5. Treatment: surgical drainage and antibiotics

V. Other Bacterial Infections of the Nervous System

A. Botulism
   1. Pathophysiology
      a. Caused by the neurotoxins of gram-positive spore-forming anaerobes *Clostridium botulinum* and, in rare cases, *Clostridium butyricum* and *Clostridium baratii*
      b. Eight distinct type of botulism toxins; neurotoxins types A, B, and E are most frequently responsible for disease in humans, whereas types F and G have been reported only occasionally.
c. Mechanism:
   i. Irreversible binding to the presynaptic membrane of cholinergic nerve endings in the neuromuscular junction, parasympathetic and sympathetic ganglia
   ii. Toxin is internalized.
   iii. Cleaves SNAP-25 (A, C, E), synaptobrevin (B, D, F, G) and syntaxin (C) required for neuroexocytosis of acetylcholine

d. Three forms
   i. Food-borne botulism—associated with home-canned vegetables
   ii. Wound botulism— injection drug use and trauma
   iii. Infant botulism— most common type, ages 1 week to 11 months; type A and B

2. Clinical features
   a. Adult botulism:
      i. Symptoms 12 to 38 hours after ingestion of food due to ingestion of preformed toxin
      ii. Descending weakness from cranial nerves (ptosis, diplopia, blurred vision, dysphagia, and dysarthria) to proximal muscles, including respiratory muscles
      iii. Autonomic symptoms: dilated pupils, dry mouth, urinary retention, ileus, vomiting, abdominal cramping, constipation
   b. Infant botulism:
      i. Ingestion of pathogenic spores with slow production of toxins in the gastrointestinal (GI) tract
      ii. Constipation, lethargy, hypotonia, poor sucking, weak cry, poorly reactive pupils, respiratory distress
      iii. Most patients recover completely within 6 months.

3. Diagnosis
   a. Clinical exam
   b. Electrodiagnostic tests
      i. Nerve conduction study: normal to mildly reduced compound muscle action potential (CMAP)
      ii. Repetitive stimulation: abnormal incremental response
      iii. Single-fiber electromyography (EMG): jitter and blocking
   c. Tensilon® (edrophonium chloride) test: false positive in 30% cases

4. Treatment
   a. Supportive care
   b. Antitoxin: human-derived botulinum immunoglobulin for infants and equine serum botulism antitoxin for children older than 1 year and adults
   c. Antibiotics: penicillin G or metronidazole may be helpful in eradicating C. botulinum in wound botulism, after antitoxin has been administered.

B. Brucellosis (Malta fever)

1. Pathophysiology and epidemiology
   a. Facultative intracellular bacilli of the genus Brucella (B. melitensis, B. abortus, B. suis, and B. canis)
   b. Disease of domestic animals transmitted to humans by close contact with infected animals (through skin abrasions), by contaminated aerosols, or by consumption
B. Brucellosis (Malta fever) (cont’d)

2. Pathology
   a. Systemic: primary involvement of lymph nodes, spleen, and bone marrow, but almost every organ may be involved.
   b. Neuropathology: granulomas, demyelination, thickening of leptomeninges, angiitis, mycotic aneurysms, and degeneration of anterior horn cells

3. Clinical features
   a. Systemic: chills, fever, headache, generalized weakness, muscle pain, and arthralgias with lymphadenopathy
   b. Neurologic: 5% of patients
      i. Usually acute encephalitis with drowsiness, seizures, and signs and symptoms of increased ICP
      ii. Mononeuritis, acute inflammatory polyradiculoneuritis

4. Diagnosis: brucella microagglutination test; identification in blood or CSF

5. Prevention: avoid consumption of undercooked meat and unpasteurized dairy products.

6. Treatment: doxycycline (200 mg/day) plus rifampin (600–900 mg/day); longer duration for neurological involvement

C. Leprosy (Hansen’s disease)

1. Pathophysiology and epidemiology
   a. Caused by Mycobacterium leprae (obligate intracellular acid-fast bacillus)
   b. Transmitted by skin-to-skin contact or through nasal secretions of infected individuals
   c. M. leprae only replicates in body areas where the temperature is low (i.e., skin, distal peripheral nerves).

2. Clinical: differences in the host’s susceptibility to infection result in marked differences in the severity of disease.
   a. Tuberculoid
      i. Intense cell-mediated immune reaction at the portal of entry reduces organism proliferation but causes circumscribed acute peripheral nerve and skin damage.
      ii. Skin lesions: well demarcated hypopigmented anesthetic lesions on face, arm, chest
      iii. Thickened nerves and asymmetric neuropathy: ulnar = claw-hand, radial = wristdrop, peroneal = footdrop, and/or facial nerves
   b. Borderline forms: borderline tuberculoid, borderline intermediate and borderline lepromatous
   c. Lepromatous
      i. Do not mount an adequate immune reaction and more generalized
      ii. Skin lesions poorly demarcated
      iii. Thickened nerves and peripheral neuropathy with symmetric loss of pain and temperature sensations in the distal portions of the extremities and relative preservation of deep sensation
      iv. Anesthetic hands are prone to repeated trauma and infection, leading to ulcerated skin lesions, bone destruction, finger loss, and deformities.
      v. Trigeminal nerve involvement leads to facial hypoalgesia with associated corneal ulcerations and blindness.

3. Diagnosis: identification of M. leprae in skin smears, full-thickness edge biopsy of active skin lesions, nasal smear or peripheral nerve biopsy
4. Treatment: multidrug therapy (MDT)
   a. Paucibacillary: rifampin (600 mg/day) and dapsone (100 mg/day) for 6 months
   b. Multibacillary: clofazimine (50–300 mg/day), rifampin (600 mg/day), and dapsone (100 mg/day) for 2 years

D. Tuberculosis

1. Pathophysiology and epidemiology
   a. Causative organism: gram-positive aerobic bacterium *Mycobacterium tuberculosis*
   b. Transmission: droplet infection, hematogenous spread to extrapyramidal sites
   c. Increased incidence due to HIV

2. Neurological manifestations
   a. Subacute to chronic meningitis:
      i. Most common CNS presentation
      ii. Usually basilar meningitis causing fever, headache, neck stiffness, cranial neuropathies, and altered mentation; seizures can also occur.
      iii. Complications: hydrocephalus and strokes due to vascular involvement of leptomeningeal inflammation.
   b. Parenchymal tuberculosis:
      i. Tuberculoma (central caseating necrosis with collagenous capsule of mononuclear inflammatory cells) or tuberculoid abscess (liquefactive necrosis with neutrophilic infiltrate)
      ii. Cerebral or cerebellar parenchyma and deep gray matter
      iii. Causes headaches, focal neurological deficits, seizures, papilledema, increased ICP
      iv. Very rarely causes tuberculous encephalopathy with diffuse edema and extensive demyelination
   c. Spinal tuberculous meningitis
      i. Rare, causes subacute or chronic radiculomyelitis
   d. Spinal tuberculomas—intramedullary lesions causing myelopathy

3. Diagnosis:
   a. Tuberculin skin test followed by further testing if positive; blood tests—interferon gamma release assays (QuantiFERON® TB Gold In-Tube test or T-SPOT®).
   b. CSF in tuberculous meningitis:
      i. Lymphocytic pleocytosis, decreased glucose and increased protein
      ii. CSF PCR: sensitivity = 54% to 100%; specificity = 94% to 100%
      iii. CSF amplified *M. tuberculosis* direct test—nucleic acid test, rapidly available
      iv. CSF tests may be negative in only parenchymal disease.
   c. Neuroimaging
      i. Meningitis: meningeal enhancement of the basal cisterns
      ii. Tuberculomas: isointense on T1, central hyperintensity on T2 with ring enhancement and surrounding edema; calcifications in mature lesions
c. Neuroimaging (cont’d)
   iii. Radiculomyelitis: meningeal enhancement; clumping and enhancement of nerve roots
   iv. Pott’s disease: hypointense marrow on T1 with hyperintensity on T2, enhancement of dura, discs; epidural or paraspinal fluid collection; may have evidence of cord compression

4. Treatment:
   a. Antituberculous therapy
      i. Intensive phase for 2 months with isoniazid, rifampin, pyrazinamide, and either fluoroquinolone or injectable aminoglycoside
      ii. Continuation phase for 9 to 12 months with isoniazid and rifampin
   b. Glucocorticoids: controversial in treatment of tuberculous meningitis
   c. Surgical treatment:
      i. Surgical decompression in hydrocephalus
      ii. Surgical resection of tuberculoma if diagnosis uncertain or if poor response to medical management
      iii. Spine surgery if progressive symptoms, instability, or poor response to medical management

E. Rheumatic fever
1. Causative organism: Group A β-hemolytic streptococci
2. Clinical features
   a. Systemic: 1 to 5 weeks after an acute episode of streptococcal pharyngitis; acute migratory polyarthritis, subacute/chronic carditis, subcutaneous nodules and erythema marginatum, congestive heart failure, and valvular heart disease
   b. Neurologic complications
      i. Delirium, seizures
      ii. Embolic stroke due to valvular disease
      iii. Sydenham’s chorea:
         (A) Occurs in children, female-to-male ratio of 2:1.
         (B) Usually months after initial infection
         (C) Symptoms: chorea, ballismus, hypotonia, and dysarthria; psychiatric symptoms of irritability, emotional lability, obsessive-compulsive symptoms
         (D) Treatment: oral corticosteroids; valproate and carbamazepine; pimozide or haloperidol if refractory

F. Whipple’s disease
1. Pathophysiology
   a. Caused by Tropheryma whippelii
   b. Impaired cell-mediated immunity
   c. Pathology: infiltration of tissues with foamy macrophages containing periodic acid–Schiff-positive bacilli in the cytoplasm (rectal or jejunal biopsy)
2. Clinical features
   a. Systemic: chronic migratory arthralgias; GI tract involvement—abdominal pain, diarrhea with steatorrhea, weight loss; cutaneous hypopigmentation; adrenal insufficiency
   b. Neurological manifestations in 10% to 15% (can present with isolated CNS symptoms)
i. Triad
   (A) Slowly progressive dementia
   (B) Supranuclear vertical-gaze palsy
   (C) Myoclonic jerks

ii. Other manifestations
   (A) Oculomasticatory myorhythmia (OMM) and oculofacial-skeletal myorhythmia (OFSM): seen in 20% of cases, pathognomonic of Whipple's disease
      (1) Due to hypothalamic involvement
      (2) Pendular vergence oscillations of the eyes with synchronous rhythmic contractions of the masticatory muscles; can involve proximal and distal skeletal muscles
   (B) Meningitis
   (C) Dysarthria, ataxia
   (D) Deafness, tinnitus
   (E) Seizures
   (F) Visual field loss, motor deficits
   (G) Neuropathy
   (H) Myopathy

3. Diagnosis:
   a. Periodic acid–Schiff-positive macrophage inclusions in biopsy of gastrointestinal (GI) tract
   b. CSF PCR for T. whippelii DNA if suspected

4. Treatment
   a. Antibiotics: penicillin G (12–24 million u/day) and ceftriaxone (50–100 mg/kg/day) for 2 to 4 weeks in the initial phase followed by trimethoprim (320 mg) and sulfamethoxazole (1,600 mg) for 1 year in the maintenance phase
   b. Symptomatic treatment of myoclonus, OMM, OFSM: valproate and benzodiazepines

VI. Spirochete Infections of the Nervous System

A. Lyme disease

1. Pathophysiology
   a. Caused by Borrelia burgdorferi
   b. Vector: deer tick Ixodes dammini
   c. Early summer most common

2. Clinical features
   a. Primary stage (within 4 weeks of tick bite): erythema chronicum migrans, constitutional symptoms
   b. Secondary stage (weeks after rash): systemic with cardiac arrhythmias, arthralgia, lymphadenopathy; neurological manifestations:
      i. Aseptic meningitis
      ii. Encephalitis
      iii. Cranial neuropathy—most commonly lower motor neuron (LMN) facial nerve palsy, unilateral or bilateral
      iv. Mononeuritis multiplex, peripheral neuropathy, polyradiculopathy, AIDP
   c. Tertiary stage (months after secondary): neuropathy, encephalomyelitis, dementia
A. Lyme disease (cont’d)

3. Diagnosis: enzyme immunoassay or immunofluorescence assay, if equivocal or positive test for serum antibodies; CSF antibodies for neuroborreliosis; MRI may show leptomeningeal enhancement.

4. Treatment of neuroborreliosis: IV ceftriaxone or penicillin G for 2 to 4 weeks

B. Syphilis

1. Pathophysiology
   a. Caused by *Treponema pallidum*
   b. Transmitted by sexual contact and vertical transmission

2. Clinical
   a. Primary syphilis: painless genital chancre with asymptomatic systemic spread
   b. Secondary syphilis:
      i. 2 to 12 weeks after exposure
      ii. Systemic dissemination with constitutional symptoms, lymphadenopathy, and rash
      iii. Syphilitic meningitis and cranial neuropathies
   c. Latent phase: asymptomatic
   d. Tertiary syphilis: cardiovascular and delayed neurological complications of tabes dorsalis or dementia

3. Neurological manifestations <10%
   a. Meningeal and meningovascular syphilis
      i. Meningeal invasion with endarteritis obliterans and vasculitis, causing strokes
      ii. Usually occurs in 4 to 7 years
   b. Tabes dorsalis
      i. Myelopathy symptoms: areflexia, loss of pain and temperature, sensory ataxia, and Charcot’s joints
   c. Parenchymatous syphilis
      i. Encephalitic form with progressive dementia, psychiatric disorders, speech disturbance, pupillary abnormalities (Argyll–Robertson pupils—accommodation present; light reflex absent)

4. Diagnosis
   a. Use both serum nontreponemal and treponemal tests to avoid false positives.
   b. Nontreponemal tests: Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR)
   c. Treponemal tests: fluorescent treponemal antibody absorbed (FTA-ABS), *Treponema pallidum* particle agglutination assay (TP-PA), syphilis enzyme immunoassay (EIA), immunoblot, or rapid assays
   d. If serum test is positive and neurosyphilis suspected, CSF VDRL should be done.
   e. CSF lymphocytic pleocytosis and/or elevated protein should be treated as neurosyphilis even when CSF VDRL is negative if serum tests are positive.

5. Treatment of neurosyphilis
   a. IV penicillin G 4 million units q 4 hours for 14 days
   b. Repeat CSF analysis to assess response to therapy.
VII. Fungal Infections of the Nervous System

A. Cryptococcosis

1. Pathophysiology
   a. Caused by *Cryptococcus neoformans*
   b. Spread by respiratory droplet; found in soil and bird feces
   c. Opportunistic infections of cell-mediated immunity (AIDS, lymphoreticular malignancy, chronic steroids)
   d. Most common CNS fungal infection

2. Clinical
   a. Chronic basilar meningitis
      i. Fever, headache, neck stiffness, encephalopathy, behavioral changes, seizures, cranial neuropathies due to basilar meningitis
      ii. Complications: infarctions, hydrocephalus
   b. Cryptococcomas, gelatinous pseudocysts: focal neurological deficits

3. Diagnosis:
   a. CSF
      i. Elevated CSF opening pressure, lymphocytic pleocytosis, increased protein and low glucose
      ii. CSF and serum cryptococcal capsular polysaccharide antigen, CSF fungal cultures (high sensitivity and specificity)
   b. MRI brain:
      i. Leptomeningeal enhancement in meningitis
      ii. “Soap bubble” appearance of gelatinous pseudocysts with hypointense/indeterminate on T1 and FLAIR, hyperintense on T2
      iii. Cryptococcomas: hypointense on T1, hyperintense on T2 and FLAIR with variable enhancement

4. Treatment
   a. Antibiotics
      i. Amphotericin B (0.7 mg/kg/day) plus flucytosine (100 mg/kg/day) for 2 weeks, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for 8 weeks
      ii. Long-term maintenance therapy with fluconazole to prevent recurrence
   b. Surgical management for hydrocephalus

B. Aspergillosis

1. Pathophysiology
   a. *Aspergillus fumigatus* (85%–90% of cases): septated hyphae
   b. Acquired by inhalation of airborne spores
   c. CNS infection by hematogenous spread or through contiguous structures
   d. May occur in immunocompetent hosts but usually opportunistic infection
   e. Pathology: angioinvasive hyphae in blood vessels, causing inflammation and necrosis

2. Clinical
   a. *Aspergillus meningitis* with cranial neuropathies (rare)
   b. Vasculitis due to angioinvasion, causing strokes and parenchymal and subarachnoid hemorrhages
2. Clinical (cont’d)
   c. Parenchymal disease, causing granulomas and abscesses
   d. Multiple organs involved
   e. Mortality: 80% to 90%
3. Imaging: CT/MRI—mass lesions with minimal mass effect or contrast enhancement
4. Treatment:
   a. IV voriconazole with liposomal amphotericin or posaconazole for secondary therapy
   b. Consider resection for diagnosis and/or treatment.
C. Candidiasis
1. Pathophysiology
   a. Various species of Candida
   b. Typically opportunistic infection
   c. Most cases of CNS candidiasis are caused by Candida albicans.
2. Neurologic
   a. Meningitis
   b. Parenchymal microabscesses
   c. Granulomas
   d. Angioinvasive, causing infarcts and subarachnoid and parenchymal hemorrhages
3. Treatment: induction of IV lipid-formulation amphotericin with or without fluconosine intravenously for several weeks followed by maintenance with fluconazole until resolution of imaging and CSF abnormalities
D. Coccidioidomycosis
1. Pathophysiology
   a. Caused by Coccidioides immitis
   b. Inhabits dry acidic soil endemic in southwestern United States
   c. Inhalation of arthroconidia that is transformed into nonbudding spherules composed of hundreds of endospores
   d. Elicits a caseating granulomatous reaction
   e. CNS involvement occurs in <1%
2. Neurologic: arachnoiditis, chronic basilar meningitis, brain abscesses
3. Diagnosis: serum and CSF enzyme-linked immunosorbent assay (ELISA) and CSF complement fixation
4. Treatment:
   a. Oral fluconazole or itraconazole with or without intrathecal amphotericin B followed by lifelongazole therapy after normalization of CSF
   b. Surgical management for hydrocephalus
E. Mucormycosis (zygomycosis)
1. Pathophysiology
   a. Rhizopus arrhizus (90% of cases with CNS involvement)
   b. Inhabits soil, plants, and certain foods in a mold form
   c. Infection acquired by the inhalation of airborne spores or through direct inoculation of fungi into subcutaneous tissue or bloodstream
   d. Risk factors: diabetic ketoacidosis or acidemia from other causes, malignancies, immunosuppression, organ transplant, iron chelation therapy
   e. Pathology: broad hyphae invade arteries and veins, causing tissue necrosis.
2. Clinical
   a. Rhinocerebral form usually begins with fever and a painful swelling of the nose and fronto-orbital area, which rapidly progresses to the striking necrotic lesions.
   b. Sinusitis
   c. Orbital cellulitis
   d. Vascular thrombosis with stroke
   e. Venous sinus thrombosis, most frequently cavernous sinus
   f. Focal CNS involvement via direct extension of infection
   g. Usually fatal disease
3. Treatment
   a. Surgical debridement of necrotic tissue
   b. Amphotericin B, 1.5 mg/kg/day intravenously, for a total dose of 1.0 to 1.5 g; renal function and serum potassium levels should be closely monitored.

F. Blastomycosis
1. Pathophysiology
   a. Caused by Blastomyces dermatitidis
   b. Infection acquired by inhalation of spores found in soil and vegetation in Mid-west United States
   c. Can cause disease readily in immunocompetent host
   d. Pathology: affects lungs, skin, bones, retina, urinary tract, and CNS (25% of patients)
2. Clinical
   a. Systemic: nonspecific fever, malaise
   b. Neurologic in one-third of disseminated disease
     i. Meningitis with neutrophilic pleocytosis
     ii. Blastomycomas/abscess in brain or spine
     iii. Cranial neuropathies due to skull-base lytic lesions; vertebral osteolytic lesions
3. Treatment: induction with IV liposomal or standard amphotericin for 4 to 6 weeks followed by maintenance therapy with oral azole for >12 months and resolution of CSF abnormalities

G. Histoplasmosis
1. Pathophysiology
   a. Caused by Histoplasma capsulatum
   b. Acquire the infection by inhalation of aerosolized contaminated soil or bird and bat droppings; endemic in Mississippi and Ohio River valleys
   c. Usually self-limiting
2. Clinical
   a. Systemic: hepatosplenomegaly, lymphadenopathy, diffuse pulmonary infiltrates, mucosal ulcerations
   b. Neurologic: subacute meningitis and abscesses
3. Diagnosis: CSF Histoplasma polysaccharide antigen test
4. Treatment: induction with IV lipid-formulation amphotericin for 4 to 6 weeks followed by maintenance therapy with oral azole for >12 months and resolution of CSF abnormalities, including Histoplasma antigen
VIII. Prion Infections of the Nervous System

- Incidence of human prion disease (PrD) is 1 to 1.5 per 1,000,000/ year.
- Normal cellular prion protein $PrP^C$ is transformed to $PrP^S$.
- 85% = sporadic; 10% to 15% = genetic; <1% = acquired
- Sporadic Creutzfeldt–Jakob disease (sCJD)
- Genetic prion disease (gPrD) occurs due to mutation of PRNP gene encoding prion protein PrP.
  - The three clinico-pathological forms are familial CJD (fCJD), Gerstmann–Staüssler–Scheinker syndrome (GSSS), and fatal familial insomnia (FFI).
  - Mostly autosomal dominant
  - Younger age at onset
  - Insidious course
- Iatrogenic form: cadaver-derived growth hormone, corneal transplants, neurosurgical procedures
- New variant CJD: transmitted from ingestion of cattle products contaminated with agent of bovine spongiform encephalopathy

A. Creutzfeldt–Jakob disease (CJD)

1. Clinical features of sCJD
   a. Usual age at onset is 60s.
   b. Rapidly progressive dementia, neuropsychiatric features, cerebellar ataxia, and myoclonus
   c. $\geq 90\%$ mortality within 1 year
2. Diagnosis
   a. Definitive diagnosis: detecting CJD-specific mutations by prion gene analysis
   b. 14-3-3 protein in CSF: in the appropriate setting, 94% sensitivity and 93% specificity
   c. Pathology: diffuse spongiform encephalopathy with widespread neuronal loss, gliosis, and amyloid plaques
   d. EEG: 80% periodic sharp wave complexes by 12 weeks, which evolve to diffuse slowing
   e. MRI: increased T2 signal in basal ganglia and thalamus; in some CJD variants can see pulvinar sign. Hyperintensity in anterior putamen and caudate head is known as the hockey-stick sign.
   f. May show cortical ribboning in diffusion-weighted MRI in parietal, occipital, or temporal regions

B. Gerstmann–Staüssler–Scheinker syndrome

1. Clinical features
   a. Begins in third to fourth decade
   b. Slowly progressive over 3 to 8 years
   c. Subacute progressive ataxia/parkinsonian disorder with later-onset cognitive impairment
   d. Mortality within 1 to 10 years
2. Diagnosis
   a. EEG: diffuse slowing
   b. MRI: cerebellar atrophy or T2 prolongation involving the basal ganglia (iron deposition)
c. Confirmed by detection of prion gene mutations; P102L is most common
d. Pathology: spongiform changes are seen; Kuru-like plaques in cerebellum and other areas.

C. Fatal familial insomnia

1. Clinical features
   a. Progressive insomnia, sympathetic hyperactivity, and mental status changes
   b. Typically begins between ages 30 and 60
   c. Death within 6 to 36 months of onset
   d. Loss of circadian rhythm with insomnia to ≈<2 hours; behavioral changes, including inattention, poor concentration and memory, hallucinations; dementia is rare. Later, myoclonus, ataxia, spasticity, and parkinsonian features can be seen. Endocrine disturbances are also seen.
   e. Neurophysiologic and polysomnographic features
      i. EEG: diffuse slowing
      ii. Polysomnography: physiologic sleep is absent or decreased to only a few minutes’ duration; brief REM sleep may occur but usually has incomplete muscle atonia and may have dream-enacting behavior late in course; myoclonic jerks may accompany periodic slow waves (similar to CJD).

2. Diagnosis
   a. MRI: normal
   b. Fluorodeoxyglucose (FDG) PET: thalamic and cingulate hypometabolism
   c. Pathology: spongiform degeneration with severe neuronal loss and reactive gliosis in anterior and dorsomedial thalamic nuclei
   d. DNA: single-point mutation of PRNP (prion protein) D178N/129M

D. Kuru

1. Pathophysiology and epidemiology
   a. Tribes in New Guinea (particularly in women and children) secondary to consumption of brain and/or mucosal and cutaneous contact with neural tissues
   b. Long incubation period (>5–20 years)
   c. Genetics: homozygosity for methionine at codon 129 is a risk factor.

2. Clinical
   a. Dysarthria, gait ataxia, truncal instability, titubation and postural
   b. Emotional lability, psychomotor retardation, and uncontrollable laughter

3. Diagnosis/pathology: neuronal loss highest in cerebellum, basal ganglia, thalamus, and mesial temporal lobes; PrPSc reactive plaques called Kuru plaques at highest density in the cerebellum.

4. Prognosis: death within 1 year

IX. Parasitic Infections of the Nervous System

A. Primary amebic meningoencephalitis

1. Caused by Naegleria fowleri that inhabits soil and water (especially warm climates)
2. Infections are linked to freshwater swimming between July and August
3. Enters the nasal cavity and migrates through cribriform plate via olfactory nerves to the frontal lobes
A. Primary amebic meningoencephalitis (cont’d)

4. Pathology: purulent meningitis with microabscesses and extensive necrotizing destruction of parenchyma

5. Clinical:
   a. Severe headache, fever, nausea, vomiting, meningeal signs, seizures, hallucinations, altered consciousness progressing to coma
   b. Rapidly progressive, with mortality > 97%

6. Diagnosis:
   a. CSF shows elevated opening pressure, neutrophilic pleocytosis, increased protein, and decreased glucose.
   b. Motile trophozoites in CSF on wet mount; negative Gram stain

7. Treatment: supportive only

B. Cerebral amebiasis

1. Caused by *Entamoeba histolytica*
   a. Common intestinal parasite
   b. Infects almost 10% of the world population, causing 100,000 deaths every year
   c. May become aggressive and enter the bloodstream to cause systemic disease and CNS involvement; can cause amebic brain abscess.

2. Clinical: fever, altered mentation, focal neurological signs, seizures

3. Diagnosis:
   a. Parasites in fresh-mount preparations of stool
   b. Antibody detection useful in extraintestinal disease—EIA test

4. Treatment
   a. Metronidazole or tinidazole followed by paromomycin or iodoquinol
   b. Surgical resection of accessible lesions

C. Toxoplasmosis

1. Caused by *Toxoplasma gondii* (intracellular parasite)

2. Humans are infected by eating undercooked meat or by ingestion of contaminated cat feces.

3. Seropositive in 30% to 75% of the general population, varies by country

4. Congenital toxoplasmosis
   a. Transmission of the infection from mother to fetus when women acquire the infection during pregnancy
   b. Clinical: hydrocephalus, microcephalus, intracranial calcifications, mental retardation, seizures, deafness, blindness, and hepatomegaly
   c. CT: periventricular or diffuse parenchymal calcification

5. Acquired toxoplasmosis
   a. May occur in immunocompetent (usually asymptomatic and without CNS involvement) or immunocompromised (frequent opportunistic infection)
   b. Clinical: acute mass lesion with focal signs or subacute encephalitis
   c. MRI brain: multiple ring-enhancing lesions with surrounding edema (diffuse focal lesions with predilection for basal ganglia and deep gray matter); differentiate from primary CNS lymphoma (PCNSL).

6. Pathology: cerebral abscesses consisting of a necrotic center and a periphery in which multiple tachyzoites and cysts are seen together with patchy areas of necrosis, perivascular cuffing of lymphocytes, and glial nodules composed of astrocytes and microglial cells
7. Diagnosis:
   a. Definite diagnosis requires biopsy; not commonly performed.
   b. CSF (contraindicated if mass lesion) lymphocytic pleocytosis, increased protein; PCR very specific (>95%), not sensitive (50%–60%)

8. Treatment
   a. Cerebral toxoplasmosis: pyrimethamine (100–200 mg the first day, followed by 50–75 mg/day) plus sulfadiazine (4–6 g/day) for >2 months
   b. Supplement with folate, 8 to 10 mg/day, to avoid the toxic effects of pyrimethamine.
   c. Clindamycin (2,400 mg/day) is an alternative drug in AIDS patients developing skin reactions to sulfadiazine.

D. Trypanosomiasis

1. Chagas disease (American trypanosomiasis)
   a. Caused by Trypanosoma cruzi
   b. Found in southern United States, Central and South America
   c. Transmitted by the bite of Triatoma (reduviid or kissing bug)
   d. Clinical
      i. Acute stage: meningoencephalitis (more common in children with HIV) with multiple areas of hemorrhagic necrosis, glial proliferation, and perivascular infiltrates of inflammatory cells; myocarditis and hepatosplenomegaly
      ii. Chronic stage: dilated cardiomyopathy, cardioembolic stroke due to heart disease, megacolon, and megaesophagus
   e. Diagnosis: microscopic examination of thin and thick blood smear demonstrate the parasite in the acute phase.
   f. Treatment
      i. Nifurtimox (8–10 mg/kg/day) or benznidazole (5–10 mg/kg/day)

2. Sleeping sickness (African trypanosomiasis)
   a. Caused by subspecies of Trypanosoma brucei transmitted by tsetse fly
   b. Clinical features
      i. Painful erythematous nodules associated with regional lymphadenopathy that disappear spontaneously
      ii. Stage I (lasting months): Winterbottom’s sign—fever, cervical lymphadenopathy, and hepatosplenomegaly
      iii. Stage II (lasting years): meningoencephalitis—somnolence, apathy, involuntary movements, cerebellar ataxia, delayed hyperesthesia with eventual progression to dementia, stupor, coma, and death if untreated
   c. Diagnosis: clinical signs, parasites in body fluids; CSF exam for Stage II
   d. Treatment
      i. Stage I: pentamidine or suramin
      ii. Stage II: melarsoprol, eflornithine, combination of nifurtimox and eflornithine

E. Cysticercosis

1. Humans are intermediate hosts of the pork tapeworm Taenia solium.
2. Acquired by ingesting its eggs from contaminated water/food or by the fecal–oral route
3. After 1 to 3 months, eggs hatch into oncospheres in the human intestine that cross the intestinal wall into the bloodstream and spread mainly to the eye, skeletal muscles, and the CNS, where the larvae (cysticercus) develop.
E. Cysticercosis (cont’d)

4. Considered the most common helminthic disease of the CNS in the developing world

5. Clinical
   a. Seizures
      i. Most common presentation
      ii. Most common cause of epilepsy in Central America
   b. Focal neurologic deficits from CNS lesions
   c. Vasculitic type: strokes, increased ICP, headaches, hydrocephalus, and (rarely) coma

6. Neuroimaging
   i. Migrating intraventricular cyst is pathognomonic.
   ii. Cystic lesions with or without contrast enhancement and surrounding edema; cysts can be meningoobasal, parenchymal, or intraventricular.
   iii. Parenchymal calcification, hydrocephalus, leptomeningeal enhancement

7. Treatment
   a. Calcified lesions: symptomatic treatment only (i.e., antiepileptic drugs)
   b. Viable cysts
      i. Albendazole (10 mg/kg/day divided in 2 doses) for 15 days; better CNS penetration, more effective cyst destruction
      ii. Praziquantel (3 doses of 25–30 mg/kg given every 2 hours)
      iii. If >50 cysts or with subarachnoid or ventricular involvement, treat for increased ICP/edema prior to initiation of anthelmintics.
   c. Surgical management for hydrocephalus

F. Trichinosis/Trichinellosis

1. Intestinal nematode infection due to ingestion of undercooked pork containing encysted larvae of Trichinella spiralis.

2. After initial gastroenteritis, may have invasion of skeletal muscle, but weakness is mainly limited to muscles innervated by CNs (e.g., tongue, masseters, extraocular muscle, oropharynx)

3. Rarely, in acute phase may have cerebral symptoms due to emboli from trichinella myocarditis

4. Diagnosis:
   a. Serology positive after 2 to 3 weeks: indirect hemagglutination, indirect immunofluorescence, ELISA
   b. CSF: eosinophilic meningitis may be present, larvae seen in 8% to 24% of patients.
   c. Muscle biopsy: rarely done

5. Neuroimaging: may reveal 3- to 8-mm nodular ring-like lesions

6. Treatment
   a. Prevents systemic invasion when given within 1 week of ingestion
      i. Albendazole, mebendazole, or thiabendazole, 25 mg/kg bid
      ii. Add prednisone, 40 to 60 mg/day, to decrease inflammatory response if hemodynamic instability, CNS, cardiac, or pulmonary involvement.
## CHEAT SHEET

<table>
<thead>
<tr>
<th>Disease</th>
<th>Signs/Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies</td>
<td>Negri bodies, Babès nodules</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Multifocal confluent T2 subcortical white matter, JC virus</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis (SSPE)</td>
<td>Persistent measles infection in brain</td>
</tr>
<tr>
<td>Adult botulism</td>
<td>Descending weakness from cranial nerves, autonomic symptoms with dilated pupils</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Hansen's disease, tuberculoid, borderline, lepromatous</td>
</tr>
<tr>
<td>Pott's disease</td>
<td>Tuberculosis (TB) of spine</td>
</tr>
<tr>
<td>Whipple's disease</td>
<td>Oculomasticatory myorhythmia and oculofacial-skeletal myorhythmia</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>Cavernous sinus fungal infection in diabetics</td>
</tr>
<tr>
<td>Creutzfeldt-Jacob disease</td>
<td>MRI pulvinar sign, hockey-stick sign, cortical ribboning</td>
</tr>
</tbody>
</table>

### Suggested Readings


CHAPTER 16

Sleep and Sleep Disorders

I. Wakefulness and Sleep Overview

A. Arousal system has two main ascending pathways:
   1. Cholinergic neurons in the pedunculopontine and laterodorsal tegmentum → ventroposterior and mediodorsal nuclei of thalamus ← self-inhibits gamma-aminobutyric acid (GABA) in reticular nucleus (as GABA mediates sleep)
   2. Monoamine neurons
      a. Noradrenaline in locus ceruleus
      b. Serotonin in dorsal and medial raphe nuclei
      c. Glutamate in parabrachial nucleus
      d. Dopamine in periaqueductal gray nucleus
      e. Histamine in tuberomamillary nucleus → lateral thalamus (picking up orexin and glutamate) → basal forebrain and cerebral cortex

B. Sleep-promoting pathway:
   1. GABA and galanin from ventrolateral preoptic (VLPO) nucleus and GABA from median preoptic nucleus → inhibit arousal systems.
   2. VLPO important in sleep promotion
   3. Two separate systems are necessary to be able to switch completely from wakefulness to sleep (rather than have in-between states). Orexin stabilizes the flip-flop switch.

II. Basics of Sleep Stages

A. Sleep makeup: N1 = 5% to 10%, N2 = about 50%, N3 = 15% to 20%, rapid eye movement (REM) = 20%

B. Wake
   1. Mediated by arousal pathways
   2. Electroencephalogram (EEG) will show prominent rhythmic alpha in occipital channels with eyes closed and low-amplitude mixed-frequency (LAMF) with eyes open.

C. Non-REM (NREM) sleep (N1, N2, N3)
   1. VLPO and basal forebrain critical in initiating sleep
   2. In N1, alpha is replaced by LAMF; in N2, sleep spindles and K-complexes; in N3, delta.

D. REM
   1. Driven by the pons
   2. Pontine cholinergic neurons induce REM.
   3. Serotonergic neurons suppress REM.
   4. Glutaminergic neurons in sublaterodorsal area induce atonia during REM.
   5. EEG: LAMF with sawtooth waves
D. REM (cont’d)

6. Polysomnography (PSG) findings in early life key points:
   a. At 26 weeks: will see trace discontinuans—indepedent activity over each hemisphere or hemispheric asynchrony
   b. At 37 weeks: will see trace alternans—short bursts of high-voltage mixed-frequency activity alternating with low-voltage mixed-frequency activity
   c. At 30 weeks: REMs
   d. At 2 months: sleep spindles
   e. At 4 to 6 months: K complexes

7. Clinical correlates
   a. REM sleep behavior disorder can be caused by lesion of sublaterodorsal nucleus (REM atonia is lost). Remember that REM sleep behavior disorder (RBD) is associated with parkinsonian syndromes (often a precursor).
   b. Loss of orexin causes narcolepsy and incomplete switching of sleep states.

III. Circadian Rhythm Overview

A. The circadian system has three main components: a circadian pacemaker (the suprachiasmatic nucleus [SCN] in the anterior hypothalamus), input pathways (receive light and other stimuli), and output signals regulated by the SCN.

B. Light is the most important and powerful stimulus for regulating sleep cycles.

IV. Sleep Disorders

A. Insomnia

1. Most common sleep disorder
2. Defined as difficulty initiating, maintaining, or staying asleep despite adequate opportunity and environment for sleep; must also have at least one form of daytime impairment (fatigue, sleepiness, mood disorder, lack of concentration, etc.)
3. Disorder of the wake system resulting in round-the-clock hyperarousal
4. Increases risk of comorbid chronic health conditions
5. Diagnosis: sleep history and sleep log; PSG not necessary unless insomnia is felt to be secondary to another sleep disorder (such as obstructive sleep apnea or periodic limb movements)
6. Treatment (of primary insomnia): cognitive behavioral therapy +/- medications (benzodiazepine [BZD], non-BZD hypnotics, melatonin receptor agonist, or selective histamine receptor antagonist)

B. Circadian rhythm disorders

1. Delayed sleep phase syndrome
   a. Go to bed late, wake up late
   b. Most common in teens and young adults
   c. Diagnosis by sleep history and sleep log +/- actigraphy
   d. Triggers: light exposure and stimulating activity in evening
   e. Treatment: first line is morning light exposure with evening melatonin. Light should be used shortly after core body temp nadir, which occurs 2 to 3 hours before natural wake time. Melatonin should be given 5 to 6 hours prior to dim-light melatonin onset (DLMO). DLMO is 13 to 14 hours after natural wake time.
2. Advanced sleep phase disorder
   a. Go to sleep early, wake up early
   b. Linked to hPer2 gene; less common than delayed phase; occurs in middle-aged adults
   c. Diagnosis: sleep history and sleep log +/- actigraphy
   d. Treatment: early-evening light therapy (7–9 p.m.) or chronotherapy (advance bedtime by 3 hours every few days)

3. Non-24-hour sleep wake disorder
   a. Sleep occurs later and later each day and then the cycle repeats itself.
   b. Mostly seen in the blind (no light to regulate cycle)
   c. Diagnosis: sleep history and sleep log; complaint has to be present for at least 2 months; actigraphy can be helpful.
   d. Treatment: melatonin (3–10 mg) 1 hour before bedtime and structured bedtime routines

4. Irregular sleep–wake cycle
   a. Disorganized: intermittent periods of sleep and wake throughout 24-hour period
   b. Common in older adults with dementia
   c. Diagnosis: sleep history and sleep log +/- actigraphy
   d. Treatment: morning light exposure, structured daytime activities, and sleep-conducive nocturnal environment

5. Jet lag
   a. Recurrent insomnia and daytime somnolence due to rapid travel across two or more time zones
   b. Non-sleep symptoms can include malaise, impaired daytime alertness, poor appetite, gastrointestinal (GI) disturbances, menstrual irregularities, decreased cognitive processing, depression, anxiety, and irritability
   c. Eastward travelers may be more at risk.
   d. Diagnosis: sleep history +/- sleep log
   e. Treatment: if the expected stay in the destination is going to be 2 days or less, adapting to the destination's time zone is not needed. Appropriately timed light exposure is a key component: if traveling eastward, light exposure in the mornings to advance circadian clock; if traveling westward, light exposure in evening to delay circadian rhythm.
   f. Melatonin can be used (best if used with appropriate light exposure). If traveling east, take melatonin in the evening for 2 weeks prior to travel and then at bedtime once in destination.

6. Shift-work sleep disorder
   a. Sleepiness during work hours and insomnia during designated sleep periods for at least 1 month
   b. Overnight shift most susceptible
   c. Can result in chronic sleep deprivation and lead to fatigue, mood disorder, GI disturbance, decreased libido; increased risk for polysubstance abuse, weight gain, hypertension, and coronary artery disease
   d. Diagnosis: sleep history and at least 2 weeks of sleep log
   e. Treatment: aimed at increasing alertness during work hours and facilitating sleep during designated sleep hours. For night-shift workers, bright light exposure up to 2 hours before end of shift can increase alertness. Minimize light exposure on commute home (sunglasses) and have dark, quiet environment to help fall asleep.
6. Shift-work sleep disorder (cont’d)
   f. Melatonin can be taken at time of sleep, which may help to improve daytime sleep, but does not help with work-hour alertness. Modafinil and armodafinil are treatments approved by the U.S. Food and Drug Administration (FDA) to improve work-hour performance/alertness.

C. Sleep-disordered breathing

1. Key definitions
   a. Obstructive apnea: cessation of airflow with continued respiratory effort, due to complete upper airway occlusion.
   b. Hypopnea: significant decrease in airflow with associated EEG arousal or oxygen desaturation due to partial upper airway collapse
   c. Central apnea: cessation of airflow without respiratory effort
   d. Mixed apnea: components of central and obstructive apneas
   e. Upper airway resistance syndrome: flow limitation, not meeting criteria for apnea or hypopnea; due to narrowed upper airway
   f. Primary snoring: snoring without respiratory compromise

2. Obstructive sleep apnea (OSA): 1.5 to 4 times more common in men, prevalence increases with age
   a. Anatomical risk factors: high arched palate, narrow airway, retrusion, adenotonsillar hypertrophy, elongated/edematous uvula, enlarged tongue, increased neck circumference, obesity
   b. STOP BANG screening tool; high risk is yes to 5 or more questions
      i. Snoring, tired, observed apneas, pressure (elevated blood pressure), body mass index (BMI) (greater than 35), age (over 50), neck circumference (greater than 40 cm), gender (male)
         (A) Snoring most common symptom
         (B) Diagnosis: by PSG (apnea hypopnea index [AHI] of 5–15 with daytime symptoms or AHI greater than 16)
            (1) AHI: mild = 5 to 14, moderate = 15 to 30, severe = greater than 30
         (C) Treatment: conservative therapies include weight loss, sleep repositioning therapy (if OSA was more prominent during supine position sleep in nonsupine position), maintaining patency of nasal airway, and avoiding sedatives, narcotics, opioids, and alcohol (ETOH).
         (D) First-line therapy is positive airway pressure (PAP) [Continuous PAP (CPAP), Bilevel PAP (BIPAP), Automatic PAP (APAP)]—pressurized air in oronasal cavity to act as a stent to maintain patency of airway.
         (E) If intolerant to PAP or mild to moderate OSA, can use dental appliance (tongue retaining device or mandibular advancement device) or nasal Expiratory PAP (EPAP)
         (F) If severe OSA and unable to use PAP, surgical intervention can be considered (uvulopalatopharyngoplasty most common, but variety of procedures, including septoplasty or turbinate reduction, tonsillectomy, hyoid suspension, and mandibular advancement)
         (G) If patient is morbidly obese, bariatric surgery may help to improve sleep-disordered breathing.
         (H) The main health risk associated with untreated OSA is cardiovascular, including hypertension, atrial fibrillation, myocardial infarction, congestive heart failure, and stroke.
         (I) OSA also linked to increased risk of metabolic syndrome and autonomic alterations
3. Central sleep apnea (CSA)  
   a. Normally, when CO$_2$ levels rise, there is a certain point at which central sensors in the medulla are stimulated and peripheral sensors in the carotid body are activated to initiate a breath.  
   b. Central sleep apnea can occur in association with chronic hypocapnic states (such as congestive heart failure (CHF) or high altitude) in which the body becomes accustomed to lower CO$_2$ states and the set point to trigger a breath is reduced, leading to apneas.  
   c. Other conditions in which CSA is common: with reduced respiratory drive (with opiates/narcotics) or in association with diaphragmatic weakness as can be seen in neuromuscular disorders such as Amyotrophic Lateral Sclerosis (ALS)  
   d. Diagnosis: PSG with same AHI criteria as OSA  
   e. Treatment: PAP therapy; sometimes triggered respirations are required. Acetazolamide can be used.  
   f. Appropriate cardiopulmonary and neurologic workup

4. Sleep-related hypoventilation  
   a. Most commonly seen with obesity hypoventilation syndrome (OHS)  
   b. OHS diagnosis: BMI greater than 30, waking PaCO$_2$ level of 45 mmHg or greater, hypoxemia PaO$_2$ of 70 mmHg or less  
   c. Higher risk of pulmonary hypertension

D. Hypersomnia  

1. Narcolepsy with cataplexy  
   a. Excessive daytime sleepiness (EDS) for at least 3 months  
   b. Cataplexy (loss of muscle tone triggered by strong emotions)  
   c. Diagnosis: Multiple Sleep Latency Test (MSLT) with mean sleep-onset latency (MSOL) 8 minutes or less and two or more sleep-onset REM periods (SOREMPs) or a decreased cerebrospinal fluid (CSF) hypocretin level (less than 110 pg/mL)

2. Narcolepsy without cataplexy  
   a. EDS for at least 3 months  
   b. No cataplexy  
   c. Diagnosis: MSLT criteria only (MSOL of 8 minutes or less and two or more SOREMPs)  
   d. Narcolepsy key points:  
      i. Narcolepsy with cataplexy associated with HLA-DQB1-0602 and low hypocretin levels  
      ii. Bimodal peak at 15 years of age and near 35 years of age  
      iii. Clinical features aside from EDS and cataplexy include sleep hallucinations, sleep paralysis, and nonconsolidated sleep.

3. Idiopathic hypersomnia (IH)  
   a. EDS for 3 months or more  
   b. Diagnosis: MSLT with MSOL 8 minutes or less and less than two SOREMPs  
   c. Can be further classified as IH with long sleep time (patient getting 10 or more hours of sleep per sleep period) or without long sleep time (6–10 hours of sleep)

4. Kleine-Levin syndrome and menstrual-related hypersomnia  
   a. Recurrent episodes of EDS for 2 days to 4 weeks  
   b. Episodes occur at least yearly  
   c. Baseline (normal) function between attacks
4. Kleine-Levin syndrome and menstrual-related hypersomnia (cont’d)
   d. Often accompanied by mood and cognitive alterations, increased appetite, aggressive or hypersexual behavior

5. Treatment
   a. Traditional stimulants (amphetamines, methamphetamine, methylphenidate) or wake-promoting agents that act primarily on norepinephrine and dopamine (modafinil, armodafinil); sodium oxybate acting on GABA-b receptors consolidates sleep and can increase slow-wave sleep—better sleep may allow for more alertness during the day.
   b. Cataplexy is treated with tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs).

E. Parasomnias: undesirable behaviors that occur during sleep, characterized by complex, seemingly purposeful behaviors, usually longer than 2 minutes, with no conscious recollection of event

1. The first distinction to make is NREM versus REM parasomnias:
   a. NREM parasomnias: usually arise from slow-wave sleep during the first half of the night
      i. Confusional arousal: mental confusion or confusional behavior that occurs from waking during nocturnal sleep or a nap; episodes usually last a few minutes; generally no recollection of the event; abnormal sexual behavior (sexsomnia) is a type of confusional arousal.
         (A) Treatment: episodes starting in childhood usually spontaneously remit.
      ii. Sleepwalking or somnambulism: walking or more complex behaviors with eyes generally open
         (A) Peak prevalence ages 8 to 12 years; usually remits spontaneously in teens/early adulthood
      iii. Sleep terrors or parvors nocturnus: sudden arousal, sitting up with cry/vocalization and look of fear; associated with tachycardia, tachypnea, diaphoresis, mydriasis, and facial flushing; episodes usually last a few minutes and then patient returns to normal sleep, with no recollection of event upon waking
         (A) Peak prevalence is early school age, with remission usually by teens.
   b. REM parasomnias—occur during second half of night (when REM periods are longer)

2. Nightmares: although similar to night terrors in that patient appears to have a sudden arousal with fear/panic, the patient is cognizant that he or she is waking up because of a nightmare and is often able to recall the dream with detail. Most often, there is recollection of the event in the morning.

3. REM sleep behavior disorder (RBD)
   a. Dream reenactment behavior with motor activity and vocalization
   b. Usually occurring about once per week
   c. This is the only parasomnia that has a definitive PSG diagnosis: there is REM sleep without atonia (RSWA), which is demonstrated by persistent chin EMG activity during REM sleep.
   d. Can be due to bilateral pontine tegmental lesions
   e. Associated with alpha synucleinopathies (Parkinson’s disease, dementia with Lewy bodies), with RBD often preceding the neurodegenerative disorder
   f. RBD can also be secondary (induced by medications, including SSRIs, SNRIs, alcohol withdrawal, caffeine)
g. Pseudo RBD: occurs with untreated OSA; subsides with appropriate treatment of OSA

h. Treatment: safe sleep environment and clonazepam

F. Nocturnal epilepsies

1. Two main types: frontal lobe and temporal lobe epilepsy


3. Frontal lobe seizures associated with clonic activity, dystonic posturing, vocalization, and tendency toward secondary generalization; awareness can be preserved; minimal post-episode confusion

4. Temporal lobe seizures are usually longer episodes associated with automatisms. Awareness is usually preserved, but post-episode confusion is more common. Less likely to generalize.

G. Periodic limb movement disorder/restless leg syndrome (RLS)

1. Periodic limb movement disorder (PLMD): PSG diagnosis with increased PLMs (significant if PLM index is greater than 15); generally no treatment unless clinical complaints (poor sleep with increased nocturnal waking, EDS) with no other explanation

2. RLS

   a. Clinical diagnosis often associated with increased PLMs (but not a requirement)

   b. RLS can be secondary to other medical conditions, including iron deficiency, diabetes mellitus, renal failure, and pregnancy.

   c. Prevalence of RLS is 5% to 10% in general population, but 10% to 26% in pregnancy, with peak in the third trimester.

   d. Diagnosis of RLS (four key features)

      i. An urge to move legs; can be accompanied by uncomfortable and unpleasant leg sensations

      ii. The symptoms begin or worsen during times of rest.

      iii. The symptoms improve with movement.

      iv. The symptoms are worse during evening/night.

   e. Workup: check ferritin level (can be associated with low ferritin) and peripheral neuropathy labs (B12, TSH, HgbA1c).

   f. Treatment: if serum ferritin levels less than 50 u/L, treat with iron supplementation +/− medical workup for anemia. Other treatments include dopaminergic agents (dopamine agonists and dopamine replacement—first line), GABA agents, BZDs, and opioids (last line).

   g. Monitor for compulsive behaviors with dopaminergic agents.

   h. Augmentation (where symptoms occur earlier in the day, are more severe, or involve more body parts) can occur with dopaminergic agents; initially can increase frequency of doses, but eventually may require discontinuation of medication.

V. Pharmacology Overview

A. Medications for insomnia

1. BZDs act as GABA agonists. However, because they have nonspecific GABA attachment sites, BZDs may have a more widespread brain effect (versus just sleep effects).
A. Medications for insomnia (cont’d)

2. FDA-approved BZDs include flurazepam and quazepam (long half-lives), temazepam and estazolam (medium half-lives), and triazolam (short half-life)
3. BZDs are most commonly used for short-term treatment of insomnia.
4. The most common side effects are drowsiness, dizziness, and headache.
5. There is habit-forming potential.
6. Use with caution in patients with untreated OSA or respiratory disease, as these medications can potentially lower respiratory drive.
7. Non-BZD receptor agonists are modulators of GABA-a receptor complex.
8. FDA-approved non-BZDs include eszopiclone (long half-life), zolpidem (medium half-life), and zaleplon (short half-life)
9. Can be used for short-term or, if needed, longer-term treatment of insomnia
10. Remember that eszopiclone is associated with metallic taste and smell.
11. All non-BZDs have the potential to increase parasomnias (abnormal nighttime behaviors).
12. There are extended-release formulations as well as oral spray and sublingual forms of zolpidem.
13. Selective melatonin receptor agonist
   a. Ramelteon: used mostly for sleep-onset insomnia
14. Selective histamine H1 receptor antagonist
   a. Doxepin: long half-life, used for sleep maintenance insomnia; can have side effect of upper respiratory tract infection

B. Medications for hypersomnia

1. Stimulants include amphetamine, methamphetamine, and methylphenidate.
2. Side effects include palpitations, tachycardia, hypertension, anorexia, psychosis, insomnia, and high abuse potential.
3. Wake-promoting agents
   a. Modafinil and armodafinil (act on dopamine receptors) to enhance wakefulness state; common side effect is headache/nausea
4. Sodium oxybate
   a. Activates GABA-b receptors
   b. Consolidates sleep; increases slow-wave sleep; by providing improved sleep quality, enhances daytime alertness

C. Medications for cataplexy

1. Tricyclic antidepressants (imipramine, protriptyline, clomipramine)
   a. SSRIs (fluoxetine and fluvoxamine)
   b. SNRI (venlafaxine)
   c. Sodium oxybate

D. Medications for RLS

1. Dopamine agonists (generally first-line treatment)
   a. Include pramipexole, ropinirole, rotigotine patch, carbidopa/levodopa
   b. These medications are most often efficacious for RLS.
   c. Side effects include risk of augmentations (making RLS symptoms worse during the daytime), impulse control disorders, and daytime sleepiness.
   d. Impulse control disorders can occur in 6% to 17% of people taking dopaminergic agents and can manifest months after starting treatment.
2. Calcium channel alpha 2 delta ligands (generally first- or second-line agents)
   a. Gabapentin, gabapentin enacarbil, pregabalin
   b. Especially helpful if patients also have neuropathic symptoms
   c. BZDs and opioids are useful as third-line agents for RLS treatment.

<table>
<thead>
<tr>
<th>CHEAT SHEET</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>Most powerful zeitgeber</td>
</tr>
<tr>
<td>Sleep promoting</td>
<td>VLPO (ventrolateral pontine nucleus)</td>
</tr>
<tr>
<td>Flip-flop switch</td>
<td>Stabilized by orexin</td>
</tr>
<tr>
<td>Sleep onset</td>
<td>DLMO (dim-light melatonin onset)</td>
</tr>
<tr>
<td>Advanced phase sleep disorder</td>
<td>hPER2 gene</td>
</tr>
<tr>
<td>K complexes and sleep spindles</td>
<td>Stage II sleep</td>
</tr>
<tr>
<td>Delta waves</td>
<td>Stage III sleep</td>
</tr>
<tr>
<td>Sawtooth waves</td>
<td>REM sleep</td>
</tr>
<tr>
<td>REM behavior disorder</td>
<td>Loss of muscle atonia</td>
</tr>
<tr>
<td>REM behavior disorder</td>
<td>Alpha synucleinopathy association</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>HLA-DQB1-0602</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Low hypocretin level</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td>Low ferritin level</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Airway obstruction with respiratory effort</td>
</tr>
<tr>
<td>Central sleep apnea</td>
<td>No respiratory effort</td>
</tr>
<tr>
<td>Nightmares</td>
<td>Later in night, REM sleep, memory</td>
</tr>
<tr>
<td>Night terrors</td>
<td>Later in night, REM sleep, memory</td>
</tr>
<tr>
<td>Sleep seizures</td>
<td>ADNFLE, associated with CHRNA gene</td>
</tr>
<tr>
<td>Eszopiclone/Lunesta</td>
<td>Metallic taste and smell</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Augmentation, impulse control disorders</td>
</tr>
</tbody>
</table>

**Suggested Readings**
