***Continuum: Lifelong Learning in Neurology*—Neurology of Systemic Disease, Volume 23, Issue 3, June 2017**

Issue Overview

Neurology of Systemic Disease 2017;23(3)

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Neurology of Systemic Disease issue, participants will be able to:

- Discuss the most commonly described autoimmune neurologic conditions affecting the central nervous system and develop an approach to the diagnostic workup of patients presenting with central nervous system symptoms or signs that could be immune mediated, either paraneoplastic or idiopathic, to guide therapeutic decision making
- Discuss neurologic complications of cardiac and aortic disease
- Discuss the neurologic complications of lymphoma, leukemia, and paraproteinemic disorders, recognize the clinical presentation and imaging findings of these diseases, and apply appropriate management
- Diagnose rheumatologic disorders associated with neurologic manifestations and recognize possible neurologic complications of treatment of rheumatologic disease
- Describe the overlap between renal disease and the nervous system, including genetically determined and acquired diseases affecting both organ systems and the effects of kidney failure and dialysis on the nervous system
- Discuss the range of neurologic symptoms that may develop in selected gastrointestinal disease processes
- Diagnose and manage neurologic problems that may arise in association with diseases of the liver
- Identify the neurologic manifestations of endocrine emergencies and formulate the appropriate diagnostic evaluation and medical management of these clinical entities
- Recognize common causes of neurologic dysfunction at various intervals following hematopoietic cell transplantation and solid organ transplantation and design comprehensive

diagnostic strategies for potential infections, drug complications, strokes, seizures, and autoimmune sequelae of transplantation

- Diagnose and manage patients with neurologic manifestations of various nutrient deficiencies
- Recognize and treat neurologic complications of environmental injuries
- Define medical error and describe the ethical rationale for reporting medical errors and disclosing them to patients and families
- Discuss potential safety risks that arise as patients transition from an inpatient to an outpatient care setting and methods to decrease risks and improve the quality of patient care during the transition period

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Neurology of Systemic Disease issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

Disclosures

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Methods of Participation and Instructions for Use

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills. In *Continuum,* the process of absorbing, integrating, and applying the material presented is as important as, if not more important than, the material itself.

The goals of *Continuum* include disseminating up-to-date information to the practicing neurologist in a lively, interactive format; fostering self-assessment and lifelong study skills; encouraging critical thinking; and, in the final analysis, strengthening and improving patient care.

Each *Continuum* issue is prepared by distinguished faculty who are acknowledged leaders in their respective fields. Six issues are published annually and are composed of review articles, case-based discussions on ethical and practice issues related to the issue topic, coding information, , and comprehensive CME and self-assessment offerings, including a self-assessment pretest, multiple-choice questions with preferred responses, and a patient management problem. For detailed instructions regarding *Continuum* CME and self-assessment activities, visit *aan.com/continuum/cme*.

The review articles emphasize clinical issues emerging in the field in recent years. Case reports and vignettes are used liberally, as are tables and illustrations. Video material relating to the issue topic accompanies issues when applicable.

The text can be reviewed and digested most effectively by establishing a regular schedule of study in the office or at home, either alone or in an interactive group. If subscribers use such regular and perhaps new study habits, *Continuum*'s goal of establishing lifelong learning patterns can be met.

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LIFELONG LEARNING IN NEUROLOGY®

Neurology of Systemic Disease

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CONTINUUM

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Neurology of Systemic Disease

Guest Editor: Neeraj Kumar, MD

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CONTINUUM
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ETHICAL AND MEDICOLEGAL ISSUES

PRACTICE ISSUES

SELF-ASSESSMENT AND CME

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He Ain't Heavy, He's My *Continuum* Issue

At the risk of using another outdated (and to some, incomprehensible) pop-culture reference, I want to use the preface to this *Continuum* issue to discuss my editorial vision for *Continuum* that has had an obvious outcome in the increasing girth of our issues. There has, in fact, been an increase in the number of pages per issue under my tenure as editor-in-chief: from 2009 to 2012, the average number of pages per issue was 252, while from 2013 to 2016, subsequent to my becoming editor, the average number of pages per issue grew to 312, a 24% increase.

Dr Neeraj Kumar has expertly crafted a weighty issue that will be of great benefit to us as we encounter patients with the large variety of disorders that occur in association with, or as a complication of, systemic (medical) disorders or their treatments.

This has been purposeful, primarily due to my editorial intention to provide more articles per issue so that each issue is as inclusive as possible of the information we each need as we see our many patients. In addition, it is my intent to ensure that the actual topic-based themes of each issue are as broad as possible (eg, the recent issue Muscle and Neuromuscular Junction Disorders rather than an issue devoted entirely to a single disorder or two within this subject area [eg, myasthenia gravis]) to allow for inclusion of as much information as possible in each 3-year *Continuum* curriculum cycle. The result of this editorial direction has been thicker individual issues while allowing for more breadth in the entire curriculum. In summary, I feel that by being more encompassing of many topics in the curriculum and including more (albeit sometimes large) individual articles per issue, *Continuum* becomes more useful as our source of practical office and bedside information regarding the many entities we see daily, even at the risk of diminishing the ease of cover-to-cover reading. On the other hand, while ensuring that the content is as thorough, diverse, and practical as possible, we will continue to seek practical solutions, such as making some content online only (eg, some Coding articles and supplementary content) and removing much of the previous redundancy in the CME pages of each issue.

In this issue, Guest Editor Dr Neeraj Kumar, Professor of Neurology at the Mayo Clinic, Rochester, Minnesota, has expertly crafted a weighty issue that will be of great benefit to us as we encounter patients with the large variety of disorders that occur in association with, or as a complication of, systemic (medical) disorders or their treatments. The issue begins with the article by Drs W. Oliver Tobin and Sean J. Pittock, who provide us with the most up-to-date information regarding the diagnosis and management of the evolving spectrum of autoimmune neurologic disorders. Next, Dr James P. Klaas reviews the many neurologic complications that can occur in our patients with cardiac and aortic diseases. Dr Michelle L. Mauermann then summarizes the neurologic complications of lymphomas, leukemias, and paraproteinemias and includes an overview of the diagnostic tests that inform our diagnosis of these disorders. Next, Dr Elliot L. Dimberg discusses the many rheumatologic disorders and their various potential associated neurologic complications and associations.

Dr Sara E. Hocker reviews the overlap between renal disease and disorders of the

nervous system, including the conditions that affect both the renal and the nervous systems, the neurologic disorders that occur as a consequence of renal failure, and the neurologic complications of dialysis. Dr Ronald F. Pfeiffer then discusses the neurology of gastrointestinal disorders, highlighting the neurologic complications of inflammatory bowel diseases and Whipple disease and providing a clear and up-to-date discussion of the somewhat controversial concept of neurologic complications of celiac disease and gluten-related disorders.

Drs Robert N. Schwendimann and Alireza Minagar review the neurologic signs and symptoms that occur in patients with chronic and acute liver diseases. Dr Makoto Ishii next summarizes for the neurologist the various endocrine emergencies and their neurologic manifestations to broaden our differential diagnosis as we encounter patients with these signs and symptoms.

Dr Amy A. Pruitt next reviews the many neurologic complications that can, and often do, occur in patients who have undergone hematopoietic cell or solid organ transplantation. Dr Pruitt's article is an example of a single article and single expert author providing all the important critical, relevant, and contemporary information that has previously filled an entire issue devoted to the topic. Dr Kumar next provides a truly encyclopedic and authoritative review of the many nutrients that, primarily in deficiency but some in excess, cause neurologic dysfunction. In the final review article of the issue, Dr Rodolfo Savica discusses the neurologic complications that can arise from environmental injuries, including thermal and electrical injuries and injuries related to aviation, altitude, and diving.

In this issue's Ethical and Medicolegal Issues section, Dr Adam Webb discusses the ethical, legal, regulatory, and practical considerations regarding providers' appropriate reporting and disclosing of medical errors to our patients. In the Practice Issues article, Drs Marcus Ponce de Leon and Anna D. Hohler provide an illustrative case example to review the safety considerations that are important for us to address during transitions of our patients' care from inpatient to outpatient settings. In the Coding article (accessed online and on the *Continuum* apps), Dr Melissa Yu reviews diagnostic coding for medication-related poisoning and adverse effects.

As with every issue of *Continuum*, several opportunities exist for CME. After reading the issue and taking the Postreading Self-Assessment and CME Test written by Drs D. Joanne Lynn and Joseph E. Safdieh, you may earn up to 12 *AMA PRA Category 1 Credits*™ toward self-assessment and CME. The Patient Management Problem, written by Dr Hocker, describes the case of a 74-year-old man who develops restlessness, diaphoresis, tremors, and tachycardia in the postoperative period. By following his case and answering 12 multiple-choice questions corresponding to diagnostic, management, and prognostic decision points along the course of his disorder, you will have the opportunity to earn up to 2 *AMA PRA Category 1 CME Credits*. Canadian participants can now claim a maximum of 14 hours toward the Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, for completing the Postreading Self-Assessment and CME Test and the Patient Management Problem.

My sincere gratitude to Dr Kumar for his expert and meticulous stewardship of this issue. I would like to extend a similar thank-you to the authors who have so thoughtfully and carefully provided us with the benefit of their substantial expertise to guide us as we consult on the many patients with neurologic signs and symptoms that occur in the setting of systemic disease.

—Steven L. Lewis, MD, FAAN
Editor-in-Chief

Autoimmune Neurology of the Central Nervous System

W. Oliver Tobin, MBBCh, BAO, PhD; Sean J. Pittock, MD

ABSTRACT

Purpose of Review: This article reviews the rapidly evolving spectrum of autoimmune neurologic disorders with a focus on those that involve the central nervous system, providing an understanding of how to approach the diagnostic workup of patients presenting with central nervous system symptoms or signs that could be immune mediated, either paraneoplastic or idiopathic, to guide therapeutic decision making.

Recent Findings: The past decade has seen a dramatic increase in the discovery of novel neural antibodies and their targets. Many commercial laboratories can now test for these antibodies, which serve as diagnostic markers of diverse neurologic disorders that occur on an autoimmune basis. Some are highly specific for certain cancer types, and the neural antibody profiles may help direct the physician's cancer search.

Summary: The diagnosis of an autoimmune neurologic disorder is aided by the detection of an objective neurologic deficit (usually subacute in onset with a fluctuating course), the presence of a neural autoantibody, and improvement in the neurologic status after a course of immunotherapy. Neural autoantibodies should raise concern for a paraneoplastic etiology and may inform a targeted oncologic evaluation (eg, *N*-methyl-D-aspartate [NMDA] receptor antibodies are associated with teratoma, antineuronal nuclear antibody type 1 [ANNA-1, or anti-Hu] are associated with small cell lung cancer). MRI, EEG, functional imaging, videotaped evaluations, and neuropsychological evaluations provide objective evidence of neurologic dysfunction by which the success of immunotherapy may be measured. Most treatment information emanates from retrospective case series and expert opinion. Nonetheless, early intervention may allow reversal of deficits in many patients and prevention of future disability.

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Unlabeled Use of Products/Investigational Use Disclosure: Drs Tobin and Pittock discuss the unlabeled/investigation use of azathioprine, IV immunoglobulin (IVIg), mycophenolate mofetil, and rituximab for the treatment of autoimmune neurologic diseases.

INTRODUCTION

Autoimmune neurologic disorders should be suspected in patients with a subacute onset of neurologic disease. Patients may have a single symptom but more typically have multifocal symptoms and signs. A personal or family history of autoimmune disease or malignancy should heighten suspicion, and an inflammatory CSF profile is also supportive (although a normal CSF does not rule out an autoimmune disorder).[1] In patients for whom an autoimmune or paraneoplastic syndrome is suspected, the clinician will typically request a neural autoantibody evaluation, which is a profile of neural antibodies packaged according to the clinical presentation. An example (an autoimmune encephalopathy evaluation) is shown in **Supplemental Digital Content 1-1**, *links.lww.com/CONT/A218*; this is quite different from the profile of antibodies that would be

Supplemental digital content: Direct URL citations appear in the printed text and are included in the HTML, PDF, and app versions of this article.

KEY POINTS

- Unless a high degree of suspicion exists for a single antigenic target in patients presenting with neurologic disorders, such as in neuromyelitis optica, the authors advocate a global screen for a number of potential causative antibodies.
- Indirect tissue immunofluorescence and immunohistochemistry serve as excellent screening tools for the presence of neural antibodies.

pertinent to a myasthenia gravis or autoimmune gastrointestinal dysmotility evaluation. The following section reviews the typical assays performed and implications for the clinical evaluation.

MECHANISMS OF ANTIBODY INJURY

The presence of a neural-specific antibody is often classically associated with a neurologic syndrome; however, the pathophysiology of this association varies widely between diseases. In some cases, particularly in cases of intracellular antigenic targets, the antibody is likely to be a marker of disease and is likely not to be pathogenic. In these cases, it is thought that the pathogenic agent is likely to be an undiscovered antibody or, more likely, T-cell effector cells. In cases of extracellular antigens, a direct causal link is more plausible, given that the antibody may have direct access to the cell surface antigen. For such diseases, direct pathogenicity is likely mediated through a variety of mechanisms, as outlined in **Figure 1-1**.[2]

Competitive binding (agonistic and antagonistic) occurs when an antibody prevents binding of the endogenous ligand to the target receptor. This can result in blocking of receptor function in the absence of internalization (eg, γ-aminobutyric acid [GABA]-B). In contrast, binding of other pathogenic antibodies leads to internalization of the target receptor, resulting in a lower surface density of receptors for the native ligand to bind (eg, *N*-methyl-D-aspartate [NMDA] receptor antibody, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor antibody), with a subsequent reduction in receptor activation. Antibody binding can also lead to secondary cellular- or complement-mediated cytotoxicity. In the case of neuromyelitis optica (NMO)-IgG, binding to aquaporin-4 causes rapid downregulation of aquaporin-4 via endocytosis, degradation, and activation of the lytic complement cascade.[3] The different clinical phenotypes associated with pathogenic antibodies may be at least partly explained by host factors. For example, in patients with NMO spectrum disorders, the relative distribution of aquaporin-4 isoforms causes different downstream effects following NMO-IgG binding. As is apparent from these examples, a variety of pathogenic mechanisms lead to the clinical phenotype associated with each antibody, with some neural antibodies exerting their effects through several pathways. A more detailed understanding of these pathogenic mechanisms has led to several new therapies, such as the use of eculizumab to target complement activation in NMO spectrum disorders.[4] A summary of extracellular and intracellular antibody targets are schematized in **Figure 1-1**, **Table 1-1**,[5] and **Table 1-2**.[6]

OVERVIEW OF THE METHODOLOGY OF NEURAL AUTOANTIBODY EVALUATION

Most laboratories perform either targeted testing for a single antigen (such as NMDA receptor antibody) or a global screen for a number of antibodies. Unless a high degree of suspicion exists for a single antigenic target, such as in NMO, the authors advocate a global screen for a number of potential causative antibodies. For example, in patients presenting with an encephalitic clinical picture, testing by cell binding assay for NMDA receptor, AMPA receptor, and GABA-B receptor antibodies, in addition to tissue immunofluorescence/immunohistochemistry and radio precipitation assays, may be beneficial.

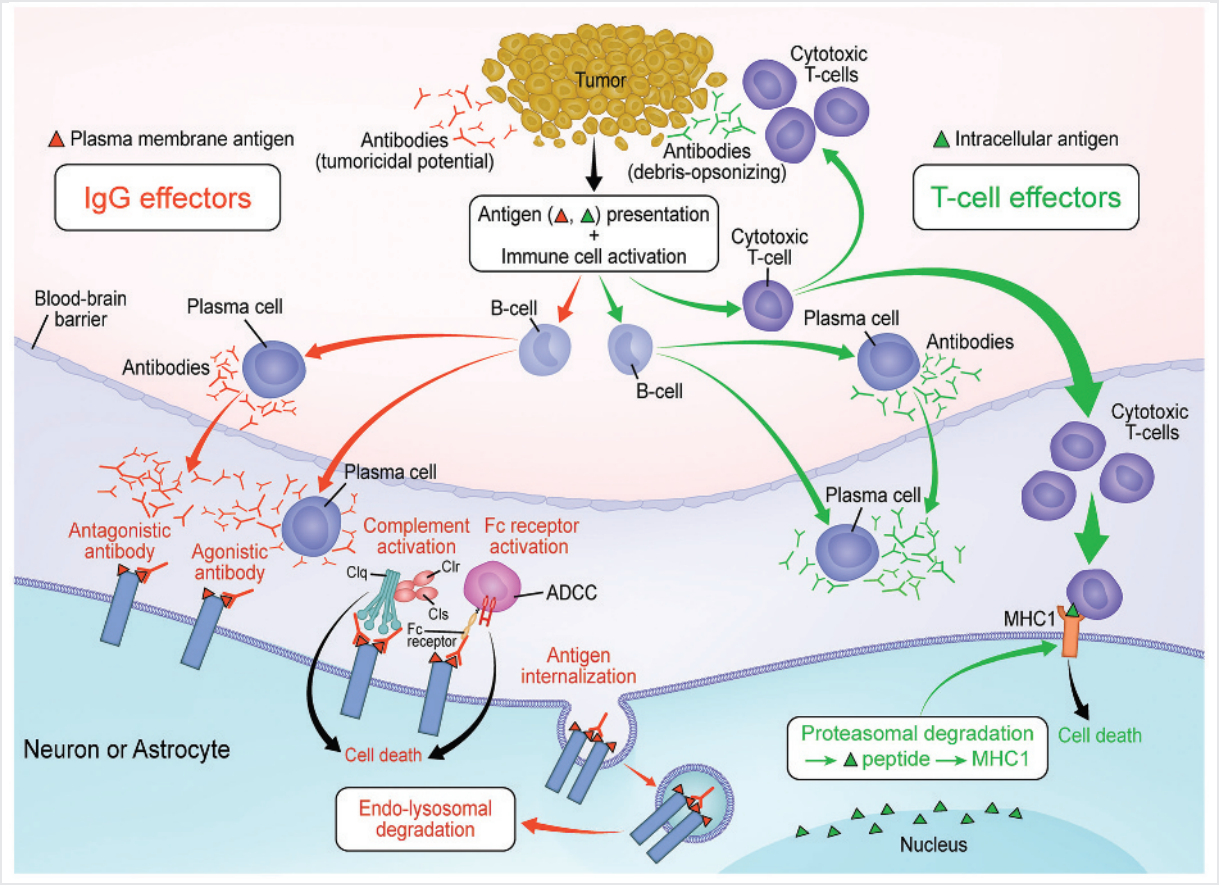

FIGURE 1-1 Paraneoplastic neural autoantibodies and immunopathogenic mechanisms. Tumor-targeted immune responses are initiated by onconeural proteins expressed in the plasma membrane (*red triangle*) or in the nucleus, cytoplasm, or nucleolus (*green triangle*) of certain tumors. These antigens are presented to the adaptive immune system, and immune cell activation results. These antigens are also expressed in neural cells (neurons or glia) and thus are coincidental targets. Antibodies targeting plasma membrane antigens are effectors of injury (*red*): antibodies (*red*) directed at neural cell plasma membrane antigens (eg, voltage-gated potassium complex [VGKC], *N*-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA], γ-aminobutyric acid [GABA]-B receptor, aquaporin-4) are effectors of cellular dysfunction or injury through multiple effector mechanisms. These mechanisms include receptor agonist or antagonist effects, activation of the complement cascades, activation of Fc receptors (leading to antibody-dependent cell-mediated cytotoxicity [ADCC]), and antigen internalization (antigenic modulation), thereby altering antigen density on the cell surface. Antibodies targeting nuclear or cytoplasmic antigens are serum markers of a T-cell effector–mediated injury (*green*): intracellular antigens (*green triangles*) are not accessible to immune attack in situ, but peptides derived from intracellular proteins are displayed on upregulated MHC class-I molecules in a proinflammatory cytokine milieu after proteasomal degradation and are then accessible to peptide-specific cytotoxic T cells. Antibodies (*green*, eg, antineuronal nuclear antibody type 1 [ANNA-1], Purkinje cell antibody 1 [PCA-1]) targeting these intracellular antigens (*green*) are detected in both serum and CSF but are not pathogenic. In clinical practice, these antibodies serve as diagnostic markers of a T-cell–predominant effector process.

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Indirect Immunohistochemistry

Binding of antibodies present in the patient's serum can be detected using indirect tissue immunofluorescence (**Figure 1-2**[7]) or immunohistochemistry. These techniques serve as excellent screening tools. Serum or CSF of the patient of interest is incubated on a slide of mouse, rat, or primate tissue in the presence of an antihuman secondary antibody conjugated to fluorescent dyes or enzymes. The presence of a neural antibody is detected by demonstrating a typical binding pattern

TABLE 1-1 Neural Antibodies Targeting Nuclear and Cytoplasmic Antigens[a]

Autoantibody	Antigen	Oncologic Association	Neurologic Presentation
ANNA-1 (Hu)	ELAVL (Hu)	Small cell lung cancer, rarely thymoma Children: neuroblastoma or no detectable tumor	Neuropathies (80%; pure sensory, mixed sensorimotor, predominantly autonomic, rarely motor), gastrointestinal dysmotilities (25%), limbic encephalitis, subacute cerebellar degeneration, myelopathy, radiculopathy
ANNA-2 (Ri)	NOVA 1, 2 (Ri)	Lung and breast cancers	Brainstem syndrome (opsoclonus-myoclonus, cranial neuropathy, laryngospasm, and trismus), cerebellar syndrome, myelopathy, neuropathy (sensorimotor > polyradiculopathy > cauda equina syndrome), movement disorder, encephalopathy, seizures
ANNA-3	Unknown	Small cell lung cancer	Sensory and sensorimotor neuropathies, cerebellar ataxia, myelopathy, brainstem and limbic encephalopathy
Zic4	Zic4	Small cell lung cancer	Pure or predominant cerebellar syndrome
Anti-MA	PNMA1 PNMA2	Breast, lung (small cell and non–small cell), gastrointestinal tract, germ cell, and renal cancers; non-Hodgkin lymphoma	Females > males: cerebellar/brainstem syndrome > limbic encephalitis > polyneuropathy > extrapyramidal symptoms > myelopathy
Anti-Ta	PNMA2	Testicular or extragonadal germ cell, breast, lung, and ovarian cancers; non-Hodgkin lymphoma	Males > females: limbic encephalitis, cerebellar/brainstem syndrome, extrapyramidal symptoms, diencephalic (narcolepsy/cataplexy), polyneuropathy, myelopathy
AGNA (SOX1)	SOX1	Small cell lung cancer	Lambert-Eaton myasthenic syndrome, cerebellar syndrome, limbic encephalitis, sensorimotor neuropathy
Amphiphysin-IgG	Amphiphysin	Breast and small cell lung cancers	Peripheral neuropathy, encephalopathy, myelopathy, encephalomyelitis with rigidity, cerebellar syndrome, myoclonus, focal pain, pruritus; a minority exhibit stiff person phenomena
CRMP-5 IgG	CRMP-5	Small cell lung cancer, thymoma, thyroid and renal cancers	Peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, cerebrocortical disorders, basal ganglionitis (chorea, parkinsonism, hemiballismus), cranial neuropathies (particularly loss of vision, smell, and taste), myelopathy and radiculoplexopathy, neuromuscular junction disorders

Continued on page 631

TABLE 1-1 **Neural Antibodies Targeting Nuclear and Cytoplasmic Antigens**[a] *Continued from page 630*

Autoantibody	Antigen	Oncologic Association	Neurologic Presentation
PCA-1 (Yo)	CDR2	Ovarian and fallopian tubal cancers, serous surface papillary > breast adenocarcinoma	Cerebellar dysfunction predominates in 90%; 10% have isolated peripheral nerve disorder
PCA-2	MAP1B	Small cell lung cancer	Brainstem or limbic encephalitis, cerebellar ataxia, neuropathy
PCA-Tr	Delta notchlike growth factor related receptor	Hodgkin lymphoma	Cerebellar dysfunction
Recoverin (anti–CAR)	Recoverin	Endometrial, cervical, ovarian, breast, and small cell lung cancers	Painless and progressive visual loss, loss of rod and cone junction (demonstrated by electroretinography)
GAD65	GAD65	Uncommon: thymoma, breast cancer	Stiff person syndrome, limbic encephalitis, cerebellar ataxia, palatal tremor, downbeat or periodic alternating nystagmus, myelopathy, brainstem disorders

AGNA = antiglial nuclear antibody; ANNA-1 = antineuronal nuclear antibody type 1; ANNA-2 = antineuronal nuclear antibody type 2; ANNA-3 = antineuronal nuclear antibody type 3; CAR = cancer associated retinopathy; CDR2 = cerebellar degeneration protein 2; CRMP–5 = collapsin response mediator protein-5; GAD65 = glutamic acid decarboxylase 65; IgG = immunoglobulin G; NOVA = neuro-oncologic ventral antigen; PCA-1 = Purkinje cell cytoplasmic antibody 1; PCA-2 = Purkinje cell cytoplasmic antibody 2; PCA-Tr = Purkinje cell cytoplasmic antibody Tr; PNMA = paraneoplastic Ma antigens.

[a] Modified with permission from Pittock SJ, Palace J, Handb Clin Neurol.[5] © 2016 Elsevier.

TABLE 1-2 **Antibodies With Specificity for Neural Antigens, Accompanying Cognitive Disorders, and Other Reported Neurologic Findings and Oncologic Associations**[a]

Antibody	Reported Cognitive Disorders	Other Neurologic Findings	Cancer Association
VGKC	Limbic encephalitis, amnestic syndrome, executive dysfunction, personality change, disinhibition	Hypothalamic disorder, brainstem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral and autonomic neuropathy	Small cell lung cancer, thymoma, adenocarcinoma of breast or prostate
NMDA	Amnestic syndrome	Anxiety, psychosis, seizures, extrapyramidal disorders	Teratoma, usually ovarian
GAD65	Limbic encephalitis, other encephalitides	Stiff person syndrome, ataxia, seizures, brainstem encephalitis, ophthalmoplegia, parkinsonism, myelopathy	Thymoma
AMPA	Limbic encephalitis	Nystagmus, seizures	Thymic tumors, lung carcinoma, breast carcinoma

Continued on page 632

TABLE 1-2 **Antibodies With Specificity for Neural Antigens, Accompanying Cognitive Disorders, and Other Reported Neurologic Findings and Oncologic Associations**[a]

Continued from page 631

Antibody	Reported Cognitive Disorders	Other Neurologic Findings	Cancer Association
ANNA-1 (anti-Hu)	Limbic encephalitis	Brainstem encephalitis, autonomic neuropathies, sensory neuronopathy	Small cell lung cancer
ANNA-2 (anti-Ri)	Dementia, limbic encephalitis	Brainstem encephalitis, myelopathy, peripheral neuropathy	Small cell lung cancer, breast adenocarcinoma
ANNA-3	Limbic encephalitis	Brainstem encephalitis, myelopathy, peripheral neuropathy	Small cell lung cancer
AGNA (SOX-1 antibodies)	Limbic encephalitis	Neuropathy, Lambert-Eaton myasthenic syndrome	Small cell lung cancer
PCA-2	Limbic encephalitis	Ataxia, brainstem encephalitis, Lambert-Eaton myasthenic syndrome, peripheral and autonomic neuropathies	Small cell lung cancer
CRMP-5 IgG	Subacute-onset dementia, personality change, aphasia	Depression, chorea, ataxia, myelopathy, radiculopathy, neuropathy, Lambert-Eaton myasthenic syndrome	Small cell lung cancer, thymoma
Amphiphysin	Limbic encephalitis, aphasia, other subacute-onset dementias	Stiff person phenomena, myelopathy, neuropathy	Breast adenocarcinoma, small cell lung cancer
Anti-Ma proteins (usually Ma2, sometimes Ma1)	Limbic encephalitis	Hypothalamic disorder, brainstem encephalitis	Testicular cancer, small cell lung cancer, other solid organ cancers
NMO-IgG	Reports of encephalopathies in children	Optic neuritis, transverse myelitis	Some reports of thymoma and other solid tumors

AGNA = antiglial nuclear antibody; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA-1 = antineuronal nuclear antibody type 1; ANNA-2 = antineuronal nuclear antibody type 2; ANNA-3 = antineuronal nuclear antibody type 3; CRMP-5 = collapsin response mediator protein-5; GAD65 = glutamic acid decarboxylase 65; IgG = immunoglobulin G; NMDA = *N*-methyl-D-aspartate; NMO = neuromyelitis optica; PCA-2 = Purkinje cell cytoplasmic antibody-2; VGKC = voltage-gated potassium channel.

[a] Modified with permission from McKeon A, et al, Continuum (Minneap Minn).[6] © 2010 American Academy of Neurology. *journals.lww.com/continuum/Fulltext/2010/04000/IMMUNOTHERAPY_RESPONSIVE_DEMENTIAS_AND.8.aspx*.

under a microscope and comparing it to samples from healthy and diseased controls. Occasionally a pattern of neural-specific binding that has not been described will be found, indicating the presence of an unidentified neural-specific antibody. Neural-specific antibodies that can be detected by this method are outlined in **Table 1-3**.[8] This technique is occasionally limited by the presence of nonspecific binding, the presence of multiple antibodies in an individual patient, and the need for a trained evaluator in the laboratory.

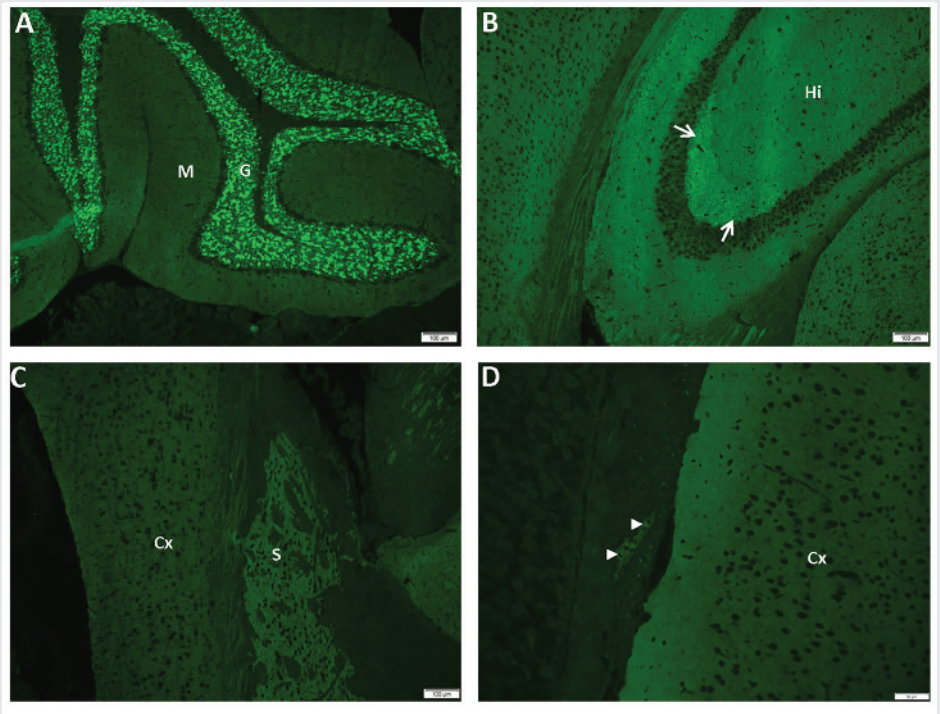

FIGURE 1-2 Synaptic pattern of dipeptidyl-peptidase-like protein-6 (DPPX) immunoreactivity in mouse central and enteric nervous systems revealed by IgG in serum or CSF of patients by tissue immunofluorescence assay. *A*, IgG binds more prominently to the cerebellar granular layer (G) than molecular layer (M); Purkinje neurons are not reactive. *B*, In hippocampus (Hi), the mossy fibers of the stratum lucidum (*arrows*) stain most brightly. *C*, In the cerebrum, the cortex (Cx) and striatum (S) are reactive. *D*, IgG binds to ganglionic neurons in the myenteric plexus of the gut wall (*arrowheads*).

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KEY POINT

■ Western blot is best suited for detecting antibodies that bind to cytosolic or nuclear antigens.

Western Blot or Similar Assay

Several pathogenic antibodies are commonly present in the serum of patients with autoimmune disease. In these cases, and in cases of low-titer antibodies, confirmatory testing may be performed by Western blot. Western blot is best suited for detecting antibodies that bind to cytosolic or nuclear antigens. The substrate for Western blot is generated from neural tissue solubilized in detergent. The proteins are denatured; coated with a negative charge; and separated electrophoretically by size, charge, and isoelectric point. The proteins are then transferred to nitrocellulose membranes or similar and incubated with preadsorbed serum or CSF to allow the neural antibody to bind to the epitopes. These are then detected with an antihuman secondary antibody.

Radioimmunoprecipitation Assays

Ion channel antibodies are typically assessed using a radioimmunoprecipitation assay.[9] This indirectly quantifies a pathogenic antibody using radioactive iodine–labeled antigen, which binds the pathogenic antibody and is subsequently precipitated from solution by an antihuman IgG.

TABLE 1-3 Neural Antibody Associations With Malignancy[a]

	Assay[b]							
Antigen	**IHC**	**WB/LB**	**RIPA**	**FIPA**	**CBA**	**FC**	**PC**	**ELISA**
Cytosolic/nuclear								
ANNA-1 (Hu)	X	X	-	-	-	-	-	-
ANNA-2 (Ri)	X	X	-	-	-	-	-	-
ANNA-3	X	X	-	-	-	-	-	-
Ma1/Ma2	X	X	-	-	-	-	-	-
CV2/CRMP-5	X	X	-	-	-	-	-	-
PCA-1 (Yo)	X	X	-	-	-	-	-	-
PCA-2	X	X	-	-	-	-	-	-
ARHGAP26 (Ca)	X	X	-	-	-	-	-	-
Zic4	X	X	-	-	-	-	-	-
SOX1	X	X	-	-	-	-	-	-
Titin	X	X	-	-	-	-	-	-
Recoverin	X	X	-	-	-	-	-	-
Intracellular synaptic								
Amphiphysin	X	X	-	-	-	-	-	-
GAD65	X	X	X	-	X	-	-	X
Surface								
AQP4	X	X	X	X	X	X	-	X
NMDA receptor	X	-	-	-	X	X	X	-
AMPA receptor	X	-	-	-	X	-	X	-
LGI1	X	-	-	-	X	-	X	-
CASPR2	X	-	-	X	X	-	X	-
GABA-B receptor	X	-	-	-	X	-	X	-
GABA-A receptor	X	-	-	-	X	-	X	X
DR2	X	-	-	-	X	X	X	-

Associations	
Tumor	**Disease**
Small cell lung cancer, neuroblastoma	Sensory neuronopathy, limbic encephalitis, encephalomyelitis
Breast cancer	Opsoclonus-myoclonus
Small cell lung cancer	Neuropathy, ataxia, encephalopathy
Testicular cancer	Brainstem/limbic encephalitis, cerebellar degeneration
Small cell lung cancer, thymoma	Subacute cerebellar degeneration, myelitis, limbic encephalitis, sensory neuropathy, optic neuritis
Gynecologic cancer	Subacute cerebellar degeneration
Small cell lung cancer	Limbic encephalitis, cerebellar ataxia, Lambert-Eaton myasthenic syndrome, motor neuropathy, autonomic neuropathy
Ovarian teratoma	Cerebellar ataxia (limbic encephalitis signs)
Small cell lung cancer (uncommon)	Paraneoplastic cerebellar degeneration, encephalomyelitis
Small cell lung cancer and neuroendocrine tumors	Lambert-Eaton myasthenic syndrome, cerebellar syndrome, limbic encephalitis, sensorimotor neuropathy
Thymoma (80%)	Myasthenia gravis
Small cell lung cancer, breast cancer, renal cell cancer	Cancer-associated retinopathy
Small cell lung cancer, breast cancer	Stiff person syndrome, myelitis, sensory neuronopathy, subacute cerebellar degeneration
Small cell lung cancer, breast cancer	Stiff person syndrome, myelitis, diabetes mellitus
Uncommon association with malignance	Neuromyelitis optica (NMO), NMO spectrum disorder (longitudinally extensive transverse myelitis, optic neuritis)
Ovarian teratoma (~30%)	Encephalitis
Small cell lung cancer, breast cancer, thymoma	Limbic encephalitis
Not common (<10%)	Limbic encephalitis, faciobrachial dystonic epilepsy, Morvan syndrome
Thymoma (~30%)	Neuromyotonia, Morvan syndrome, and, to a lesser extent, limbic encephalitis
Small cell lung cancer, breast cancer, thymoma	Limbic encephalitis
<10% (Hodgkin lymphoma)	Limbic encephalitis with refractory seizures, status epilepticus
Not found	Encephalitis with movement disorder and psychosis, Sydenham chorea, Tourette syndrome

Continued on page 636

TABLE 1-3 **Neural Antibody Associations With Malignancy**[a] *Continued from page 635*

	Assay[b]							
Antigen	**IHC**	**WB/LB**	**RIPA**	**FIPA**	**CBA**	**FC**	**PC**	**ELISA**
Surface (continued)								
MOG	X	X	-	X	X	X	-	-
VGKC	X	-	X	-	-	-	-	-
VGCC	-	-	X	-	-	-	-	-
Glycine receptor	X	-	-	-	X	-	-	-
mGluR1	X	-	-	-	-	-	-	-
mGluR5	X	-	-	-	-	-	-	-
AChR	X	-	X	X	X	-	-	X

AChR = acetylcholine receptor; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA-1 = antineuronal nuclear antibody type 1; ANNA-2 = antineuronal nuclear antibody type 2; ANNA-3 = antineuronal nuclear antibody type 3; AQP4 = aquaporin-4; ARHGAP26 = Rho GTPase activating protein 26; CASPR2 = contactin associated protein-like 2; CBA = cell-binding assay; CRMP-5 = collapsin response mediator protein 5; ELISA = enzyme-linked immunosorbent assay; FC = flow cytometry; FIPA = fluorescent immunoprecipitation assay; GABA-A = γ-aminobutyric acid type A; GABA-B = γ-aminobutyric acid type B; GAD = glutamic acid decarboxylase; IHC = immunohistochemistry; LGI1 = leucine rich glioma inactivated 1; mGluR1 = glutamate metabotropic receptor 1; mGluR5 = glutamate metabotropic receptor 5; MOG = myelin oligodendrocyte glycoprotein; NMDA = *N*-methyl-D-aspartate; PC = primary culture; PCA-1 = Purkinje cell cytoplasmic antibody type 1; PCA-2 = Purkinje cell cytoplasmic antibody type 2; RIPA = radioimmunoprecipitation assay; SOX1 = SRY-related HMG box 1; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel; WB/LB = Western blot/line blot; ZIC4 = Zic family member 4.

[a] Modified with permission from Waters P, et al, Handb Clin Neurol.[8] © 2016 Elsevier.

[b] X indicates that antigen is detectable using this assay.

Quantification of the radioactivity in the sediment allows for a semiquantitative analysis. Small protein toxins from venomous animals, such as snakes, frogs, or snails, bind to many neural antibodies of interest. Thus labeling these toxins with radioactive iodine and mixing them with extracts of brain, muscle, or other tissue of interest is a useful way of generating antibody targets. Note that generating targets by this method may cause misidentification of the target antigen. In the case of voltage-gated potassium channel (VGKC) antibodies, the target was subsequently found to be other proteins that remained complexed with the VGKC.[10,11] Positive VGKC results at a low titer outside of the correct clinical context are often of questionable clinical significance.

Cell-based Assays

Cell-based assays offer improved specificity over the previously discussed assays. The target antigen is natively expressed in mammalian cells present on a microscopy slide, and binding of a pathogenic antibody is detected using an antihuman secondary antibody. As with tissue immunohistochemistry techniques, a trained evaluator is required. The technique is limited by the presence of multiple isoforms of a particular antigenic target (eg, M1 and M23 isoforms of aquaporin-4) and the fact that cells are permeabilized, allowing binding to the cytosolic component of the target antigen. The subjective interpretation of assays with titers near the cutoff has led to the development of semiautomated, quantitative flow cytometric techniques.

Associations	
Tumor	**Disease**
No definite association	Demyelinating disorders, NMO spectrum disorder
Small cell lung cancer, thymoma, adenocarcinoma of breast or prostate	Limbic encephalitis, agrypnia excitata, neuromyotonia, Morvan syndrome
Small cell lung cancer	Lambert-Eaton myasthenic syndrome
Rare (thymoma <10%)	Progressive encephalomyelitis with rigidity and myoclonus, Stiff person syndrome, NMO spectrum disorder
Hodgkin lymphoma	Ophelia syndrome
Hodgkin lymphoma	Paraneoplastic cerebellar degeneration
Thymoma	Myasthenia gravis

These have the additional benefit of using live cells, in which the cytosolic component of the target antigen is not available for antibody binding, thus increasing the specificity of the technique.

Enzyme-linked Immunosorbent Assay

The enzyme-linked immunosorbent assay (ELISA) technique consists of incubating patient serum or CSF with purified target attached to the walls of a plate well. After washing, the presence of antibody is detected with an antihuman secondary antibody linked to alkaline phosphatase or horseradish peroxidase. Antibody titers are inferred by quantitating the color change and comparing this to a standard curve. ELISA is a widely available and rapid test but has some limitations. The most important is the presence of false-positive results in individual sera when they bind not to the target antigen but to the plastic well of the ELISA plate. Empty control wells should be used, but commercially available assays often do not provide this. This may have led to a high rate of false-positive results in ELISA assays for NMO-IgG.[12]

TESTING SERUM OR CEREBROSPINAL FLUID

Ideally, paired samples of serum and CSF should be tested in patients with suspected autoimmune neurologic disease. In patients with NMO-IgG, serum titers of 1:250 or less are associated with undetectable NMO-IgG in CSF,[13] and NMO-IgG is not

KEY POINTS

- A high rate of false-positive results for neuromyelitis optica IgG exists with use of enzyme-linked immunosorbent assays.
- Ideally, paired samples of serum and CSF should be tested in patients with suspected autoimmune neurologic disease.

KEY POINTS

- Paraneoplastic antibodies are more strongly predictive of tumor type than of a particular clinical syndrome.
- Some antibody clusters, when present, should alert the clinician to a high probability of systemic malignancy.

detectable in CSF if it is not detectable in serum.[14] In contrast, patients with NMDA receptor antibody–associated encephalitis can have a negative serum test in over 8% of cases.[15] Data are not available for other neural antibodies, but these studies demonstrate that both serum and CSF should be analyzed in most cases (**Case 1-1**).

ASSOCIATIONS BETWEEN NEURAL ANTIBODIES AND MALIGNANCY

Evaluation for malignancy in the case of a suspected autoimmune neurologic condition is typically guided by the antibody detected.

Paraneoplastic Antibodies Can Predict the Presence of a Malignancy

Neural antibodies are sometimes associated with a systemic malignancy, with a neurologic syndrome commonly preceding the diagnosis of malignancy (**Case 1-2**).[17] Paraneoplastic antibodies are more strongly predictive of tumor type than of a particular clinical syndrome.[18] The most common malignancy associated with paraneoplastic central nervous system (CNS) syndromes is small cell lung cancer. Other antibody-associated malignancies are outlined in **Table 1-1** and **Table 1-2**.

Specific Antibody Clusters Can Predict the Presence of a Malignancy

The presence of two or more autoantibodies in an individual patient occurs more frequently than would be predicted by chance.[19] Some antibody clusters, when present, should alert the clinician to a high probability of systemic malignancy. For example, muscle acetylcholine receptor (AChR) and striational autoantibodies are associated with tumor in 45% of patients. If a third autoantibody is detected, the cancer frequency is higher.[20] Thymoma, in particular, is frequently associated with neurologic syndromes and associated neural antibodies. Antibodies are most commonly directed

Case 1-1

A 24-year-old woman presented with headache and cognitive changes. Brain MRI demonstrated right temporal lobe hemorrhagic changes with diffuse T2 signal abnormality. A CSF pleocytosis was found. She was treated with acyclovir for presumed herpes simplex virus (HSV) encephalitis, which was subsequently confirmed on CSF polymerase chain reaction (PCR) testing. Following treatment, she had persistent behavioral changes and cognitive difficulties. She presented to her neurologist 6 months later with worsening cognition and seizures. CSF analysis was normal, and *N*-methyl-D-aspartate (NMDA) receptor antibody testing was positive. She was treated with IV immunoglobulin (IVIg) and returned to her baseline cognitive function following the initial event.

Comment. The pathophysiology of many autoimmune neurologic diseases remains elusive. NMDA receptor antibody–associated encephalitis is the most common cause of autoimmune encephalitis. It has recently been demonstrated that HSV type 1 encephalitis can be followed by NMDA receptor encephalitis.[16] In these cases, the CSF analysis can be normal, and patients typically respond to immunotherapy. NMDA receptor encephalitis should be considered in patients with a history of HSV encephalitis who present with a clinical worsening.

Case 1-2

A 66-year-old right-handed woman with a history of breast cancer 15 years previously developed ataxia, diplopia, and vertigo over 4 weeks, requiring a wheelchair to mobilize. Given her age, history of cancer, and acuity of symptom onset, she was evaluated for recurrent malignancy with a brain MRI; CT of chest, abdomen, and pelvis; and transvaginal pelvic ultrasound, which were all unrevealing. CSF analysis revealed an increase in nucleated cell count. A whole-body fludeoxyglucose positron emission tomography (FDG-PET) scan demonstrated FDG uptake within a complex left ovarian mass. Biopsy of her ovarian mass revealed a high-grade serous carcinoma of fallopian tube origin. The patient was treated with IV methylprednisolone within 5 weeks of symptom onset, resulting in an improvement in gait and the ability to walk with a cane. A paraneoplastic antibody screen subsequently demonstrated Purkinje cell cytoplasmic antibody type 1 (PCA-1, anti-Yo) antibody. Her malignancy was treated with paclitaxel and carboplatin. Despite freedom from subsequent tumor disease, she continued to have periods of neurologic worsening and required treatment with a variety of immunosuppressant agents, culminating with symptom control on cyclophosphamide.

Comment. Early identification and treatment of suspected autoimmune and paraneoplastic conditions is thought to lead to the best chance of a good outcome. Factors that raised the suspicion for a paraneoplastic cause in this case were the patient's age, history of malignancy, acuity of onset of symptoms, and abnormal CSF findings. Treatment with steroids is often instituted before the results of neural antibody testing are available, serving as both a diagnostic test and a treatment, as a clinical response to steroids suggests a possible autoimmune phenomenon. In patients with antibodies targeting intracellular antigens, such as in this case, the prognosis for complete recovery is often guarded, and patients often require long-term immunosuppression.

against muscle AChR but also against ganglionic AChR, voltage-gated Kv1 potassium channel complex, and the AMPA receptor.[21] Similarly, P/Q-type and N-type calcium channel antibodies, associated with SOX1 antibodies are associated with small cell lung cancer in over 80% of cases.[20] In contrast, detection of neuronal voltage-gated calcium channel autoantibodies has a negative predictive value for the presence of a thymic tumor.[22]

Evaluation for a Suspected Malignancy

The presence of risk factors for malignancy, such as smoking or a family history, or the presence of a neural antibody with an oncologic association should prompt an evaluation for malignancy. Following a detailed history and clinical examination, CT of the chest, abdomen, and pelvis; mammography; testicular ultrasound; and prostate-specific antigen should be considered. Where neuroblastoma is suspected, chest and abdominal CT or MRI along with urine testing for homovanillic acid metabolites should be performed. Antibodies with a particular specificity for cancer (eg, NMDA receptor antibody and teratoma) may require a more targeted oncologic evaluation. PET imaging increases the diagnostic yield by 20% when all standard evaluations (eg, whole-body CT scan) have been uninformative.[23] PET is unable to detect gonadal tumors (ovary or testis), neuroblastoma, or thymoma. MRI has

KEY POINT

- The presence of risk factors for malignancy, such as smoking or a family history, or the presence of a neural antibody with an oncologic association should prompt an evaluation for malignancy.

KEY POINTS

- Cytologic and molecular classification systems have been proposed to describe antibody-associated diseases.
- The most recent iteration of the diagnostic criteria for neuromyelitis optica spectrum disorder emphasizes the importance of detecting neuromyelitis optica IgG with a sensitive and specific assay in the correct clinical context (optic neuritis, brainstem or area postrema syndrome, myelitis, symptomatic narcolepsy, or diencephalic syndrome with neuromyelitis optica spectrum disorder– typical brain MRI).

good sensitivity for both ovarian and thymic tumors.

CLASSIFICATION AND NOMENCLATURE

Neurologic diseases related to neural antibodies have been traditionally described using the clinical phenotype. Clinical entities such as stiff person syndrome and limbic encephalitis allow the clinician to conceptualize a typical presentation, with the intent of identifying such a clinical entity in the future. As more disease entities have been discovered, it has become apparent that individual neural antibodies are associated with significant heterogeneity in clinical phenotype, with a wide range of overlap in the clinical presentation of different antibodies. Given the failure of clinical and phenomenologic classification systems to predict neural antibody–associated syndromes or underlying malignancy, some experts have advocated a cytologic or molecular classification system to describe these diseases. Patients with myelin oligodendrocyte glycoprotein (MOG) antibody–associated demyelinating disease may fulfill the diagnostic criteria for seronegative NMO. This may not be a clinically useful classification for several reasons. MOG antibody–associated demyelinating disease targets oligodendrocytes in contrast to the predominantly astrocytic pathology in NMO spectrum disorder. Both diseases result in complement activation; however, disease-specific treatments, such as aquaporumab (a monoclonal antibody targeting aquaporin-4 that lacks an Fc receptor, thus not capable of activating complement, that is a proposed treatment for NMO spectrum disorder), would not be expected to be effective in treating MOG antibody–associated disease.[24] Terms such as *autoimmune aquaporin-4 channelopathy* and *MOGopathy* may be more appropriate. Similarly, the entity of limbic encephalitis has been separated into many phenotypes, primarily based on the antigenic target, which can differ in oncologic association and clinical phenotype even within an apparently homogenous antibody-associated disease.[25] Identifying the antigenic target (eg, NMDA receptor, contactin associated protein-like 2 [CASPR2] receptor) in the nomenclature may help to clarify the diagnostic evaluation and treatment. This parallels the move to classify neurodegenerative diseases by their associated proteinopathies.[26]

GLIAL AUTOIMMUNITY

Recognition of the importance of so-called supportive cells of the CNS in the pathogenesis of autoimmune diseases has led to a new wave of discovery and potential treatments.

Aquaporin-4 Autoimmunity

Discovery of the aquaporin-4 water channel, located primarily on astrocytes, as an immune target in NMO spectrum disorder has led to distinction of this disease from multiple sclerosis (MS) and a divergence of therapies. Although initially thought to be a demyelinating disease, the central cellular pathology in this condition relates to astrocyte dysfunction.[27] The most recent iteration of the diagnostic criteria emphasizes the importance of detecting NMO-IgG with a sensitive and specific assay in the correct clinical context (optic neuritis, brainstem or area postrema syndrome, myelitis, symptomatic narcolepsy or diencephalic syndrome with an NMO spectrum disorder–typical brain MRI).[28] Identification of one of these typical syndromes in association with the detection of NMO-IgG in

serum allows one to make the diagnosis of NMO spectrum disorder. The entity of seronegative NMO spectrum disorder requires a more stringent set of criteria to be filled in the absence of NMO-IgG detection. This may be useful in areas where NMO-IgG testing is not readily available with a sensitive assay but should be used with caution. Prevention of NMO spectrum disorder relapses with agents targeting B cells, plasma cells, plasmablasts, complement, and blockade of NMO-IgG binding is currently being evaluated in randomized clinical trials.[29–32] Current treatment varies by region but includes oral steroids, azathioprine, mycophenolate mofetil, and rituximab as the most commonly used agents. The duration of treatment is controversial. No evidence exists of disease quiescence after a long duration of disease, such as is present in MS, prompting some experts to advocate lifelong immunosuppression.

Myelin Oligodendrocyte Glycoprotein Autoimmunity

MOG is a component of myelin. Antibodies directed against this glycoprotein have been postulated to be involved in demyelinating-type diseases for decades. Prior testing strategies, including ELISA assays, were of low specificity, rendering the results uninterpretable. Recently, cell-based assays have been found to be much more sensitive and specific for MOG antibodies.[33] In addition, the selection of secondary antibody has been found to be important, with antihuman IgG1–specific secondary antibodies effectively distinguishing a distinct group of patients with non-MS CNS demyelinating disorders from patients with MS.[33] Several groups have reproduced findings indicating that MOG-specific antibodies are associated with a distinct phenotype of CNS demyelinating disease, including conus-predominant myelitis and bilateral optic neuritis, often occurring simultaneously, associated with ''cotton wool'' brain lesions with poorly defined margins.[34] The long-term outcome for patients with MOG antibody–associated CNS inflammatory disease is uncertain. Relapsing disease has been described, so a medium-term course of immunosuppression (1 to 2 years) could be considered.

Glial Fibrillary Acidic Protein Autoimmunity

Antibodies to the glial fibrillary acidic protein (GFAP)-α isoform have recently been described as a biomarker of a steroid-responsive autoimmune meningoencephalomyelitis.[35] Neurologic manifestations are diverse and include headache, transverse myelitis, cognitive decline, optic neuropathy, and cerebellar ataxia that improve with high-dose corticosteroid treatment. Relapses require long-term immunosuppressive therapy. Some patients have associated neoplasms, such as prostate and gastroesophageal adenocarcinomas, myeloma, melanoma, colonic carcinoid, parotid pleomorphic adenoma, and teratoma. CSF is generally inflammatory. Cranial MRI often reveals linear perivascular enhancement oriented radially to the ventricles.

NEURONAL AUTOIMMUNITY

Autoimmunity to neuronal targets results in both neuronal loss and neuronal dysfunction to varying degrees.

Encephalitides, Neuropsychiatric Disorders, and Dementia

Antibodies directed against targets at or near the NMDA receptor account for the second most common form of autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM)[36] and over half of undiagnosed

KEY POINTS

- The entity of seronegative neuromyelitis optica spectrum disorder requires a more stringent set of criteria to be filled in the absence of neuromyelitis optica IgG detection.
- Myelin oligodendrocyte glycoprotein–specific antibodies are associated with a distinct phenotype of central nervous system demyelinating disease, including conus-predominant myelitis and bilateral optic neuritis, often occurring simultaneously, associated with ''cotton wool'' brain lesions with poorly defined margins.
- Antibodies to the glial fibrillary acidic protein-α isoform have recently been described as a biomarker of a steroid-responsive autoimmune meningoencephalomyelitis.
- Antibodies directed against targets at or near the *N*-methyl-D-aspartate receptor account for the second most common form of autoimmune encephalitis after acute disseminated encephalomyelitis.

KEY POINTS

- Viral herpes simplex type 1 encephalitis can be followed by *N*-methyl-D-aspartate receptor encephalitis.
- Rapid-onset cognitive impairment, in particular if associated with a personal or family history of autoimmunity or abnormal CSF findings, should prompt consideration of an autoimmune cause.
- Any treatment of cognitive impairment with immunotherapy should be accompanied by careful objective documentation of cognitive deficits before embarking on an immunotherapy trial to allow an objective demonstration of any treatment response.
- Features that should prompt the clinician to consider an autoimmune cause for seizures include a new-onset seizure disorder with frequent events; new-onset refractory status epilepticus; multiple event types in one individual; antiepileptic drug treatment resistance; CSF abnormalities; and a history of malignancy, smoking, or autoimmune disease.

encephalitides previously thought to be viral in nature.[37]

The clinical phenotype is that of initial agitation with subsequent catatonia and seizures, memory loss, decreased level of consciousness, central hypoventilation, and characteristic orofacial and ''piano-playing'' dyskinesias. Although the original description of this entity was in women with teratomas, the disease has been found in all age groups, and approximately 40% of patients are found to have a neoplasm, predominantly teratoma.[38] The glutamatergic NMDA receptor is thought to be the primary antigenic target of NMDA receptor antibodies. Recent evidence suggests that dysregulation of extracellular cross talk between the GluN2-NMDA receptor subtype with the membrane receptor ephrin (EPHB2) causes dispersion of the GluN2-NMDA receptor away from the synapse and reduces synaptic plasticity, possibly accounting for memory loss in affected patients.[39] NMDA receptor encephalitis occurring following HSV type 1 encephalitis has been reported, giving a clue to the underlying etiology of the disorder.[16] In these cases, the CSF analysis can be normal, and patients typically respond to immunotherapy and not to antiviral therapy. NMDA receptor encephalitis should be considered in patients with a history of HSV encephalitis who present with a clinical worsening (**Case 1-1**).

Cognitive impairment secondary to an autoimmune cause is typically associated with other features, such as seizures, autonomic dysfunction, movement disorders, or other abnormal clinical findings. A summary of antibody and T-cell–mediated autoimmune causes of neuropsychiatric and dementia presentations and encephalitis are summarized in **Table 1-2**. Rapid-onset cognitive impairment, in particular if associated with a personal or family history of autoimmunity or abnormal CSF findings, should prompt consideration of an autoimmune cause. Any treatment of cognitive impairment with immunotherapy should be accompanied by careful objective documentation of cognitive deficits before embarking on an immunotherapy trial to allow an objective demonstration of any treatment response. While some causes of autoimmune cognitive impairment, such as NMDA receptor antibody–associated encephalitis, may require medium- to long-term immunosuppression, other presumed autoimmune causes of cognitive impairment are monophasic. In the absence of a definitively identified antibody, careful monitoring after withdrawal of an initial therapeutic trial of immunosuppressive medication may be warranted.

Epilepsy

An autoimmune basis for seizures has long been recognized and is typically associated with other neurologic symptoms, such as in the case of NMDA receptor antibody–associated encephalitis. More recently appreciated is the presence of seizures in the absence of other neurologic symptoms from an autoimmune etiology. Isolated mesial temporal sclerosis has been demonstrated in patients with autoimmune epilepsy.[40] Features that should prompt the clinician to consider an autoimmune cause for seizures include a new-onset seizure disorder with frequent events; new-onset refractory status epilepticus (NORSE); multiple event types in one individual; antiepileptic drug (AED) treatment resistance; CSF abnormalities; and a history of malignancy, smoking, or autoimmune disease. Note that CSF abnormalities are not invariable in autoimmune conditions, so the presence of a normal CSF should not dissuade the clinician from considering autoimmune causes.

Both intracellular and extracellular antigenic targets have been described in patients with autoimmune epilepsy, indicating diverse mechanisms of epileptogenesis. No trials have been performed comparing immunotherapy alone versus immunotherapy and AEDs in patients with autoimmune epilepsy. Pragmatically, patients with autoimmune epilepsy tend to be resistant to AED treatment so are on several agents by the time a therapeutic trial of immunotherapy has been administered.

Movement Disorders

Historically, chorea has been described following streptococcal infection (Sydenham chorea), in pregnancy, and in patients with serologic markers of antiphospholipid syndrome, suggesting an immune-mediated cause in these cases. More recently, antibody associations have been described in almost all types of movement disorders. Some, but not all, of these syndromes are associated with malignancy. In these cases, the antibody detected is more strongly predictive of the presence of malignancy than of a particular clinical phenotype. Variability in the clinical presentation is common. Features that should prompt the clinician to consider an autoimmune cause for a movement disorder include a subacute onset and a widespread distribution of symptoms and signs, including involvement of the trunk and head as well as extremities. Early treatment with immunotherapy can halt or reverse the progression of disease. Movement disorders associated with intracellular antigens, such as PCA-1–associated cerebellar ataxia or antineuronal nuclear antibody type 2 (ANNA-2)–associated dystonia, tend to be associated with significant disability unless early immunotherapy is initiated and malignancy identified and treated.

Stiff person syndrome is a condition of limb and paraspinal muscular rigidity characterized by hyperexcitability of the brainstem and spinal motor neurons.[41] Limited forms of the condition have been described, including stiff limb and stiff trunk. On the other end of the spectrum, rigidity can be accompanied by other neurologic features such as cerebellar ataxia and seizures. A rapidly progressive syndrome of progressive encephalomyelitis with rigidity and myoclonus (PERM) has been described, which also forms part of this spectrum.[42] Glutamic acid decarboxylase 65 (GAD65) antibodies are the most commonly encountered neural antibody in these conditions. Note that these are also detected in patients with type 1 diabetes mellitus at lower titers. Serum GAD65 titers of 20 nmol/L or higher are more commonly associated with an immunotherapy-responsive neurologic condition. Other antibodies that are associated with stiff person syndrome include amphiphysin (associated with small cell lung cancer, breast adenocarcinoma, and melanoma) glycine receptor, and gephyrin antibodies (one case reported). Patients with glycine receptor antibodies may have a more robust response to immunotherapy.[43]

Diencephalic and Brainstem Disorders

Well before neural antibodies were associated with sleep disruption, the tight linkage of human leukocyte antigen (HLA)-DR2 to narcolepsy suggested an autoimmune basis to this disorder.[44] Subsequently, several neural antibodies have been identified with characteristic sleep abnormalities. The key clinical features associated with the most commonly encountered neural antibodies in sleep disruption are summarized in **Table 1-4**.[45]

KEY POINTS

- CSF abnormalities are not invariable in autoimmune conditions, so the presence of a normal CSF should not dissuade the clinician from considering autoimmune causes.
- Features that should prompt the clinician to consider an autoimmune cause for a movement disorder include a subacute onset and a widespread distribution of symptoms and signs, including involvement of the trunk and head as well as extremities.

TABLE 1-4 Sleep Disorders Associated With Specific Autoantibodies[a]

Sleep Disorder	VGKC Complex (CASPR2/ LGI1)	Ma1/Ma2	Aquaporin-4	NMDAR	IgLON5	ANNA-2
Narcolepsy	-	++	++	-	-	-
Hypersomnolence	+	-	-	+	-	-
Rapid eye movement (REM) behavior disorder	++	+	-	-	+[b]	-
Insomnia	+++	-	-	+	-	-
Sleep apnea	-	-	-	+ (central sleep apnea)	++ (obstructive sleep apnea)	-
Central hypoventilation	-	-	-	++	+	-
Stridor	-	-	-	-	++	+

+ = association; ++ = frequent association; +++ = very frequent association; - = not commonly associated; ANNA-2 = antineuronal nuclear antibody type 2; CASPR2 = contactin associated protein-like 2; IgLON5 = IgLON family member 5; LGI1 = leucine rich glioma inactivated 1; NMDAR = *N*-methyl-D-aspartate receptor; VGKC = voltage-gated potassium channel.
[a] Modified with permission from Silber MH, Handb Clin Neurol.[45] © 2016 Elsevier.
[b] Also abnormal motor behavior in non–rapid eye movement (non-REM) sleep.

VGKC complex antibodies include CASPR2 and LGI1 and are associated with profound insomnia, nocturnal agitation, and dream enactment (agrypnia excitata).[46] The phenotypic variability of VGKC complex antibody–associated syndromes is still being elucidated. Even antibody subtypes such as CASPR2 appear to target a number of different antigens, giving rise to the phenotypes of neuromyotonia, Morvan syndrome, and limbic encephalitis.[25]

Aquaporin-4 is distributed throughout the brain but is localized in the periventricular regions, including the floor of the fourth ventricle.[47] Brainstem and diencephalic symptoms of hiccups, vomiting, and symptomatic narcolepsy, have been included as core clinical characteristics of the disease in the updated diagnostic criteria for NMO spectrum disorder, allowing for the diagnosis of an NMO spectrum disorder in the presence of one of these symptoms and NMO-IgG antibody.[28] In cases of NMO spectrum disorder–associated narcolepsy, bilateral hypothalamic involvement is typical, and no cases of NMO spectrum disorder–associated narcolepsy have been described with associated cataplexy. Other signs of hypothalamic dysfunction are commonly associated, including hypothermia, dysautonomia, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

NMDA receptor antibody–associated encephalitis can be associated with severe insomnia in the early excitatory phase of the disease. Central hypoventilation is present in two-thirds of patients, particularly in patients later in the disease process.[48] Even after apparent clinical recovery, 27% of patients continue to have significant sleep disturbance.[48]

IgLON5 antibodies have been demonstrated in a small number of patients

with dysarthria, dysphagia, dysautonomia, gait ataxia, ocular motility abnormalities, and chorea. Obstructive sleep apnea, nocturnal stridor, and abnormal motor behaviors of sleep were key features.[49] Curiously, autopsy findings in two patients demonstrated neuronal hyperphosphorylated tau protein in the hypothalamus and brainstem tegmentum. It is unclear whether this condition represents a neurodegenerative proteinopathy associated with nonpathogenic neural antibodies or a neuroinflammatory condition with secondary neurodegeneration.

Hypersomnolence and cataplexy have been reported in association with Ma antibody–associated narcolepsy. Hypothalamic endocrine dysfunction, seizures, and supranuclear gaze palsies have also been described.[50] Multiple sleep latency tests show findings typical of narcolepsy, with reduced sleep latencies and multiple sleep-onset rapid eye movement (REM) periods. Seropositivity for both Ma1 and Ma2 antibodies is associated with carcinoma of the lung, gastrointestinal tract, breast, salivary glands, and ovary; non-Hodgkin lymphoma; germ cell tumors; renal rhabdoid tumors; and melanoma. Seropositivity for the Ma2 antibody only is associated with testicular cancer, underscoring the need to perform a testicular examination in men with a diencephalic clinical presentation.[51] The nomenclature of Ma1/Ma2 can be confusing. Ma1 and Ma2 are distinct proteins. The entity previously described as Ma antibody described detection of both Ma1 and Ma2 antibodies. Ta antibody described detection of Ma2 alone.

ANNA-2 (anti-Ri) antibody is characteristically associated with opsoclonus-myoclonus syndrome but is also found in association with multifocal brainstem, cerebellar, and spinal cord dysfunction. Stridor is a characteristic feature, occurring frequently during sleep. Jaw-opening dystonia and laryngospasm can occur, sometimes requiring tracheostomy to manage.[52] Carcinoma of the breast, lung, and uterine cervix have been described in adult patients in association with ANNA-2. Neuroblastoma is more common in children. Other antibodies associated with opsoclonus-myoclonus syndrome include glycine receptor and human natural killer 1 (HNK-1) antibodies, both associated with lung malignancy.[53]

AUTOIMMUNE MYELOPATHIES

The differential diagnosis of myelopathies can be a challenging clinical dilemma. This section focuses specifically on autoimmune myelopathies. Similar to all autoimmune diseases, autoimmune myelopathies are more common in women. NMO spectrum disorder is more common in patients of African, Native American, and Hispanic descent. Paraneoplastic myelopathies are more common in the elderly. MS is more common among Caucasians, and a family history of the disease increases the risk of MS. Similarly, a family history of autoimmune disease, such as autoimmune thyroid disease, lupus, or rheumatoid arthritis, may suggest a predisposition toward NMO spectrum disorder or other antibody-mediated myelopathies.

The clinical course can yield clues to the differential diagnosis, with typical transverse myelitis being of subacute onset over days to weeks and conditions such as neurosarcoidosis and paraneoplastic myelopathies having a progressive course from onset.

Neuroimaging is essential in the differential diagnosis of myelopathies. A schematic of the different patterns of spinal cord abnormalities is shown in **Figure 1-3**[54] and **Figure 1-4**. A common pitfall is to mistake multiple

KEY POINTS

- A family history of autoimmune disease, such as autoimmune thyroid disease, lupus, or rheumatoid arthritis, may suggest a predisposition toward neuromyelitis optica spectrum disorder or other antibody-mediated myelopathies.
- The clinical course of a myelopathy can yield clues to the differential diagnosis, with typical transverse myelitis being of subacute onset over days to weeks and conditions such as neurosarcoidosis and paraneoplastic myelopathies having a progressive course from onset.

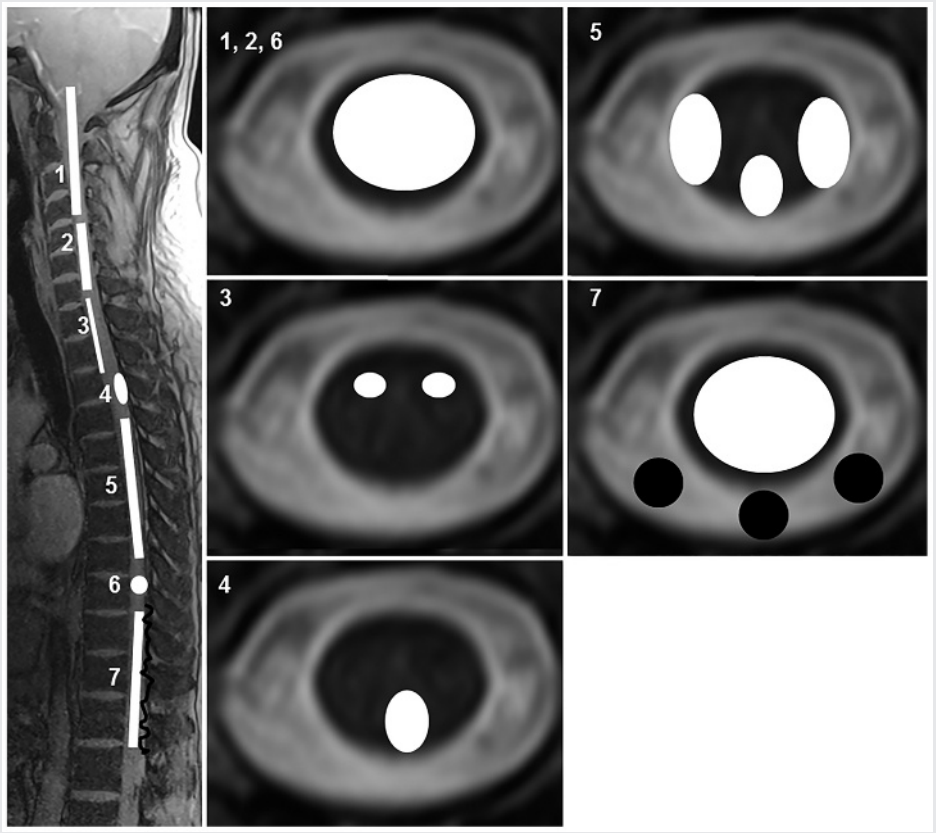

FIGURE 1-3 Summary of T2-hyperintensity patterns in autoimmune myelopathies and their mimics. Sagittal (*left panel*) and axial (*right panels*) patterns of T2-signal abnormality are shown. *1*, Neuromyelitis optica (NMO) spectrum disorder or sarcoidosis (both usually more than three vertebral segments on sagittal images and central on axial images). *2*, Cervical spondylotic myelopathy (variable length on sagittal images and central on axial images). *3*, Anterior spinal artery infarct (variable length; pencil-like long slim lesions anteriorly on sagittal images; owl eye or snake eye on axial images; may involve lower thoracic cord particularly after aortic aneurysm surgery; similar gray matter lesions may also be seen with West Nile virus and other infections). *4*, Multiple sclerosis (fewer than three vertebral segments; dorsal cord [lateral cord also common]; usually unilateral). *5*, Paraneoplastic (variable length; tractopathy: dorsal or lateral columns symmetrically; may also be seen in copper or vitamin B_{12} deficiency). *6*, Primary intramedullary spinal cord lymphoma. *7*, Dural arteriovenous fistula (usually more than three vertebral segments on sagittal images; black regions represent flow voids usually dorsal to spinal cord; often extends to conus [myelin oligodendrocyte glycoprotein (MOG)-IgG myelopathy similarly involves conus]).

contiguous short high-signal lesions on T2-weighted imaging for a longitudinally extensive lesion. Careful examination of axial T2-weighted images will typically show multiple discrete eccentrically located lesions in the case of MS in contrast to a single long centrally located lesion in NMO or tract-specific abnormalities in paraneoplastic myelopathies. Differentiation from non–immune-mediated causes of myelopathy is equally important, particularly given that compressive and vascular causes are often amenable to surgical correction. Cord enhancement has been described in cases of spondylosis with compressive myelopathy, with the enhancement typically present at or below the site of maximum compression.[55]

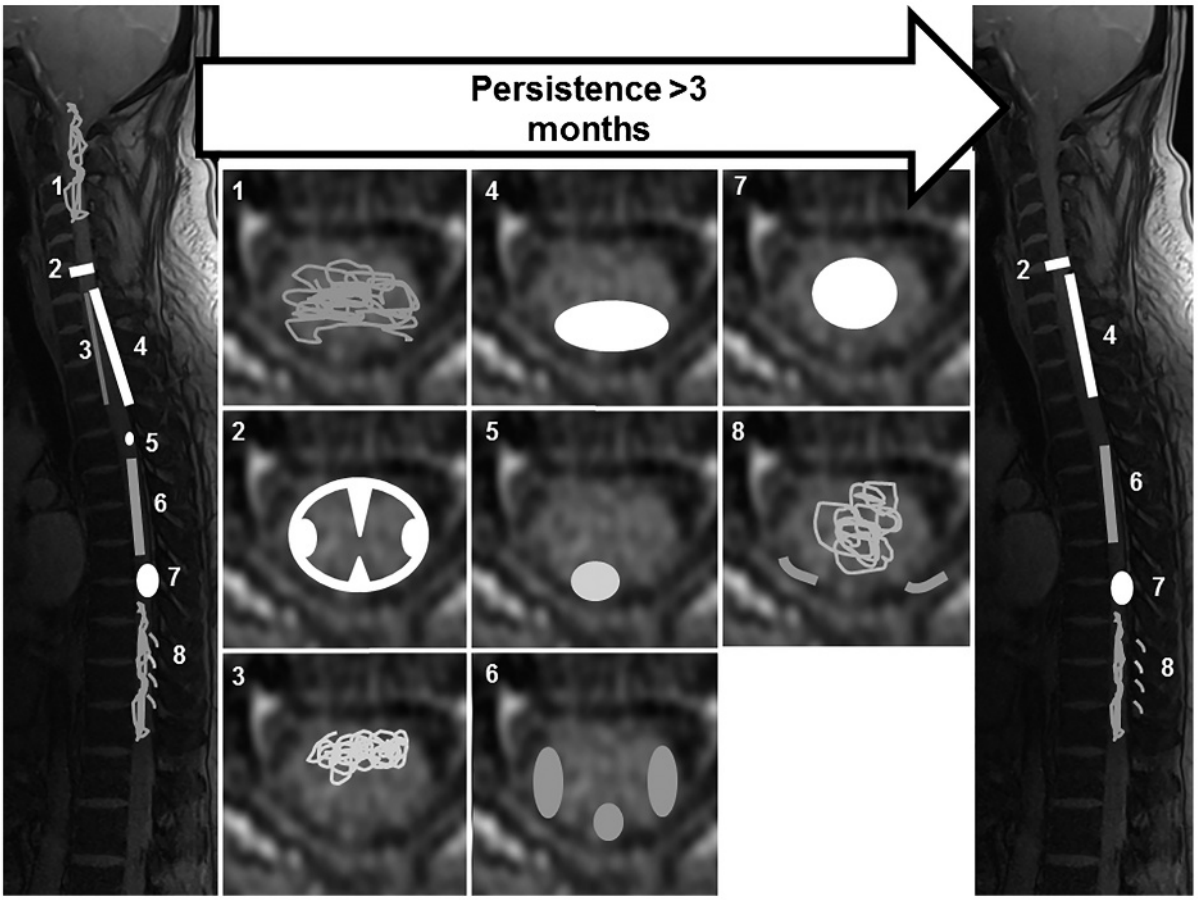

FIGURE 1-4 Summary of gadolinium enhancement patterns and evolution in autoimmune myelopathies and their mimics. Sagittal (*left panel* and *right panel* [persistently enhancing lesions shown]) and axial (*middle panels*) patterns of gadolinium enhancement. Brighter regions represent higher intensity of enhancement. *1*, Neuromyelitis optica (NMO) spectrum (patchy). *2*, Cervical spondylotic myelopathy (pancakelike or transverse band on sagittal images and circumferential white matter sparing gray matter on axial images; enhancement only present in 7% of spondylotic myelopathies but, when present, often mimics tumor or inflammation). *3*, Anterior spinal artery infarct (patchy in anterior spinal cord). *4*, Spinal cord sarcoidosis (dorsal subpial linear extending over multiple segments). *5*, Multiple sclerosis (dorsal cord [lateral cord may also be seen]; may be nonenhancing; often asymmetric). *6*, Paraneoplastic symmetric tract-specific enhancement. *7*, Primary intramedullary spinal cord lymphoma (bright homogeneous enhancement). *8*, Dural arteriovenous fistula (patchy; enhancing veins dorsal to spinal cord may be seen; may or may not be associated with gadolinium enhancement).

Dural arteriovenous fistula should also be considered in the case of thoracolumbar myelopathy.[56]

PRINCIPLES OF TREATMENT

Although several trials are under way in the treatment of NMO, no large randomized controlled trials have been performed in patients with the majority of the conditions discussed here. The goal of initial treatment is to determine the maximum response that can be obtained with immunotherapy. Immunotherapy serves both as an initial treatment and a diagnostic test. Patients who have no response to immunotherapy, in the absence of an antibody known to require long-term treatment (such as NMO-IgG or NMDA receptor IgG), should prompt reevaluation for alternative etiologies (**Case 1-3**). Treatment typically

KEY POINT

- The goal of initial treatment of neuromyelitis optica is to determine the maximum response that can be obtained with immunotherapy.

KEY POINTS

- In patients with a suspected autoimmune neurologic syndrome with no therapeutic response to immunotherapy, the diagnosis should be reevaluated.
- Objective measures of disability and treatment response should be obtained before and after treatment of suspected autoimmune neurologic conditions.
- In patients treated with IVIg, false-positive antibody results can be seen due to the transfused immunoglobulin.

Case 1-3

A 68-year-old man presented for a second opinion about a diagnosis of stiff person syndrome. He reported progressive pain, stiffness, and gait difficulty associated with cognitive changes. Glutamic acid decarboxylase 65 (GAD65) antibodies were noted to be elevated. He had been treated with steroids, azathioprine, mycophenolate mofetil, IV immunoglobulin (IVIg), and cyclophosphamide. Despite treatment, he did not report an improvement in symptoms. Repeat neural antibody testing demonstrated elevated GAD65 antibodies in the serum (titer 12 nmol/L) but not in CSF. Neuropsychometric testing demonstrated mild cognitive inefficiencies with primarily attentional cognitive deficits. Neurophysiologic testing for agonist and antagonist muscle cocontraction was normal. Immunosuppressive treatments were withdrawn, and a repeat evaluation 6 months later was unchanged.

Comment. Autoimmune syndromes are diagnosed on the basis of a typical clinical syndrome and supportive findings, such as abnormal MRI brain or CSF analysis or the presence of a pathogenic neural antibody. The presence of a neural antibody alone does not constitute a disease and is not a requirement for the diagnosis of an autoimmune neurologic syndrome. Care must be taken when interpreting neural antibody testing results to avoid overdiagnosis of autoimmune neurologic diseases and consequent inappropriate immunosuppression. In this case, the patient presented with symptoms which, although they can be present in stiff person syndrome, were relatively nonspecific. The presence of GAD65 antibodies had led to the diagnosis of stiff person syndrome. GAD65 is commonly elevated in patients with a predisposition to autoimmunity. GAD65 titers of more than 20 nmol/L, detectable antibody in CSF, and the presence of other potentially pathogenic neural antibodies are more likely to be associated with an immunotherapy-responsive neurologic syndrome.[57] In patients with a suspected autoimmune neurologic syndrome with no therapeutic response to immunotherapy, the diagnosis should be reevaluated. In some cases, a trial of immunotherapy may be helpful to clarify the diagnosis.

consists of IV methylprednisolone or IV immunoglobulin (IVIg) in patients who may not tolerate steroids. Plasma exchange can be used in patients with treatment-refractory disease or in patients with contraindications to other treatments. The intensity and duration of the initial phase of treatment varies depending on the clinical syndrome and severity of illness. Patients who are clinically unstable, such as those requiring intensive care unit support, may require a rapid escalation of treatment strategies. In the outpatient setting, patients are typically treated with 5 days of IV methylprednisolone 1 g/d or IVIg 0.4 g/kg/d, followed by once weekly methylprednisolone 1 g or once weekly IVIg 0.4 g/kg, for 6 to 12 weeks (**Case 1-4**). Where possible, objective measures of disability and treatment response should be obtained before and after treatment (eg, EEG, MRI, CSF, video). Clinical response is a more important outcome measure than change in antibody titers. Note that in patients treated with IVIg, false-positive antibody results can be seen due to the transfused immunoglobulin.

Once reversibility of the clinical syndrome has been established by objective improvements following an initial treatment trial and a maximal response is deemed to have been

Case 1-4

A 66-year-old man presented with subacute cognitive decline, encephalopathy, and a CSF pleocytosis. He returned to normal cognition with a course of IV steroids. His cognition deteriorated again after 1 month, and he was treated with IV immunoglobulin (IVIg) for 5 days and then azathioprine and monthly IVIg. On a return visit, he reported a deterioration in cognition in the week before his IVIg infusion. His mean corpuscular volume (MCV) was noted to have increased by only 3 femtoliters (fL) from his baseline. The dose of azathioprine was increased. At a return visit 6 months later, he no longer reported an end-of-dose phenomenon with IVIg, and his MCV had risen 6 fL from his baseline before azathioprine therapy.

Comment. The half-life of IVIg is 18 to 32 days. The effect of IVIg on autoimmune encephalopathies tends to wear off after 4 to 5 weeks. The presence of an end-of-dose worsening with IVIg suggests that the autoimmune disease continues to be active and require treatment. Patients who have a clinical response when treated with azathioprine tend to have a 5 fL or more elevation in MCV in response to treatment. In this case, the lack of compete clinical response was accompanied by only a 3 fL rise in MCV. The dose of azathioprine was increased, and the patient demonstrated a sustained response to treatment.

KEY POINTS

- Patients who have a clinical response when treated with azathioprine tend to have a 5-femtoliter or more elevation in mean corpuscular volume in response to treatment.
- Therapeutic drug monitoring is not routinely recommended in patients treated with mycophenolate mofetil; however, in patients with loss of disease control, mycophenolic acid serum levels are useful to guide treatment toward dose escalation or drug switching.

achieved, long-term management should be addressed. The duration of long-term treatment should be tailored based on the clinical syndrome and associated neural antibodies. Autoimmune encephalitis may be monophasic in nature, such as in the case of NMDA receptor encephalitis or LGI1 antibody encephalitis. Conversely, NMO is known to relapse even after 40 years of disease quiescence. In the authors' practice, patients who require long-term treatment are prescribed oral or IV steroids for 6 months while a steroid-sparing agent such as azathioprine or mycophenolate mofetil is initiated. When evaluating treatment response, medication regimen adherence is important to consider. Treatment with azathioprine is typically associated with a rise in mean corpuscular volume of 5 or more femtoliters from the pretreatment value.[58] Detecting such a rise is consistent with medication regimen adherence. Serum mycophenolic acid, the active metabolite of mycophenolate mofetil, can be quantified to ensure therapeutic levels. After 6 months, steroids are tapered slowly over a further 6 months, and patients are watched carefully for a symptom relapse. It is important to continue corticosteroid or immunoglobulin treatment for approximately 12 weeks after initiation of azathioprine and 8 weeks after initiation of mycophenolate mofetil (**Case 1-5**). No data exist to guide the duration of long-term immunosuppression. The authors generally start a trial of medication withdrawal after 2 years, with objective monitoring where possible before and after treatment withdrawal.

General precautions should be undertaken for patients on long-term steroid and immunosuppressant use. Apart from the drug-specific monitoring recommendations, the authors recommend that all patients have a tuberculosis test before starting treatment and a baseline chest x-ray. Vaccinations should be up-to-date, including pneumococcal vaccine and seasonal inactivated influenza vaccine, and live vaccines should be avoided for the duration of treatment. Preventive

Case 1-5

A 36-year-old man was diagnosed with *N*-methyl-D-aspartate (NMDA) receptor encephalitis after an episode of subacute cognitive decline, weight loss, and abnormal hand movements. He was treated with IV immunoglobulin (IVIg) and subsequently with mycophenolate mofetil. On returning for review after starting mycophenolate mofetil, he reported worsening cognition and hallucinations. Serum mycophenolic acid levels were found to be low. He was treated with a brief course of IV steroids and the dose of mycophenolate mofetil was increased, resulting in symptom resolution.

Comment. Mycophenolate mofetil is rapidly hydrolyzed after absorption to its active metabolite, mycophenolic acid. Therapeutic drug monitoring is not routinely recommended in patients treated with mycophenolate mofetil; however, in patients with loss of disease control, mycophenolic acid serum levels are useful to guide treatment toward dose escalation or drug switching.

medications for pneumocystis (eg, trimethoprim-sulfamethoxazole, atovaquone, or nebulized pentamidine) should be considered.

CONCLUSION

The identification of autoimmune and paraneoplastic neurologic diseases requires a high degree of clinical suspicion in the setting of subacute-onset symptoms. The clinical response is best if treated early, so a trial of immunosuppression should be considered in the correct clinical context, even in the absence of identified neural antibodies. A favorable response to treatment supports the diagnosis, whereas a lack of treatment response should prompt a reevaluation for alternative etiologies. Comprehensive clinical, neuropsychological, radiologic, electrophysiologic, serologic, and CSF evaluation permits accurate characterization of the neurologic deficits, immunologic abnormalities, and risk for an underlying cancer.

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Neurologic Complications of Cardiac and Aortic Disease

James P. Klaas, MD

ABSTRACT

Purpose of Review: This article discusses neurologic complications that can arise from cardiac and aortic disease and dysfunction.

Recent Findings: Advances in the care of patients with cardiac or aortic disease include the use of prolonged cardiac monitoring in cryptogenic stroke and the approval of the use of left atrial appendage closure devices for stroke prevention in patients with atrial fibrillation who are not candidates for anticoagulation. Continuing controversy surrounds patent foramen ovale closure, and new evidence indicates that cognitive impairment following coronary artery bypass grafting surgery may be less common than previously thought.

Summary: Dysfunction of the cardiovascular system can cause serious neurologic injury. In some cases, both the initial presenting symptom and the most serious damage done by cardiac or aortic dysfunction may be neurologic. Prompt recognition of the symptoms, combined with recent advances in both cardiology and neurology, may permit more accurate diagnoses, more effective treatment, and less injury to patients.

Continuum (Minneap Minn) 2017;23(3):654–668.

INTRODUCTION

The cardiovascular system and the nervous system are intimately intertwined: proper function in one is essential to proper function of the other, and dysfunction in one can cause complications in the other. This article focuses on how dysfunction in the cardiovascular system can cause neurologic complications.

Stroke is the most common and most widely recognized neurologic complication of cardiac and aortic disease. However, many neurologic complications may arise from cardiovascular dysfunction and are less common than stroke but still important to recognize, including dementia, meningoencephalitis, cerebritis, aneurysm formation, myelopathy, radiculopathy, neuropathy, and possibly even migraines. Recent advances in devices and technologies allow clinicians to better diagnose, treat, and perhaps even prevent many neurologic complications of cardiac and aortic disease.

HEART

Neurologic complications related to heart disease include complications related to arrhythmias, patent foramen ovale, endocarditis, cardiac tumors, heart failure, and cardiac surgery.

Cardioembolic Stroke

Stroke is the most common neurologic complication of cardiac disease. Roughly 20% to 30% of all strokes are cardioembolic.[1,2] Emboli can arise from valvular disease, stasis of blood

flow, or a systemic venous source that reaches the brain via an abnormal connection between the right and left sides of the heart (**Table 2-1**). Once the emboli reach the brain, the effect can be devastating, even fatal.

Nonvalvular atrial fibrillation (AF) is the main risk factor for cardioembolic stroke. Atrial flutter carries the same risk for cardioembolic stroke as AF. AF is age related; as the average age of the population rises, the incidence and prevalence of AF is expected to increase substantially.[3] However, AF can be difficult to detect. Because AF is often paroxysmal and patients are usually asymptomatic, cardiac monitoring is often necessary to diagnose AF. However, even conventional cardiac monitoring (eg, ECG, 24-hour or 48-hour Holter monitor) may not be sufficient. Roughly 20% to 40% of all ischemic strokes are still classified as cryptogenic (ie, no definitive cause of stroke is identified).[1,2] For patients with a cryptogenic stroke, prolonged cardiac monitoring may be indicated.[4,5] Recent prolonged cardiac monitoring studies detected AF in 10% to 15% of patients with cryptogenic stroke.[6,7] The likelihood of detection increases with age, radiographic evidence of prior cortical or cerebellar infarct, prolonged PR interval or frequent premature atrial contractions, or higher $CHADS_2$ (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and previous stroke/transient ischemic attack [TIA]) score.[8–10]

TABLE 2-1 Potential Etiologies of Cardioembolic Stroke

▶ **Valvular Disease**
Infective and noninfective endocarditis
Tumor (eg, papillary fibroelastoma)
Artificial valve
Rheumatic disease
Annular calcification
▶ **Stasis of Blood Flow**
Arrhythmias
Atrial fibrillation/flutter
Other atrial tachyarrhythmias
Left atrial appendage enlargement/dysfunction
Left ventricular thrombus as a complication of myocardial infarction
Congestive heart failure
▶ **Paradoxical Embolism**
Patent foramen ovale
Congenital heart disease (eg, atrial septal defect)

The increasing incidence and detection of AF has led to an increase in the number of patients being treated with anticoagulant medications for stroke prevention. However, for some patients, the risk of bleeding precludes the use of anticoagulants. For example, current guidelines recommend against long-term anticoagulation of patients with a lobar intracerebral hemorrhage and AF because of the high risk of recurrent hemorrhage.[11] For these patients, left atrial appendage closure is an emerging alternative treatment option. The left atrial appendage is the main site of intracardiac thrombus formation for patients with AF; closure substantially reduces the risk of thromboembolism without the need for long-term anticoagulation. Various surgical procedures and devices can be used to close the left atrial appendage, including a catheter-based left atrial appendage closure implant (**Figure 2-1**) that is percutaneously placed into the entrance of the atrial appendage. Based on clinical trial data that demonstrated

KEY POINTS

- Prolonged cardiac monitoring should be considered for patients with cryptogenic stroke.
- Left atrial appendage closure is an emerging stroke prevention treatment option for patients with atrial fibrillation for whom anticoagulation is problematic.

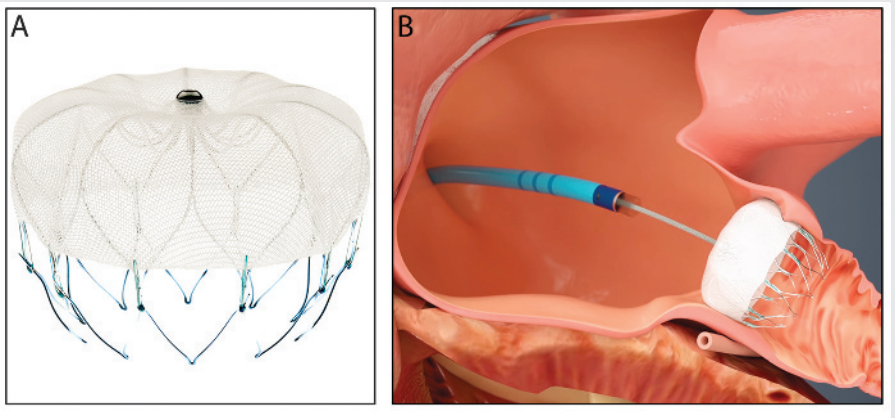

FIGURE 2-1 Left atrial appendage closure device (*A*) being implanted in the left atrial appendage (*B*).

noninferiority to warfarin, use of the implant was approved by the US Food and Drug Administration (FDA) in 2015.[12]

For more information on AF and stroke, refer to the article "Cardioembolic Stroke" by Cumara B. O'Carroll, MD, MPH, and Kevin M. Barrett, MD, MSc,[13] in the February 2017 Cerebrovascular Disease issue of *Continuum*.

Patent Foramen Ovale

In utero, the foramen ovale is an opening between the right and left atria of the heart, allowing maternally oxygenated blood to bypass the fetal lungs. At birth, pressure changes close the foramen ovale. In approximately 25% of individuals, however, closure fails or is incomplete,[14] so those patients live their lives with a patent foramen ovale (PFO). A PFO is usually not harmful, but epidemiologically, PFO prevalence is higher than expected in patients with cryptogenic stroke and migraine, especially migraine with aura.[15,16]

One possible mechanism of cryptogenic stroke is paradoxical embolism from right-to-left shunting through a PFO. Potential sources of emboli include venous thromboembolism, air or fat emboli, right-sided valve disease, or thrombi attached to leads from an implanted cardiac device. Additionally, although conflicting evidence exists, the presence of both a PFO and an atrial septal aneurysm, defined as redundant or hypermobile interatrial tissue, increases stroke risk.[17] Clinically, however, unless an embolic source is identified, it is difficult to determine if a PFO is incidental or not, and a complete evaluation to exclude other causes of stroke is usually necessary. A tool that may aid clinicians in determining whether a PFO is incidental or not is the Risk of Paradoxical Embolism (RoPE) score; the higher the score, the more likely the PFO is relevant (**Table 2-2**).[18] The RoPE score, however, should not be overly relied upon until further external validation studies have been completed.

For patients with stroke attributable to a PFO, secondary stroke prevention treatment options include medical therapy or device or surgical closure. In terms of medical therapy, unless an indication for anticoagulation exists, such as an acute deep vein thrombosis, treatment with an antiplatelet agent is recommended.[5] Closure, typically with the use of an atrial septal occluder device (although some devices have

been FDA approved for PFO closure, use of others is still off-label), is an alternative treatment option that is being used. However, multiple randomized controlled trials have not shown a clear benefit over medical therapy.[19–21] As such, PFO closure remains controversial. In 2016, the American Academy of Neurology published a guideline recommending against PFO closure for patients with cryptogenic stroke outside of a research setting.[24] The authors' rationale for this recommendation was a combination of the inability to determine if a PFO is incidental or not, the unproven effectiveness of closure versus medical therapy for reducing recurrent stroke risk, and the potential for procedural and device-related complications (**Case 2-1**).

It is unclear whether PFO plays a causal role in migraine or not. The theorized mechanism is similar to that of stroke: abnormal right-to-left shunting of microemboli or neuroactive substances, such as serotonin, that would normally be removed by the lungs. Observational studies have reported a significant reduction in migraine following PFO closure, which could suggest a causal relationship.[16] However, randomized controlled trials

KEY POINT

- Randomized controlled trials have not shown a benefit of patent foramen ovale closure over medical therapy for prevention of recurrent stroke or transient ischemic attack.

TABLE 2-2 Risk of Paradoxical Embolism (RoPE) Score Calculator[a–c]

Characteristic and Point Value
No history of hypertension (1 point)
No history of diabetes mellitus (1 point)
No history of stroke or transient ischemic attack (1 point)
Nonsmoker (1 point)
Cortical infarct on imaging (1 point)
Age
18–29 years (5 points)
30–39 years (4 points)
40–49 years (3 points)
50–59 years (2 points)
60–69 years (1 point)
Greater or equal to 70 (0 points)
Total RoPE score (sum of individual points)

[a] Modified with permission from Kent DM, et al, Neurology.[18] © 2013 American Academy of Neurology. *neurology.org/content/81/7/619.short*.

[b] Minimum score is 0 (a patient 70 years of age or older with hypertension, diabetes mellitus, prior stroke, current smoker, and no cortical infarct). Maximum score is 10 (a patient younger than 30 years of age with no hypertension, no diabetes mellitus, no history of stroke or transient ischemic attack, nonsmoker, and cortical infarct).

[c] The higher the score, the more likely a patent foramen ovale is stroke related as opposed to an incidental finding. RoPE score X: patent foramen ovale–attributable fraction percent (ie, percent of likelihood that the patent foramen ovale is relevant):
0–3: 0%
4: 38%
5: 34%
6: 62%
7: 72%
8: 84%
9–10: 88%

Case 2-1

A 42-year-old man with a history of a cryptogenic ischemic stroke presented for evaluation of a 2-year history of lower extremity claudication. His claudication symptoms began shortly after he underwent percutaneous patent foramen ovale closure with an occluder device at a different institution following the stroke. He was an avid runner, and before the procedure he could easily run distances of 10 to 15 miles. However, after the procedure, he developed lower extremity claudication and occasional low back pain while running; he could only run 2 to 3 miles as a result. Investigations revealed that the patent foramen ovale closure device had embolized to the iliac bifurcation in the distal aorta (**Figure 2-2A**[22]). The device was successfully removed and his symptoms resolved (**Figure 2-2B**).[22]

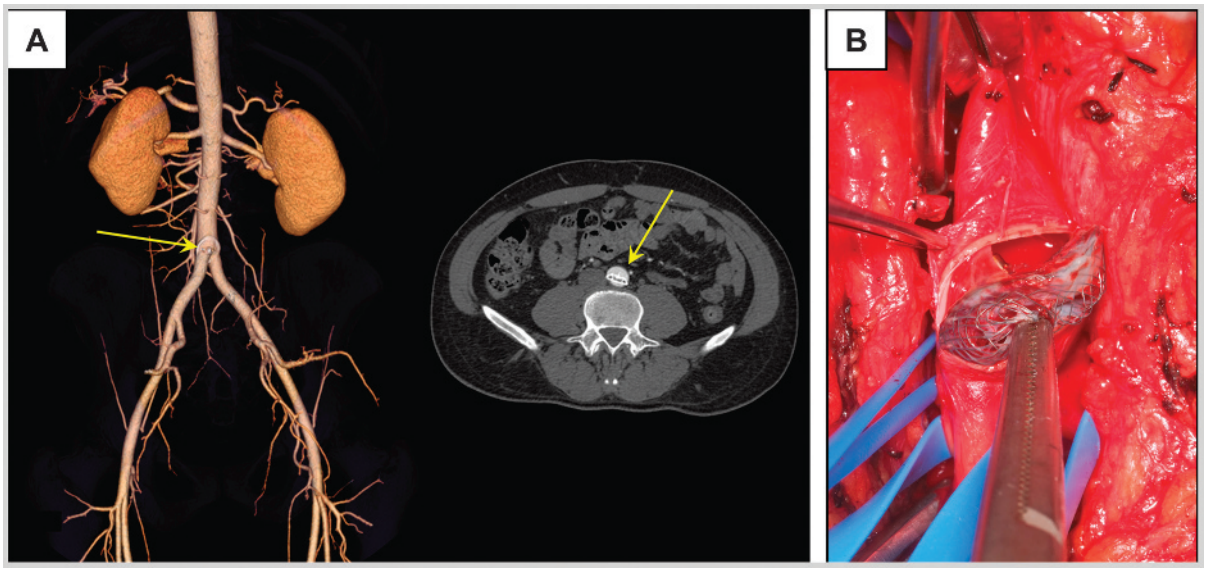

FIGURE 2-2 Imaging of the patient in **Case 2-1** showing embolization of the occluder device that had been placed for closure of a patent foramen ovale. CT images show the occluder device (*arrows*) in the distal aorta (*A*) and the device being surgically removed from the aorta (*B*).

Reprinted with permission from Braksick SA, et al, J Neurol Neurophysiol.[22] © 2015 Braksick SA. *omicsonline.org/open-access/lower-extremity-claudication-after-patent-foramen-ovale-closure-2155-9562-1000i001.php?aid=51908.*

Comment. Percutaneous patent foramen ovale closure is a fairly safe procedure. Rates of major complication are low, around 1% to 2%. Device embolization, as occurred in this case, is extremely rare. Other potential complications include cardiac tamponade, endocarditis, device erosion, device arm fracture, atrial fibrillation or other atrial arrhythmias, and hematoma or pseudoaneurysm development at the site of femoral access.[22,23]

have not demonstrated a reduction in either migraine frequency or severity following percutaneous PFO closure for patients with refractory migraine with aura.[25,26]

Endocarditis

Endocarditis is inflammation of the endocardium, the inner layer of the heart and surface of the valves. It can be categorized as either infective or noninfective. Infective endocarditis is caused by a bacterial infection or, less frequently, a fungal infection. Patients with prosthetic heart valves or valve disease, including rheumatic heart disease, are at increased risk for infective endocarditis. Although rheumatic

heart disease is a major risk factor in the developing world, it accounts for less than 10% of cases in developed countries. Other risk factors include intracardiac devices, congenital heart defects, IV drug use, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[27]

Systemic complications from infective endocarditis are protean. Between 15% and 47% of patients will develop neurologic complications. Stroke is the most common neurologic complication. In 16% to 19% of patients, stroke may also be the initial presenting symptom of infective endocarditis.[28]

The majority of strokes caused by infective endocarditis are ischemic, but subarachnoid and intracerebral hemorrhages also occur. Hemorrhages can be secondary to septic endarteritis, hemorrhagic transformation of an ischemic infarct, or rupture of a mycotic aneurysm. Mycotic aneurysms are believed to develop as a result of septic embolization to the vasa vasorum of the cerebral arteries. Mycotic aneurysms form at distal arterial branching points (unlike saccular aneurysms, which typically occur within the circle of Willis). Although associated with high mortality rates, mycotic aneurysm rupture accounts for only a small fraction of endocarditis-related hemorrhages (approximately 3%).[28,29]

Stroke is not the only possible neurologic complication of infective endocarditis. Septic emboli can also cause direct infection of the central nervous system, resulting in meningoencephalitis, cerebritis, or abscess formation. Other less common neurologic complications of infective endocarditis are listed in **Table 2-3**.

Roughly 80% of all cases of infective endocarditis are caused by either streptococcal or staphylococcal infection.[27] Infection with *Staphylococcus aureus*, in particular, is associated with a high risk for neurologic complications.[28] Although endocarditis secondary to a fungal infection is less common, 60% of patients with *Candida* or *Aspergillus* infections will develop neurologic complications.[29] The risk of neurologic complications declines dramatically within 1 week of initiating appropriate antibiotic treatment.[28]

Neither antiplatelet nor anticoagulant medication is recommended for infective endocarditis.[28,30] However,

TABLE 2-3 Neurologic Complications of Endocarditis[a]

▶ **Infective Endocarditis**
Cerebrovascular
Ischemic stroke
Hemorrhagic stroke
Mycotic aneurysm
CNS infections
Meningoencephalitis
Cerebritis
Abscess
Ventriculitis
Ependymitis
Secondary complications
Toxic-metabolic encephalopathy
Seizure
Headache
Rare complications
Myeloradiculitis
Spinal cord infarction
Discitis
Osteomyelitis
Cranial neuropathy
Mononeuropathy multiplex
Myalgia

Continued on page 660

KEY POINTS

- Infective endocarditis frequently causes neurologic complications. Stroke is the most common.
- The risk of neurologic complications from infective endocarditis declines rapidly with the initiation of antibiotics.

KEY POINT

- Atrial myxomas and papillary fibroelastomas are the most common cardiac tumor types and the types most frequently associated with neurologic complications.

TABLE 2-3 Neurologic Complications of Endocarditis[a]

Continued from page 659

▶ **Noninfective Endocarditis**
Cerebrovascular
Ischemic stroke
Hemorrhagic stroke
Secondary complications
Toxic-metabolic encephalopathy
Seizure
Headache

[a] Reprinted with permission from Prabhakaran S, Continuum (Minneap Minn).[28] © 2008 American Academy of Neurology. *journals.lww.com/continuum/Fulltext/2008/02000/NEUROLOGIC_COMPLICATIONS_OF_ENDOCARDITIS.5.aspx*.

for patients with mechanical valves, deciding whether or not to continue anticoagulation is difficult. If a patient with infective endocarditis has a stroke or hemorrhage, evidence suggests anticoagulation should be held for at least 2 weeks.[31]

Noninfective endocarditis, more often referred to now as nonbacterial thrombotic endocarditis, is characterized by sterile valvular vegetations composed of platelets and fibrin aggregates. Historically, two types of noninfective endocarditis occur: marantic and Libman-Sacks.

The term *marantic* derives from the word *marasmus*, which means withering or wasting away. As the name implies, marantic endocarditis occurs in patients in wasting states as a result of various illnesses. Although multiple causes exist, marantic endocarditis most commonly afflicts patients with cancer. Roughly 1% to 2% of patients with cancer develop marantic endocarditis. Patients with pancreatic, non–small cell lung, and hematologic malignancies are at the greatest risk.[28]

Libman-Sacks refers to noninfective endocarditis associated with rheumatologic disease. Valvular abnormalities are common for patients with systemic lupus erythematosus, and studies using echocardiography have shown that up to 40% have evidence of Libman-Sacks endocarditis.[32] It also develops in patients with antiphospholipid antibody syndrome. Patients with lupus and elevated antiphospholipid antibodies are at particular risk.[28,32]

Noninfective endocarditis of either type does not cause many of the neurologic complications that can arise from infective endocarditis. Ischemic stroke is the main complication of noninfective endocarditis, and (unlike in infective endocarditis) anticoagulation is recommended for stroke prevention.[28]

Cardiac Tumors

Primary cardiac tumors are rare, with an approximate incidence of 0.02%.[33] The overwhelming majority are classified as benign tumors. In children, rhabdomyomas are the most common tumor type and are strongly associated with tuberous sclerosis complex.[34] In adults, myxomas and papillary fibroelastomas, also known as papillomas, are the most common tumor types, followed by lipomas, fibromas, and rhabdomyomas.[29,33,35] Cardiac tumors can cause cardiac dysfunction, usually from obstruction or arrhythmias; constitutional symptoms, including fever, weight loss, malaise, arthralgias, and myalgias; and complications as a result of embolization of tumor fragments or thrombi formed on the tumor surface. Most neurologic complications are a result of embolic phenomena. Atrial myxomas and papillary fibroelastomas are the two tumor types most

frequently associated with neurologic complications.[29]

Myxomas account for roughly 50% of all primary cardiac tumors in adults. Approximately 75% are located in the left atrium, arising from the interatrial septum.[36] Of myxomas, those within the left atrium carry the highest risk of embolization, with evidence of embolization in 30% to 40% of cases.[36] Of these patients, 12% to 45% will develop neurologic symptoms, namely ischemic stroke or TIA.[37] In addition to the brain, myxomas can cause infarcts of the retina and even the spinal cord. Intracranial aneurysm formation is a rare complication, resulting from weakening of the vessel wall due to direct tumor invasion. Myxoma-induced aneurysms are typically fusiform, but saccular aneurysms have been reported. Patients may develop multiple aneurysms, all of which carry a risk of rupture and intracranial hemorrhage (**Case 2-2**).[37,38] Treatment of myxomas involves surgical resection of the tumor, which is necessary to prevent further embolic events. However, delayed complications from previously embolized tumor material can still occur.

Papillary fibroelastomas can arise from any endocardial surface but are mostly found on the surface of the valves. The aortic valve is the most common site, followed by the mitral valve.[39] These tumors are small and usually do not cause cardiac symptoms, but tumor emboli can cause systemic and neurologic complications. Stroke or TIA is the most common symptom and the presenting symptom for roughly 30% of patients.[35,39] Papillary fibroelastomas are usually identified via echocardiography. The tumors can be missed on a transthoracic echocardiogram, so transesophageal echocardiogram is recommended.[35]

Surgical excision of papillary fibroelastomas is the preferred treatment, if feasible. Tumor recurrence after surgery is rare. For patients who are not surgical candidates, initiation of either anticoagulation or antiplatelet therapy is recommended for stroke prevention. However, it is not known whether anticoagulation, antiplatelet therapy, or dual antiplatelet therapy is most effective for stroke prevention.[35]

Cognitive Impairment/Dementia

Heart disease, in general, is a risk factor for cognitive impairment and dementia. This risk is mostly attributable to stroke and vascular disease; patients with coronary artery disease are likely to also have cerebrovascular disease. However, AF and heart failure may increase the risk of cognitive impairment and dementia independent of cerebrovascular disease or stroke. Recent studies have reported that AF is associated with the development of dementia even after adjusting for stroke and cardiovascular risk factors.[40] One potential explanation is that irregular heart rates associated with AF can decrease cardiac output, which, in turn, could lead to cerebral hypoperfusion and neuronal injury.[40,41] A similar mechanism has been postulated for patients with heart failure. Studies have demonstrated reduced cerebral blood flow in patients with heart failure, and some evidence exists that improvement in cerebral blood flow, such as after heart transplantation, results in improved cognition.[41]

Cardiac surgery may also increase the risk of dementia, either from the procedure itself or from complications of the procedure, including stroke. Potential mechanisms for cognitive impairment resulting from cardiac surgery include generation of microemboli,

KEY POINT

- Atrial fibrillation and heart failure may be independent risk factors for dementia.

Case 2-2

A 53-year-old man presented for further evaluation of a recent ischemic stroke. Five years earlier, he had developed intermittent discoloration and pain in his digits. He was initially diagnosed as having Raynaud phenomenon, but eventually a left atrial myxoma was discovered and resected. He had no complications from his cardiac surgery and had done well since. Recently, though, while at work, he developed sudden-onset right facial weakness and dysarthria. An MRI of the brain demonstrated an acute infarct in the left frontal lobe (**Figure 2-3A**) adjacent to a large partially thrombosed fusiform aneurysm involving the middle cerebral artery (MCA) (**Figures 2-3B**, **2-3C**, **2-3D**, and **2-3E**). Numerous other fusiform aneurysms in multiple vascular distributions were also identified (**Figures 2-3D** and **2-3E**). No systemic aneurysms were found, and repeat cardiac imaging showed no evidence of tumor recurrence.

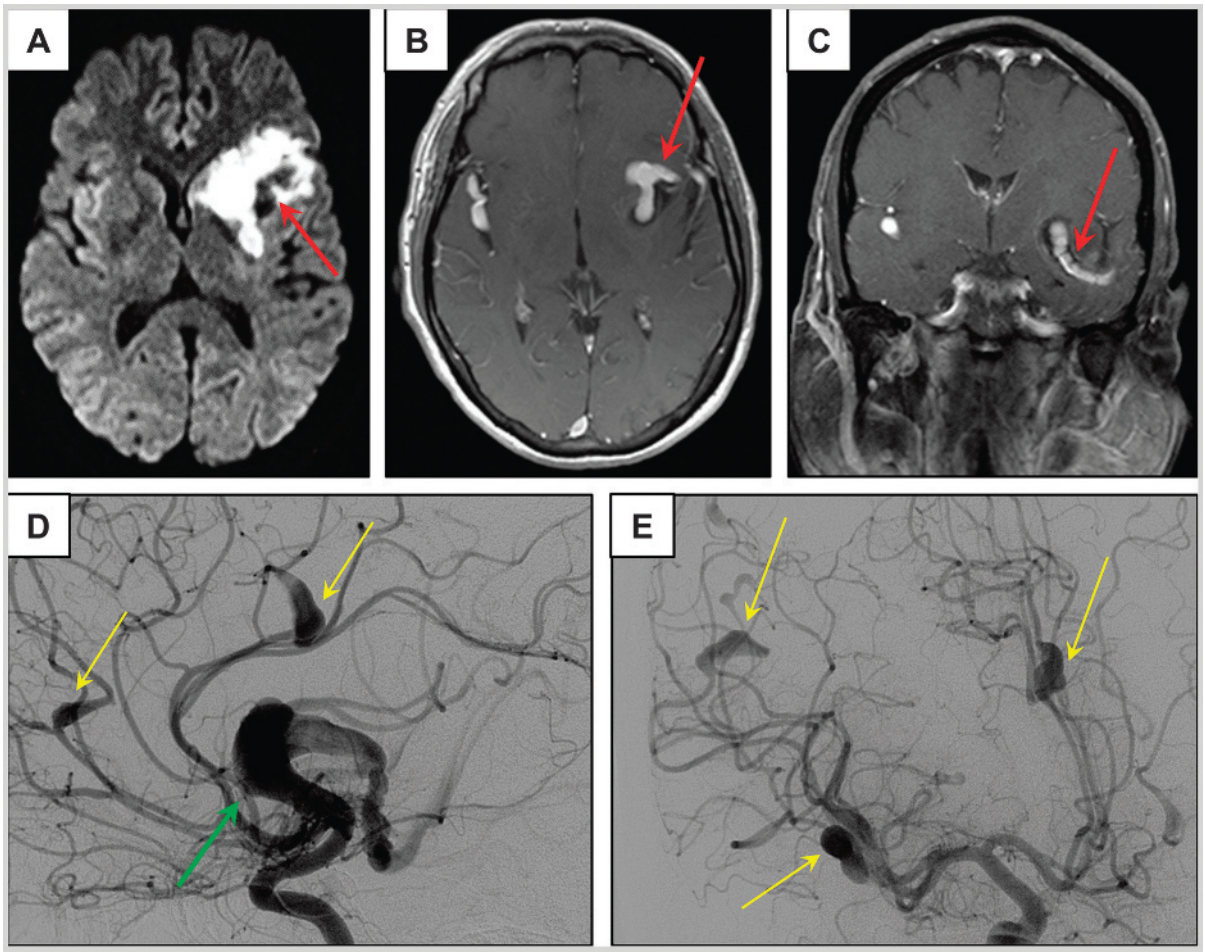

FIGURE 2-3 Imaging of the patient in **Case 2-2** showing multiple cerebral aneurysms resulting from cardiac myxoma. *A*, Diffusion-weighted MRI shows restricted diffusion in the left frontal lobe adjacent to a large middle cerebral artery fusiform aneurysm (*red arrow*); the aneurysm is better seen on postcontrast axial (*B, red arrow*) and coronal (*C, red arrow*) T1 sequences. Multiple fusiform aneurysms (*D*, *E*, *yellow arrows*) are also shown on cerebral digital subtraction angiography, including the left middle cerebral artery aneurysm (*D*, *green arrow*), with injection of the left carotid artery (*D*) and right carotid artery (*E*).

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Comment. Patients with cardiac myxomas can present with embolic injury and constitutional and other symptoms, including Raynaud phenomenon.[36] After the myxomas are detected, and even after they are resected, multiple cerebral aneurysms can develop.[37,38] The presumed mechanism is vessel wall weakening due to direct tumor invasion from previously embolized tumor cells. Myxoma-induced aneurysms can cause intracranial hemorrhage (due to aneurysm rupture) and other complications, including ischemic stroke, as a result of mass effect, in situ thrombosis, or distal embolic infarction.[38] No established treatment for myxoma-induced aneurysms is known. Chemotherapy and radiation have been tried with mixed results.[38] This patient was started on antiplatelet therapy and observed. He did well over the ensuing 3 years but then developed worsening aphasia, which corresponded with enlargement of the left MCA aneurysm. Following test balloon occlusion, he underwent successful coil embolization of the left MCA. When he was last seen, the left MCA remained occluded and the other cerebral aneurysms were stable in size.

intraoperative hypotension or oxygen desaturation, use of general anesthesia, and triggering a systemic inflammatory response. Rates of cognitive decline as high as 41% have been reported following coronary artery bypass graft surgery.[42] It was believed that the use of extracorporeal cardiopulmonary bypass during these procedures increased the risk of postperfusion syndrome or, more colloquially, ''pump head.'' However, recent studies have called this into question, noting no significant difference in cognition after coronary artery bypass graft procedures using cardiopulmonary bypass (on pump) versus those without (off pump). Furthermore, the risk of cognitive impairment following coronary artery bypass graft surgery may be exaggerated. Growing evidence exists that the cognitive decline noted in this patient population is more likely attributable to preexisting cerebrovascular disease and that cognitive impairment as a consequence of the procedure itself is uncommon.[42,43]

AORTA

Neurologic complications can occur related to aortic aneurysms, aortic dissection, thoracic aortic plaques, and coarctation of the aorta.

Aortic Aneurysms

An aortic aneurysm is usually defined as an enlargement of the aorta that is greater than 50% of the expected diameter. For the thoracic portion of the aorta, including the ascending aorta, aortic arch, and descending aorta, aortic enlargement to approximately 4.5 centimeters would be considered an aortic aneurysm; for the abdominal section of the aorta, enlargement to approximately 3.0 centimeters would qualify.[29,44]

Roughly 25% of individuals with a thoracic artery aneurysm will also have an abdominal aortic aneurysm.[45] Risk factors for the development of aortic aneurysms include older age, male sex, hypertension, atherosclerosis, tobacco use, and family history of aortic aneurysm.[46] Thoracic artery aneurysms, as opposed to abdominal aortic aneurysms, are more often associated with genetic disorders, such as Marfan syndrome, Turner syndrome, or a bicuspid aortic valve, or as a complication of inflammation of the aorta (ie, aortitis).[47] Aortitis can be due to an inflammatory disorder, most commonly giant cell/temporal arteritis, or it can be due to infection, usually caused by septic emboli. Syphilis was once a frequent cause of aortitis, but since

KEY POINT

- Cognitive impairment as a consequence of coronary artery bypass grafting surgery may be less common than previously thought.

KEY POINTS

- Aortic aneurysms can cause direct neurologic dysfunction by compressing neuronal structures, such as the left recurrent laryngeal nerve.
- Aortic dissections can be painless, and the initial presenting symptom of a dissection may be neurologic.
- Stroke is the most common neurologic complication of a type A aortic dissection.
- Development of a syndrome resembling progressive supranuclear palsy can rarely develop after surgical repair of ascending aortic dissection or aneurysm.
- Aortic plaques are an underrecognized cause of ischemic stroke.

the development of antibiotics, that has been quite rare.[44,47]

Many of the conditions associated with the development of aortic aneurysms (eg, atherosclerosis, Turner syndrome, giant cell arteritis, syphilis) also affect the nervous system. Rarely, aortic aneurysms can cause neurologic complications directly, mainly through compression of neuronal structures. For example, thoracic artery aneurysms can cause hoarseness via compression of the left recurrent laryngeal nerve, and abdominal aortic aneurysms are reported to cause lumbosacral plexopathies, radiculopathies, mononeuropathies, or even cauda equina syndrome.[44]

Aortic Dissection

Aortic aneurysms, especially large or rapidly expanding aneurysms, also increase the risk of aortic dissection. The Stanford classification system divides aortic dissections into two types: A and B. Dissections that involve the ascending aorta are classified as type A; all other aortic dissections are classified as type B. Aortic dissection and aortic aneurysms share the same risk factors. Of these, hypertension is the most significant; more than 70% of patients with an aortic dissection have a history of hypertension.[46] Some additional risk factors for aortic dissection include pregnancy and delivery, trauma, and iatrogenic injury from cardiac catheterization or surgery. Most patients with an aortic dissection present with chest or back pain, but a small percentage of dissections can be painless. For these patients, neurologic symptoms may be the initial manifestation of dissection.

Ischemic stroke is the most common neurologic complication associated with type A dissections. Cerebral ischemia can result from involvement of the great vessels, thromboembolism, or severe hypotension. Other potential neurologic complications from type A dissections include a Horner syndrome (usually from extension of the dissection into a carotid artery), left recurrent laryngeal nerve palsy, and spinal cord ischemia. Spinal cord ischemia can also occur in type B dissections. Ischemia results from interruption of blood flow to the radicular arteries.[46,48] If a dissection extends past the aortic bifurcation, peripheral nerve complications can develop, the most common of which is ischemic neuropathy.[29,46]

Surgical or endovascular repair of aortic dissections and aneurysms can also cause neurologic complications, particularly cerebral and spinal cord ischemia. Perioperative neurologic complication rates vary greatly depending on the clinical situation and procedure being performed, but range from 2% to 14% of patients.[48,49] A rare complication of repair of an ascending aortic dissection or aneurysm is development of a syndrome resembling progressive supranuclear palsy. Reported cases did not have any imaging evidence of cerebral infarction, and the exact cause of this syndrome is not known.[50]

Overall, 25% of patients with an aortic dissection experience neurologic complications.[48] Despite advances in treatment, approximately 30% of aortic dissections are fatal. Type A dissections carry the highest risk of death.

Thoracic Aortic Plaques

Atherosclerosis of the ascending aorta and aortic arch is a risk factor for ischemic stroke. Aortic plaques can be a source of thromboemboli (more common) and atheroemboli (also known as cholesterol emboli), and embolism can be spontaneous or iatrogenic. The prevalence of aortic plaques is higher in patients with

cryptogenic stroke, which suggests aortic atheroma is a potentially underrecognized stroke mechanism.[5] Transesophageal echocardiography is the preferred method to detect and characterize thoracic aortic plaques, but transthoracic echocardiography, CT, and MRI techniques can also be used. Plaques that are mobile, thick (thicker than 4 millimeters), noncalcified, lipid-rich, or ulcerated increase the risk of embolism and ischemic stroke.[5,51] Complex plaques are also associated with a significantly increased risk of recurrent stroke and death.[52]

Current guidelines recommend statin and antiplatelet therapy for secondary stroke prevention in patients with aortic plaques.[5] However, whether antiplatelet or anticoagulant medications are more effective remains unresolved. The Aortic Arch Related Cerebral Hazard (ARCH) trial is currently the only prospective randomized controlled trial available on the subject.[53] The trial compared clopidogrel plus aspirin to warfarin for the prevention of cerebral and myocardial infarction, peripheral embolism, and vascular death in patients with complex aortic arch plaques. Unfortunately, the trial was stopped because of poor recruitment and lack of funding. The available results, which suggest dual antiplatelet therapy may be superior, lack statistical power and are, therefore, inconclusive.[53]

Coarctation of the Aorta

Aortic coarctation is a congenital narrowing of the aorta. It can occur at any level of the aorta but typically occurs in the arch, around the region of the ligamentum arteriosum (the fetal remnant of the ductus arteriosus). Classically, patients with aortic coarctation have arterial hypertension in the upper extremities and relative hypotension and weak pulses in the lower extremities. Symptoms depend upon the location of the narrowing and the degree of stenosis. Common symptoms, such as shortness of breath, chest pain, fatigue, and lower extremity claudication, are attributable to the development of heart failure or poor distal perfusion. From a neurologic standpoint, the increased arterial pressure resulting from the coarctation can cause headaches and dizziness; it also increases the risk of intracerebral hemorrhage.[44] Furthermore, approximately 10% of adults with coarctation of the aorta will also harbor an unruptured intracranial aneurysm. Therefore, it is reasonable to screen patients with aortic coarctation for an intracranial aneurysm using noninvasive imaging studies, such as magnetic resonance angiography (MRA) or CT angiography. Bicuspid aortic valves and thoracic aortic aneurysms are cardiac/aortic conditions also associated with intracranial aneurysms.[54,55]

KEY POINT

- Consider screening for cerebral aneurysms in patients with coarctation of the aorta.

CONCLUSION

Cardiac and aortic disease and dysfunction can cause serious neurologic harm to patients. Stroke is the most common and most widely recognized neurologic complication, but many others exist, including dementia, meningoencephalitis, cerebritis, aneurysm formation, myelopathy, radiculopathy, neuropathy, and possibly even migraines. Recognition of the underlying cardiac or aortic dysfunction is crucial, for prompt diagnosis and treatment can minimize or even prevent these resulting neurologic injuries.

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Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias

Michelle L. Mauermann, MD, FAAN

ABSTRACT

Purpose of Review: This article reviews the spectrum of neurologic complications associated with lymphoma, leukemia, and paraproteinemic disorders. While leptomeningeal metastasis is the most common complication of lymphoma and leukemia and peripheral neuropathy is the most common complication of paraproteinemic disorders, clinicians need to be familiar with the diverse neurologic complications of these disorders.

Recent Findings: Lymphomatous nervous system involvement can be difficult to diagnose, especially when it is the presenting symptom. CSF cytology and flow cytometry, as well as the imaging pattern, assist in diagnosis. Neurologic complications are less common in Hodgkin lymphoma; however, some unique paraneoplastic syndromes are associated with Hodgkin lymphoma, including primary central nervous system angiitis, limbic encephalitis, and cerebellar degeneration. Recent reports suggest that anti–metabotropic glutamate receptor 5 (mGluR5) antibodies are associated with limbic encephalitis and that anti-Tr antibodies are associated with cerebellar degeneration in Hodgkin lymphoma. Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome is often misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). A lambda protein, thrombocytosis, and elevated vascular endothelial growth factor (VEGF) can all be helpful clues in diagnosis. Early recognition is important, as the neuropathy responds to radiation therapy or chemotherapy.

Summary: Neurologic involvement can occur throughout the disease course in lymphoma and leukemia, including at presentation, with systemic progression, and at relapse. In paraproteinemias, the peripheral neuropathy phenotype, monoclonal protein type, and associated autonomic and systemic features aid in identification of an underlying plasma cell disorder.

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INTRODUCTION

Nervous system involvement affects up to one-third of patients with lymphoma and is more common in patients with non-Hodgkin lymphoma than those with Hodgkin lymphoma. Leptomeningeal, epidural, and intraparenchymal metastases can occur in both types. Unique neurologic manifestations occur in non-Hodgkin lymphoma, including neurolymphomatosis and lymphomatosis cerebri.[1–3] Hodgkin lymphoma can be associated with paraneoplastic disorders, including primary angiitis of the central nervous system (CNS).[4,5] Leukemia can present with leukemic infiltration, extramedullary myeloid tumors, or intracranial hemorrhage.[6] Peripheral neuropathy is the most common neurologic complication of

KEY POINT

■ The majority of patients with non-Hodgkin lymphoma present with nervous system involvement during treatment or shortly following completion.

paraproteinemic disorders. In paraproteinemic disorders, the monoclonal protein subtype, systemic and autonomic features, and electrodiagnostic testing can aid in identifying a neoplastic disorder.

LYMPHOMA

Nervous system involvement by systemic non-Hodgkin lymphoma occurs in up to one-third of patients and has a diverse clinical presentation (**Table 3-1**). The incidence of nervous system involvement is highest in Burkitt and lymphoblastic lymphomas.[7] Other features associated with increased risk of CNS involvement include age greater than 60 years, high International Prognostic Index, multiple sites of extranodal involvement (especially testes, bone, breast, epidural, and paranasal sinus), elevated serum lactate dehydrogenase, and advanced stage.[8] The median time to presentation with CNS involvement is less than 1 year, and the majority present during treatment (systemic progression) or shortly after completion of treatment.[9] This suggests that successful systemic control is paramount in reducing CNS relapse.[10] The outcome of CNS relapse is poor, with a median survival of 2 to 5 months.[9] CNS prophylaxis is routinely used in the treatment of lymphoblastic and Burkitt lymphomas. In other types, no prospective studies address the issue of prophylaxis. Some favor IV methotrexate for those with high-risk features, and no evidence supports prophylactic intrathecal chemotherapy. Neurologic complications are rare in Hodgkin lymphoma. Complications can occur via

TABLE 3-1 Neurologic Complications of Lymphoma

Complication	Type of Lymphoma	MRI Features
Leptomeningeal metastases	Hodgkin and non-Hodgkin lymphoma	Focal or diffuse leptomeningeal enhancement
Epidural metastases	Hodgkin and non-Hodgkin lymphoma	Enhancing paravertebral mass invading epidural space
Intracranial metastases	Hodgkin and non-Hodgkin lymphoma	Single or multiple superficial or periventricular enhancing masses
Lymphomatosis cerebri	Non-Hodgkin lymphoma	Nonenhancing diffuse T2-hyperintense white matter disease
Intramedullary spinal cord metastases	Hodgkin and non-Hodgkin lymphoma	Focal expansile T2-hyperintense cord lesions with enhancement
Neurolymphomatosis	Non-Hodgkin lymphoma	Nerve enlargement with T2 hyperintensity and enhancement
Paraneoplastic disorders		
Limbic encephalitis	Hodgkin lymphoma	T2 hyperintensity in hippocampi
Cerebellar degeneration	Hodgkin lymphoma	Cerebellar atrophy
Primary angiitis of the central nervous system	Hodgkin lymphoma	Diffuse T2-hyperintense white matter disease, acute infarcts, and chronic microhemorrhages

MRI = magnetic resonance imaging.

direct mechanisms (metastases) or indirect mechanisms (angiitis, paraneoplastic, or treatment related).

Clinical Presentations

The clinical presentation of nervous system lymphoma varies widely depending on the site of involvement. The various types of complications with their clinical presentation are listed below.

Leptomeningeal disease. Lymphomatous infiltration of the leptomeninges is the most common neurologic complication of non-Hodgkin lymphoma, and seen in 4% to 15% of patients.[10] It has a diverse presentation, including headaches, nausea, communicating hydrocephalus, cranial neuropathy (ie, diplopia, facial weakness, hearing loss, imbalance, vertigo, dysphagia, hoarseness), extremity weakness, paresthesia, and pain. Testing should include an MRI of the entire neuraxis and CSF analysis. MRI demonstrates focal or diffuse leptomeningeal contrast enhancement, subarachnoid nodules, or intradural root enlargement with enhancement (**Figure 3-1**). CSF demonstrates lymphocytosis and increased protein, with or without hypoglycorrhachia. A unique CSF feature in Hodgkin lymphoma is eosinophilic pleocytosis. CSF evaluation should include cytology and flow cytometry. The identification of Reed-Sternberg cells in the CSF is the definitive test for leptomeningeal metastases from Hodgkin lymphoma.[11] Consideration should be given for CSF flow study to evaluate for obstruction if bulky disease or hydrocephalus occurs, as it is a relative contraindication for intrathecal chemotherapy. Rarely, a leptomeningeal biopsy may be needed. High-dose IV methotrexate is often a first-line treatment. If no CSF flow obstruction is detected, intrathecal chemotherapy can also be considered. Craniospinal radiation can be used for symptomatic or bulky sites of involvement.

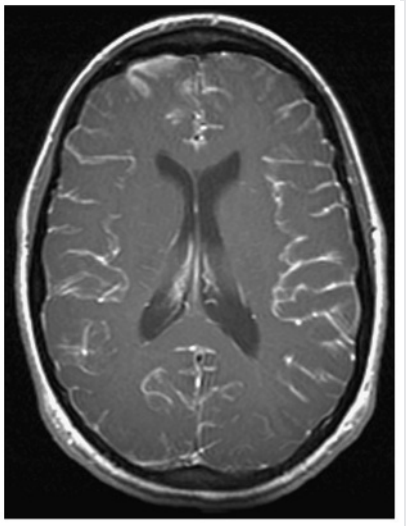

FIGURE 3-1 Axial T1-weighted MRI with contrast demonstrates diffuse leptomeningeal enhancement. CSF evaluation confirmed involvement by large B-cell lymphoma.

Epidural metastases. Epidural metastases occur in 2% to 5% of patients with non-Hodgkin lymphoma and in 0.2% of patients with Hodgkin lymphoma.[12] They develop from a paravertebral mass directly invading the epidural space through the intervertebral foramina. Back pain is the most frequent initial symptom; other symptoms include radicular pain, weakness or paraparesis, sensory level, erectile dysfunction, and bowel and bladder incontinence. MRI demonstrates a homogenous gadolinium-enhancing mass with avid fludeoxyglucose (FDG) uptake on positron emission tomography (PET) (**Figure 3-2**). Treatment includes high-dose steroids and radiation. Surgical decompression may be indicated in acute vertebral collapse with cord compression.

Intracranial metastases. Brain metastases occur in 1% to 2% of patients with non-Hodgkin lymphoma and in

KEY POINTS

- Lymphomatous infiltration of the leptomeninges is the most common neurologic complication of non-Hodgkin lymphoma.
- The identification of Reed-Sternberg cells in the CSF is the definitive test for leptomeningeal metastases from Hodgkin lymphoma.
- Epidural metastases occur in 2% to 5% of patients with non-Hodgkin lymphoma and develop from a paravertebral mass invading the epidural space through the intervertebral foramina.

KEY POINT

■ The MRI in lymphomatosis cerebri demonstrates diffuse white matter disease with little or no contrast enhancement.

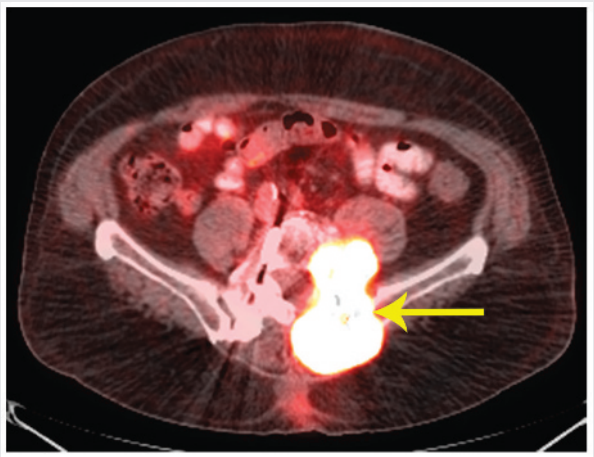

FIGURE 3-2 Patient with stage IV diffuse large B-cell lymphoma who has undergone an autologous stem cell transplant presented with back pain radiating down the left leg. Fused positron emission tomography (PET)/CT demonstrates bony and soft tissue fludeoxyglucose (FDG) uptake in the lower left lumbar spine (*arrow*) which extends into the soft tissues adjacent to the superior aspect of the left sacroiliac joint.

0.2% to 5% of patients with Hodgkin lymphoma.[13] These can occur prior to or with the development of systemic lymphoma or as a relapse with no evidence of systemic disease. The neurologic presentation is that of any mass lesion and can include focal deficits, seizure, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), or symptoms of increased intracranial pressure. MRI demonstrates single or multiple periventricular or superficial contrast-enhancing lesions (**Figure 3-3**). Immunosuppression or prior Epstein-Barr virus infection have been postulated as possible risk factors for intracranial metastases in patients with Hodgkin lymphoma.[14,15] Treatment includes systemic chemotherapy and radiation.

Lymphomatosis cerebri. Lymphomatosis cerebri is a rare pattern of diffuse infiltration of the brain parenchyma by non-Hodgkin lymphoma without the formation of discrete mass lesions. It most commonly presents with subacute personality changes, ataxic gait, and cognitive deficits. MRI demonstrates diffuse white matter disease involving the bilateral cerebral hemispheres, periventricular region, basal ganglia, thalami, or brainstem. Little or no enhancement with gadolinium occurs.[1] CSF studies may show pleocytosis and elevated protein.[16] Treatment with methotrexate-based systemic chemotherapy is recommended.

Intramedullary spinal cord metastases. Intramedullary spinal cord involvement is rare in non-Hodgkin lymphoma and Hodgkin lymphoma. In non-Hodgkin lymphoma, intramedullary spinal cord metastasis may be the presenting symptom or occur as a relapse.[17] In Hodgkin lymphoma, it most often occurs with advanced or refractory disease. Intramedullary spinal cord metastases occur either from hematogenous spread or from tumor growth along the nerve root into the spinal cord parenchyma. These patients have subacute onset with back pain, paraparesis, sensory loss, or spasticity and often require a

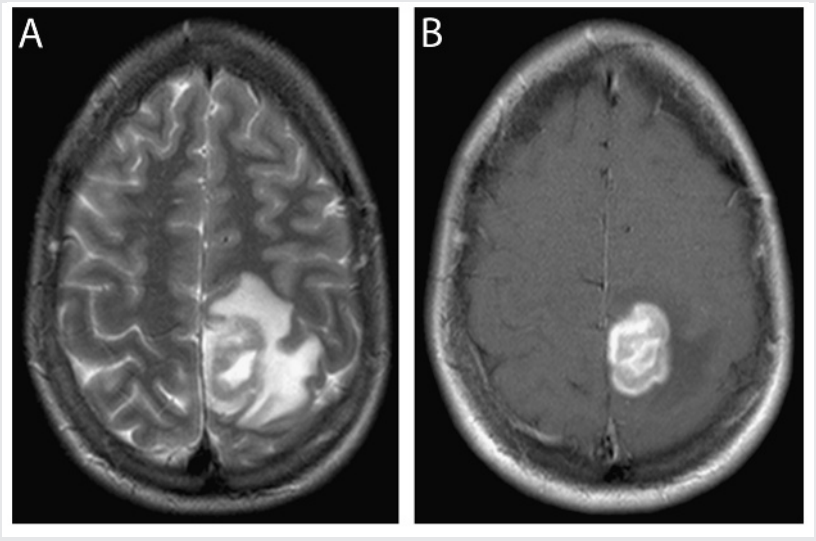

FIGURE 3-3 Brain MRI of an immunosuppressed patient who presented with right lower limb weakness. T2-weighted MRI shows an extensive region of T2 signal abnormality involving the posterior parasagittal left frontal lobe (*A*) with marked heterogeneous enhancement on postcontrast T1-weighted image (*B*). Biopsy confirmed diffuse large B-cell lymphoma.

wheelchair at diagnosis. MRI demonstrates focal expansile lesions that are T2 hyperintense and enhance with gadolinium (**Figure 3-4**). CSF cytology may be positive, and FDG-PET may show hypermetabolism. Treatment can include external beam radiation, high-dose IV methotrexate, or other systemic chemotherapy.

Neurolymphomatosis. Neurolymphomatosis is the neoplastic lymphocytic infiltration of spinal roots, dorsal root

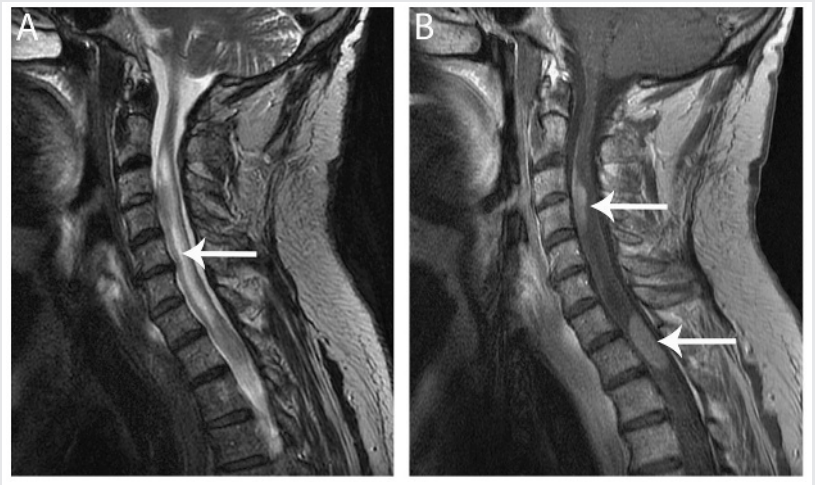

FIGURE 3-4 Sagittal MRI of the cervical spine demonstrates cord T2 hyperintensity from C2 through T4 (*A*, *arrow*) with pial enhancement at the C3 through C4 levels and large areas of nodular enhancement at C3 through C4 and T1 through T2 levels (*B*, *arrows*). CSF studies confirmed involvement with B-cell lymphoma.

KEY POINT

- Neurolymphomatosis most frequently involves the cauda equina or sciatic nerve and is very painful.

ganglia, plexus, or peripheral nerves. It is seen more commonly with B-cell versus T-cell non-Hodgkin lymphoma. It can occur in patients with widespread lymphoma, including those with CNS and leptomeningeal involvement, those with systemic lymphoma in hematologic remission, and those with primary leptomeningeal disease invading roots, or as the sole site of involvement without prior systemic disease.[2] It precedes the detection of systemic lymphoma in approximately one-half of patients.

Patients can present with subacute to chronic mononeuropathies or radiculopathies, cranial neuropathies, or a symmetric polyneuropathy.[2,3] Spontaneous pain is common and can be severe. The polyradiculopathy subtype frequently involves the cauda equina, and the sciatic nerve is the most common mononeuropathy (**Case 3-1**). Nerve

Case 3-1

A 64-year-old woman presented with subacute painful left leg weakness. She had a history of diffuse large B-cell lymphoma stage IVA and had been treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as well as intrathecal methotrexate. She had been in remission for 9 months at the time of presentation. She reported deep, aching, shocklike pain that radiated down the lumbar region into the lateral left leg. She noted numbness and tingling in the first three toes, arch, and dorsum of the left foot and lateral left leg, and she noted weakness lifting the foot. Her symptoms had progressed over 2 months to complete footdrop.

Examination demonstrated weakness and sensory loss in the left sciatic distribution. Electrodiagnostic testing demonstrated an active sciatic neuropathy. MRI demonstrated fusiform enlargement of the sciatic nerve with contrast enhancement. Standard body fludeoxyglucose positron emission tomography (FDG-PET)/CT demonstrated no evidence of abnormal FDG uptake. Targeted fascicular biopsy of the sciatic nerve showed evidence of active axonal degeneration, segmental demyelination, and lymphomatous infiltration of the endoneurium (**Figure 3-5**). She was diagnosed with neurolymphomatosis and was treated with high-dose IV methotrexate followed by chemotherapy and autologous stem cell transplantation. The patient experienced marked clinical improvement.

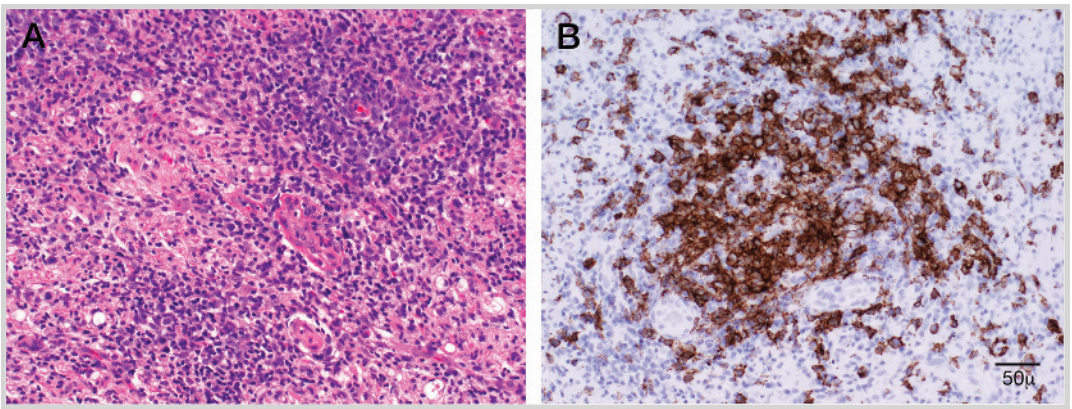

FIGURE 3-5 Targeted fascicular sciatic nerve biopsy of the patient in **Case 3-1** demonstrates immature mononuclear cells extensively infiltrating the endoneurium (*A*) with reactivity of CD20 (*B*) diagnostic of B-cell neurolymphomatosis.

Comment. This case highlights several important points: (1) neurolymphomatosis can occur when patients are in hematologic remission, (2) a high clinical suspicion must be maintained even when a PET scan is normal, and (3) high-dose IV methotrexate is needed for treatment of neurolymphomatosis.

conduction studies can show both axonal loss and demyelination. Evaluation with high-resolution MRI typically demonstrates abnormal nerve enlargement, T2 hyperintensity, and enhancement with gadolinium.[18] Fused FDG-PET/CT can show FDG uptake along the peripheral nerves. CSF cytology and flow cytometry can be diagnostic in cases with meningeal dissemination. Biopsy of an affected nerve is essential to establish the diagnosis. The nerve biopsy shows lymphomatous cell infiltration often in and around the perineurium with extension into the endoneurium.

Staging of the lymphoma is critical to the treatment of neurolymphomatosis. If neurolymphomatosis is not recognized in the setting of meningeal lymphomatosis and if only intrathecal chemotherapy or radiation therapy to cranial and spinal fields is given, then intraneural disease progression outside of the dural sleeve is inevitable. Treatment consists of systemic chemotherapy with high-dose IV methotrexate, which may be combined with intrathecal chemotherapy or external beam radiation therapy. Prognosis remains poor, with a median survival of 10 months from initial diagnosis with neurolymphomatosis.[3]

Paraneoplastic disorders. Paraneoplastic disorders in lymphoma occur in less than 1% of patients.[4] Lymphomas have unique paraneoplastic neurologic syndromes, and most do not have an associated onconeural antibody. Paraneoplastic disorders occur more commonly in Hodgkin lymphoma than non-Hodgkin lymphoma, and most patients have widespread systemic disease at time of diagnosis.

Among patients with lymphoma, limbic encephalitis occurs almost exclusively in Hodgkin lymphoma. Hodgkin lymphoma is the third most common cause of limbic encephalitis. Limbic encephalitis in the context of Hodgkin lymphoma has been referred to as Ophelia syndrome.[4] These cases are rare and have presented with neurologic symptoms that led to the diagnosis of Hodgkin lymphoma. Patients present with subacute memory loss, disorientation, confusion, depression/anxiety or psychosis with visual/auditory hallucinations, or paranoid ideation. Seizures occur in one-half of patients. MRI demonstrates increased T2 signal in the hippocampi. Diagnosis requires neuroimaging and electroencephalographic or pathologic involvement of the medial temporal lobes or amygdala.[4] An association exists with antibodies to metabotropic glutamate receptor 5 (mGluR5), which is a receptor involved in processes of learning and memory.[19] Treatment of the tumor usually results in full neurologic recovery.

Among patients with lymphoma, paraneoplastic cerebellar degeneration also occurs almost exclusively in Hodgkin lymphoma and precedes the diagnosis in 80% of patients.[20] Patients present with subacute dizziness and vertigo that rapidly progresses to severe symmetric trunk and limb ataxia.[4] It has a strong association with anti-Tr antibodies to delta/notchlike epidermal growth factor–related receptor, which can be found in serum and CSF. CSF demonstrates mild to moderate pleocytosis. Brain MRI is initially normal and evolves to show cerebellar atrophy. Although paraneoplastic cerebellar degeneration is often irreversible, the prognosis may be better in patients with Hodgkin lymphoma than in those with solid tumors.[20]

Cancer-associated myositis occurs in patients with non-Hodgkin lymphoma who are older than 50 years of age. In one-half of patients, myositis is diagnosed before the cancer. Dermatomyositis is more common than polymyositis.[4]

Primary angiitis of the CNS is a noninfectious focal and segmental

KEY POINTS

- Treatment of neurolymphomatosis consists of systemic chemotherapy with high-dose IV methotrexate.
- Limbic encephalitis and paraneoplastic cerebellar degeneration are paraneoplastic syndromes seen in Hodgkin lymphoma.
- Limbic encephalitis in Hodgkin lymphoma is associated with antibodies to metabotropic glutamate receptor 5, and paraneoplastic cerebellar degeneration in Hodgkin lymphoma is associated with anti-Tr antibodies.

KEY POINTS

- Primary angiitis of the central nervous system presents with headache, encephalopathy, and stroke.
- Intravascular lymphoma has a multifocal presentation with systemic symptoms and is due to occlusion of small vessels by lymphoma cells.

granulomatous angiitis that affects small arteries of the leptomeninges and parenchyma of the brain and spinal cord, occurring in the absence of systemic vasculitis. This condition is considered by some experts as an antibody-negative paraneoplastic syndrome associated with Hodgkin lymphoma. Patients present with the insidious onset of headache and encephalopathy or focal neurologic deficits such as hemiparesis or aphasia. Strokes or persistent neurologic deficits occur in almost one-half of patients, and seizures occur in less than one-fourth.[5,21] CSF is usually abnormal (in 75% to 90% of patients), with modest elevations in white blood cell counts and total protein. Brain MRI demonstrates small discrete infarcts in the majority, with approximately one-fourth of patients experiencing diffuse underlying T2 white matter changes. The infarcts are usually bilateral in multiple vascular territories (**Figure 3-6**). Gadolinium enhancement is seen in 30% of patients, and may include leptomeningeal enhancement.

Angiography may demonstrate vasculopathy but has limited sensitivity and specificity. Biopsy confirmation is recommended; however, a high false-negative rate is seen. Treatment is with oral cyclophosphamide (2 mg/kg/d) or IV pulse dosing with oral prednisone (1 mg/kg/d).[22] Approximately 80% of patients respond to this regimen. Given the possible association with herpes zoster, infection should be excluded by testing herpes zoster polymerase chain reaction (PCR) and serum and CSF concentrations of anti–varicella-zoster virus immunoglobulin.[23]

Intravascular lymphoma. Intravascular lymphoma is a rare subtype of extranodal large B-cell lymphoma that primarily affects the elderly. It is confined to the lumen of small- and medium-sized vessels and is characterized by occlusion of these vessels by malignant cells. Intravascular lymphoma affects many organ systems, including the nervous system and the skin, and hepatosplenic and bone marrow involvement may be seen. More than 60% of patients with this condition

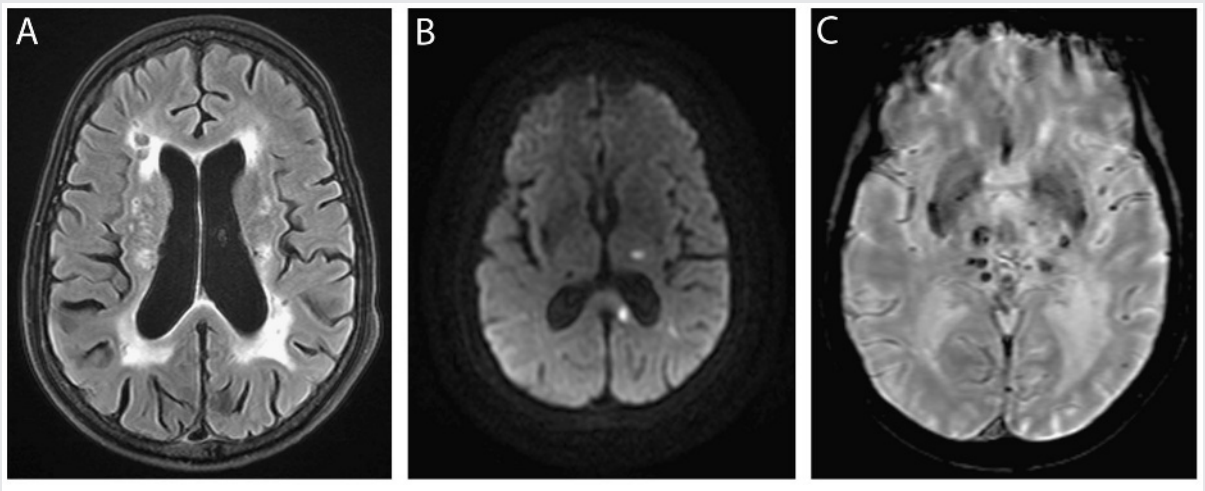

FIGURE 3-6 Primary angiitis of the central nervous system in a patient with Hodgkin lymphoma. *A*, Fluid-attenuated inversion recovery (FLAIR) MRI with confluent hemispheric white matter hyperintensities; *B*, diffusion-weighted imaging with numerous acute infarcts; and *C*, gradient recalled echo (GRE) image with chronic microhemorrhages.

develop neurologic manifestations during the disease course. An Asian variant exists that is associated with hemophagocytic lymphohistiocytosis.[24]

The clinical presentation is often multifocal and can include longitudinally extensive transverse myelitis, sensorimotor peripheral neuropathy, myopathy, polyradiculopathy, subacute encephalopathy, cognitive decline, gait instability, cranial neuropathy (particularly cranial nerves VII and VIII), stroke, or seizure.[25] Neurologic symptoms are the presenting features in one-third of patients and occur during the disease course in two-thirds of patients.[26] Systemic symptoms of fevers, night sweats, and fatigue are present in up to one-half of patients. Nonspecific elevations of inflammatory markers and lactate dehydrogenase are seen. MRI can show many patterns, such as nonspecific white matter changes, microinfarcts, and widespread enhancement.[27] FDG-PET is usually negative. Treatment is typically with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with remission rates of more than 50% reported. However, the prognosis remains poor, often because of the delay of diagnosis and more widespread disease and organ dysfunction at the time of diagnosis. Brain or leptomeningeal biopsy is often needed for diagnosis. Some authors have proposed a skin biopsy[28] or open muscle biopsy for diagnosis.[25]

Lymphomatoid granulomatosis. Epstein-Barr virus is implicated in a wide range of B-cell lymphoproliferative disorders, including Burkitt lymphoma, Hodgkin lymphoma, posttransplant lymphoproliferative disorders, and human immunodeficiency virus (HIV)-associated lymphoproliferative disorders.[29] Epstein-Barr virus is also implicated in lymphomatoid granulomatosis. Lymphomatoid granulomatosis is a rare systemic disorder characterized by B-cell proliferation and T-cell infiltration. Pathologic characteristics include angiocentric and angiodestructive infiltrates with large, atypical B cells and T cells that are positive for the Epstein-Barr virus.[30] Grading is based on the proportion of B cells positive for the Epstein-Barr virus. The majority of patients have lung involvement, but the CNS is the second most common site.[30] The most common MRI pattern is multiple focal intraparenchymal lesions with T2 hyperintensity with punctate or linear gadolinium enhancement.[31] Treatment includes steroids, interferon alfa, and chemotherapy.

Other. Patients with lymphoma can have peripheral neuropathy associated with other etiologies, such as treatment-related causes (eg, chemotherapy, radiation therapy, stem cell transplantation), malnutrition, or hyperviscosity, and as a consequence of amyloidosis.[2]

LEUKEMIA

Nervous system involvement by leukemia is varied and includes leptomeningeal or intracranial metastases and extramedullary myeloid tumors. Intracranial hemorrhage is a common complication of leukemia.

Clinical Presentations

As in lymphoma, the clinical presentations of nervous system involvement in leukemia vary by site of involvement. The potential complications with their corresponding clinical presentation are listed below.

Leptomeningeal metastases. Leptomeningeal involvement is most common in acute lymphoblastic leukemia. Leptomeningeal metastasis is identified in less than 10% of adults at diagnosis, but occurs in 30% to 50% of patients at leukemic relapse. Risk factors include younger age, mature B-cell

KEY POINT

- Leptomeningeal metastasis in leukemia is most common in acute lymphoblastic leukemia, and patients are routinely given central nervous system prophylaxis.

KEY POINTS

- Extramedullary myeloid tumors may be the initial presentation of acute myelogenous leukemia or chronic myelogenous leukemia and frequently affect the thoracic spine, causing spinal cord compression.
- Intracranial hemorrhage is the second most common complication in adult patients with hematologic malignancies, and the risk is highest in acute leukemia.
- Paraproteinemias affect 3% to 4% of the population older than the age of 50 and more than 5% of the population older than the age of 70.

acute lymphoblastic leukemia, T-cell lineage, high lactate dehydrogenase, high white blood cell count, high proliferative index, elevated β_2-microglobulin, and other extramedullary diseases.[32] CSF flow cytometry and cytology improves detection of occult leptomeningeal disease. Because of the high incidence of CNS involvement at relapse, CNS prophylaxis is recommended in all patients with acute lymphoblastic leukemia. No best regimen has been defined, but usually a combination of IV and intrathecal chemotherapy with or without craniospinal irradiation is used.

Leptomeningeal involvement is less common with acute myelogenous leukemia (less than 5%).[33] The risk is higher in patients with acute myelogenous leukemia who have any type of monoblastic differentiation and in those with high peripheral white blood cell count (more than 100,000)/μL at presentation.[34] No role exists for CNS prophylaxis. Treatment consists of intrathecal therapy with cytarabine or methotrexate.

CNS involvement in chronic lymphocytic leukemia is rare, occurring in less than 1% of patients.[35] The involvement can be due to CNS chronic lymphocytic leukemia (parenchymal or meningeal) or as a presenting sign of Richter syndrome (transformation to a more aggressive form of large cell lymphoma).

Extramedullary myeloid tumors. Extramedullary myeloid tumors, also known as chloroma and granulocytic sarcoma, have an estimated incidence of 3% in acute myelogenous leukemia and chronic myelogenous leukemia.[36] They can affect a variety of sites and rarely involve the nervous system. The spine is the most common site of involvement; however, intracranial and brachial/lumbosacral plexus extramedullary myeloid tumors can also occur (**Case 3-2**). The neurologic extramedullary myeloid tumors may be the initial presentation of leukemia and may precede diagnosis by several years.[38] The majority of patients will develop systemic leukemia. In the spine, the thoracic region is most common, with an epidural mass and associated vertebral body involvement. When intracranial, extramedullary myeloid tumors may mimic a subdural hematoma or meningioma. Presenting symptoms vary depending on the site of involvement and include headache, radicular pain, back pain, limb weakness, paraplegia with bowel and bladder disturbance, hemiparesis, seizures, and cranial neuropathy. Extramedullary myeloid tumors typically enhance homogeneously with contrast. Treatment may include external beam radiation therapy or chemotherapy. Surgery is sometimes required, especially for diagnosis.

Intracranial hemorrhage. Intracranial hemorrhage is the second most common complication in adult patients with hematologic malignancies. The highest risk is in acute leukemias (20%), and intracranial hemorrhage is the second most common cause of death in these patients. Intracranial hemorrhage can occur at the time of diagnosis or following initial treatment and is most commonly intraparenchymal. The most common etiologies in order of frequency are disseminated intravascular coagulation, disseminated aspergillosis or mucormycosis, leukemic cell infiltration, thrombocytopenia, or L-asparaginase chemotherapy. Leukemic cell infiltration occurs with marked leukocytosis and results in multiple intracranial hemorrhages. L-Asparaginase may induce hyperfibrinogenemia and result in cortical vein or sinus thrombosis with infarction and possible hemorrhage.

Case 3-2

A 70-year-old man presented with a 3-month history that began with subacute aching pain in his left upper arm and elbow and the subsequent development of numbness in the left ulnar distribution, which progressed to weakness of the hand outside of the ulnar distribution with worsening numbness. At presentation, his hand was nonfunctional, and he described contact allodynia.

Examination demonstrated moderate weakness in left wrist flexion and digit extension and severe weakness of digit flexion, thumb abduction, and finger abduction. He had a claw deformity of the left hand with sensory loss to all modalities in the ulnar distribution and medial forearm. Electrodiagnostic testing demonstrated a left lower trunk brachial plexopathy with additional involvement of the C8 paraspinals. MRI demonstrated an enlarged left C8 root with extension into the entire brachial plexus as well as the median and ulnar nerves with contrast enhancement. CSF demonstrated 53 white blood cells/μL with cellular atypia, and cytology and flow cytometry confirmed myeloblasts of granulocytic lineage. Positron emission tomography (PET) showed avid uptake in the brachial plexus (**Figure 3-7A**[37]). Targeted fascicular biopsy of the medial cord of the brachial plexus demonstrated replacement of endoneurium and epineurium with basophilic cells with immunohistochemistry positive for an extramedullary myeloid tumor (**Figure 3-7B**). Treatment with systemic and intrathecal chemotherapy initially helped; however, the disease recurred in other locations, and he ultimately died.

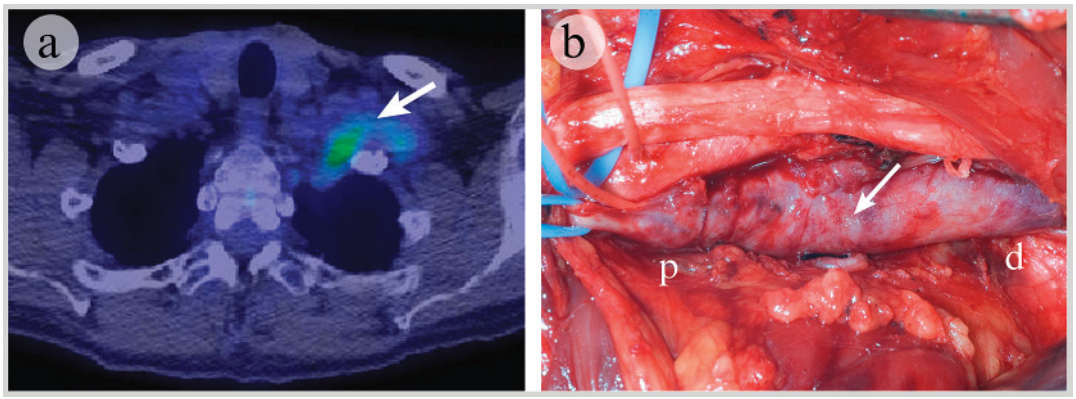

FIGURE 3-7 Extramedullary myeloid tumor of the brachial plexus in the patient in **Case 3-2.** *A*, Transverse fused positron emission tomography (PET)/CT image demonstrates avid fludeoxyglucose (FDG) uptake of the brachial plexus (*arrow*). *B*, Intraoperative photograph showing the lower blue vasoloop (a loop used by surgeons to identify and isolate vessels during surgery) around the enlarged medial cord of the brachial plexus (*arrow*) (p = proximal; d = distal).

Comment. Acute myelogenous leukemia can present with an extramedullary myeloid tumor that can involve the nervous system. Early recognition is important as extramedullary myeloid tumors eventually progress to a systemic malignancy.

PARAPROTEINEMIAS

The paraproteinemias are a heterogeneous group of disorders with secretion of monoclonal immunoglobulin produced by the bone marrow. They affect 3% to 4% of the population older than the age of 50 and more than 5% of the population older than the age of 70.[39] The paraproteinemias include multiple myeloma; Waldenström macroglobulinemia; polyneuropathy, organomegaly,

KEY POINT

■ Peripheral neuropathy is a common complication of paraproteinemias.

endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome; immunoglobulin light chain (AL) amyloidosis; and monoclonal gammopathy of undetermined significance (MGUS). These conditions are associated with a variety of neurologic complications; the most common of these is peripheral neuropathy (Table 3-2).

TABLE 3-2 Neuropathy Phenotype Associated With Paraproteinemias

Plasma Cell Disorder	Monoclonal Gammopathy	Peripheral Neuropathy	EMG Findings
Monoclonal gammopathy of undetermined significance	IgM kappa	Distal large fiber sensory	Prolonged motor distal latencies, short terminal latency indexes, reduced or absent sensory nerve action potentials (SNAPs)
Waldenström macroglobulinemia	IgM kappa	Distal large fiber sensory	Reduced or absent compound muscle action potentials (CMAPs) and SNAPs, may have prolonged motor distal latencies and short terminal latency indexes
		Multiple mononeuropathies	Reduced or absent CMAPs and SNAPs affecting individual nerve territories
		Progressive painful sensory, motor, or sensorimotor neuropathy with or without autonomic failure	Reduced or absent CMAPs and SNAPs (may be normal if strictly involves small fibers)
Multiple myeloma	IgG occurs more commonly than IgA	Length-dependent sensory, motor, or sensorimotor	Reduced or absent CMAPs and SNAPs
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome	IgG or IgA, lambda	Severe length-dependent sensorimotor or chronic inflammatory demyelinating polyradiculoneuropathy–like	Absent lower limb CMAPs and SNAPs, upper limb slowed conduction velocities and prolonged distal latencies with prolonged F-wave latencies, possible conduction block and temporal dispersion
AL amyloidosis	Lambda	Length-dependent sensory greater than motor, all phenotypes possible, autonomic failure	Reduced CMAPS and SNAPs; normal in small fiber neuropathy

AL = immunoglobulin light chain; EMG = electromyography; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M.

Monoclonal Gammopathy Testing

The International Myeloma Working Group recommends a screening panel for monoclonal proteins that includes serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE), and quantification of free light chains.[40] This panel has a 100% sensitivity for multiple myeloma and Waldenström macroglobulinemia and 97.1% sensitivity for AL amyloidosis.[40] Protein electrophoresis (PEP) separates proteins based on charge and size and is used to detect and quantitate monoclonal proteins. Once identified, immunofixation electrophoresis (IFE) is used to confirm the monoclonal protein and determine the heavy chain class or light chain type. Quantitative serum free light chain testing quantitates the amount of light chains and provides a ratio that shows unbalanced light chain synthesis. The addition of urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE) to the screening panel is recommended when AL amyloidosis is suspected.

Multiple Myeloma

The diagnosis of multiple myeloma requires a serum or urine monoclonal protein (M protein), 10% or more clonal bone marrow plasma cells or biopsy-proven plasmacytoma, and evidence of end organ damage (hypercalcemia, renal insufficiency, anemia, and bone lesions). Extramedullary organ involvement is uncommon. The risk for CNS involvement is approximately 1%.[41]

Clinical presentations. Multiple myeloma can involve the central and peripheral nervous systems. Many neurologic complications are a result of direct compression of nervous system structures by a myeloma mass lesion, while others are due to indirect causes.

Peripheral neuropathy. Symptomatic peripheral neuropathy is found in 5% to 20% of patients with multiple myeloma. Electrophysiologic studies diagnose peripheral neuropathy in almost 40% of patients with multiple myeloma. The neuropathy is not well studied but is typically slowly progressive and length dependent and can be a sensory, motor, or sensorimotor polyneuropathy.[42] Electrodiagnostic testing demonstrates an axonal neuropathy.

Neuropathy can also occur in multiple myeloma because of amyloid deposition. In these cases, the patient may experience prominent dysesthesia; dissociated sensory loss with predominant loss of nociception and thermal discrimination and relative preservation of vibration and proprioception; and autonomic symptoms such as postural lightheadedness, diarrhea or constipation, or erectile dysfunction. Carpal tunnel syndrome may be present. Electrodiagnostic testing demonstrates an axonal or mixed axonal and demyelinating neuropathy or could be normal because of selective small fiber involvement.

Toxic metabolic encephalopathy. Patients with multiple myeloma can present with altered mental status, persistent headache, lethargy, or hypersomnolence and may have underlying metabolic abnormalities such as hypercalcemia, hyperammonemia, or uremia. Hyperammonemia is most common in the IgA subtype with advanced or relapsed disease. The underlying pathophysiology remains unclear; however, several studies have demonstrated excess production of ammonia by myeloma cells.[43,44]

Spinal cord or cauda equina compression. Epidural spinal cord compression or cauda equina syndrome

KEY POINTS

- Epidural spinal cord compression occurs in 6% of patients with multiple myeloma and typically presents with back pain with radicular features or lower limb weakness.
- Hyperviscosity can occur in multiple myeloma and Waldenström macroglobulinemia and is treated with plasma exchange in addition to systemic therapy.

occurs in 6% of patients during the course of the disease.[45] These conditions can be caused by either an extramedullary plasmacytoma or a bony fragment from a vertebral body fracture. Patients typically present with back pain with radicular features or lower limb weakness. The thoracic region is most commonly affected and should be evaluated using MRI with contrast (**Figure 3-8**). Treatment of spinal cord or cauda equina compression includes high-dose corticosteroids and radiation therapy. Decompressive surgery may be needed in some cases.

Leptomeningeal/intracranial metastases. Leptomeningeal and intracranial metastases are very rare in multiple myeloma, with an incidence of 0.7%.[46] Leptomeningeal and intracranial metastases can be diagnosed by atypical plasma cells in the CSF or by identifying intraparenchymal/meningeal involvement on MRI. CNS involvement is more commonly due to hematologic spread and less often due to direct extension of calvarial or vertebral plasmacytomas. CNS involvement occurs more commonly with relapsed/refractory myeloma. Clinical symptoms include headache, double vision or other cranial nerve deficits, limb weakness, urinary incontinence, seizures, and nausea or vomiting. Risk factors include bone marrow plasma cell labeling index of 3% or more, the presence of disease at other extramedullary sites, and a high number of circulating plasma cells.[46] Overall survival is poor following the diagnosis of CNS disease.

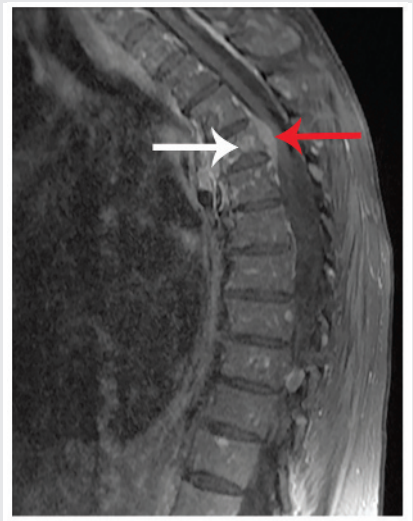

FIGURE 3-8 Sagittal T1-weighted MRI with gadolinium of the thoracic spine in a patient with multiple myeloma who presented with lower extremity weakness and urinary incontinence. There is pathologic compression fracture of T4 (*white arrow*) with spinal cord compression due to associated extraosseous epidural soft tissue mass with associated enhancement (*red arrow*) at T3 through T5.

Hyperviscosity. Hyperviscosity occurs when the immunoglobulin concentration is greater than 4000 mg/dL. Most patients develop symptoms when serum viscosity reaches 6 centipoises to 7 centipoises. Clinical symptoms include epistaxis and gingival bleeding. A variety of neurologic symptoms can occur, including headache, visual changes, vestibular symptoms, and paresthesia. Coma and hemorrhage can also develop. Funduscopic examination shows retinal vein engorgement, flame-shaped hemorrhages, and occasionally papilledema. Treatment includes plasma exchange in addition to systemic therapy to lower tumor mass and reduce immunoglobulin protein concentration.[47]

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is a lymphoplasmacytic lymphoma associated with an IgM paraprotein. Patients present with fatigue (anemia), night sweats, weight loss, thrombocytopenia, recurrent infections, peripheral neuropathy, lymphadenopathy, hepatosplenomegaly, and hyperviscosity syndrome. The diagnosis requires an IgM monoclonal gammopathy, bone

marrow biopsy with lymphoplasmacytic infiltrate (10% or more), and immunophenotype excluding other lymphoproliferative disorders.[48] The presence of *MYD88* L265P and *CXCR4* WHIM-like mutations aid in diagnosis.

Bing-Neel syndrome. Bing-Neel syndrome is the infiltration of Waldenström macroglobulinemia in the CNS. It is characterized by perivascular infiltration of small lymphocytes, lymphoplasmacytoid cells, and plasma cells surrounding Virchow-Robin spaces (perivascular spaces) and leptomeninges.[49] It is more commonly a leptomeningeal rather than an intraparenchymal mass. In approximately one-third of cases of Bing-Neel syndrome, the symptoms are the presenting manifestation of Waldenström macroglobulinemia, although some patients may have a prior diagnosis of MGUS.[50] It can also occur any time during the disease course, with a median time of onset of almost 9 years and without evidence of systemic progression.[50] Presenting symptoms are very heterogeneous but often include gait ataxia, dizziness, or cranial neuropathy. CSF may show lymphocytic pleocytosis, elevated protein level, and IgM kappa or lambda light chain restriction. The presence of *MYD88* L265 mutation in the CSF may aid in diagnosis.[51] MRI shows T2 hyperintensity in the subcortical/periventricular white matter and brainstem with leptomeningeal or dural enhancement. Biopsy is sometimes needed to demonstrate lymphoplasmacytic infiltration. Overall response to treatment with high-dose chemotherapy or intrathecal chemotherapy is 70%.[50]

Hyperviscosity. Hyperviscosity can also occur in Waldenström macroglobulinemia. The presentation and treatment are listed under multiple myeloma.

Peripheral neuropathy. Varied types of peripheral neuropathy are reported with Waldenström macroglobulinemia.[52] The majority of patients have an axonal neuropathy, which is due to various mechanisms such as amyloid, cryoglobulinemia, tumor infiltration, vasculitis, or dysimmunity. Approximately one-third of patients have a demyelinating pattern. In some cases, the peripheral neuropathy is indistinguishable from that seen in IgM MGUS neuropathy.[53] Treatment is typically aimed at the underlying disease with combination chemotherapy such as dexamethasone, rituximab, and cyclophosphamide; however, in the case of symptomatic severe peripheral neuropathy, rituximab can be used as a single agent if no evidence exists of advanced disease (bulky disease, profound cytopenias, constitutional symptoms, or hyperviscosity).[48]

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Plasma Cell Disorder, and Skin Changes (POEMS)

POEMS syndrome is a paraneoplastic disorder associated with a monoclonal plasma cell disorder, with the acronym listing some of the common features. Established diagnostic criteria exist,[54] and two major clinical features required for diagnosis are a monoclonal plasma cell disorder and a peripheral neuropathy. Other major criteria include Castleman disease, sclerotic bone lesions, and elevated vascular endothelial growth factor (VEGF). VEGF of greater than 200 pg/mL had a specificity of 95% with a sensitivity of 68% in support of a POEMS diagnosis.[55] VEGF may be normal in patients who have received corticosteroids. CT of the axial skeleton and long bones is superior to a skeletal survey in identifying sclerotic lesions.[56] The monoclonal light chain is lambda in 97% to 99% of cases. Treatment of POEMS

KEY POINT

- Bing-Neel syndrome is due to perivascular infiltration of lymphocytes and plasma cells surrounding Virchow-Robin spaces (perivascular spaces) and leptomeninges.

KEY POINTS

- Stroke occurs in 10% of patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome and is associated with thrombocytosis and bone marrow plasmacytosis.
- POEMS syndrome should be considered in patients with treatment-refractory chronic inflammatory demyelinating polyradiculoneuropathy with a lambda monoclonal protein.

syndrome is based on the extent of plasma cell infiltration.[54] Those with more than two lesions or clonal plasma cells on iliac crest biopsy are offered systemic therapy with chemotherapy or chemotherapy with peripheral blood stem cell transplantation. Those with two or fewer lesions and no clonal plasma cells on iliac crest biopsy are given curative doses of radiation to the affected sites.

Stroke. Cerebral infarction occurs in approximately 10% of patients with POEMS syndrome prior to treatment, with a 5-year risk of stroke of 13.4%.[57] Patients rarely present with stroke as the initial manifestation of POEMS syndrome.[58,59] In POEMS syndrome, stroke is associated with thrombocytosis and bone marrow plasmacytosis and not with traditional stroke risk factors. The majority of strokes occur in the cerebral hemispheres within a single vascular territory. Treatment is aimed at the underlying plasma cell disorder.

Peripheral neuropathy. Peripheral neuropathy is often the presenting or dominant clinical feature of POEMS syndrome and is required for the diagnosis. It is a length-dependent sensorimotor neuropathy or polyradiculoneuropathy. It is often quite severe, with bilateral footdrop. Pain and positive neuropathic sensory symptoms are common, and patients are often areflexic. The neuropathy is often misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) because of the clinical phenotype, albuminocytologic dissociation on CSF (elevated protein with normal white blood cell count), and demyelinating features on electrodiagnostic studies (**Case 3-3**). Compared to CIDP, the distal involvement is more severe without sural sparing, and the slowing is more uniform along the nerve.[60] Other helpful clues include thrombocytosis and elevated plasma VEGF (often greater than 200 pg/mL).[55,61] The neuropathy severity does not correlate with the level of VEGF. Treatment of the neuropathy involves treating the underlying plasma cell disorder. Retrospective studies demonstrate improvement in neuropathy and disability with treatment.[62]

Immunoglobulin Light Chain (AL) Amyloidosis

AL amyloidosis is a plasma cell proliferative disorder characterized by deposition of fibrillary monoclonal light chains in various tissues leading to structural damage and organ dysfunction. AL amyloidosis has a median age of onset of 62 years and a mean survival of 24 months. It is a multisystem disease frequently affecting peripheral and autonomic nerves and renal, cardiac, and gastrointestinal systems. The two most common symptoms in patients are fatigue and weight loss.[63] Diagnostic findings including periorbital or facial purpura, hepatomegaly, and macroglossia are present in a minority of patients. Outside of the nervous system, common manifestations include cardiac (congestive heart failure), renal (nephrotic syndrome), pulmonary (cough, dyspnea), and hepatic (hepatomegaly, jaundice). Lambda light chain is a hallmark of AL amyloidosis. Biopsy of the iliac crest bone marrow combined with abdominal subcutaneous fat aspiration will identify amyloid deposits in 85% of patients.[64] Mass spectrometry is used to determine the amyloid protein composition.[65]

Peripheral and autonomic neuropathy. Peripheral nerve involvement occurs in up to one-fourth of patients with AL amyloidosis. It is characterized by prominent early involvement of somatic and autonomic fibers, causing a symmetric length-dependent neuropathy

Case 3-3

A 51-year-old man presented after a 2-month history of bilateral foot swelling that progressed to tingling in his feet and subsequently bilateral footdrop. He noted numbness from the knees down with shooting pain in his feet. He was fatigued and required a cane.

Neurologic examination demonstrated a steppage gait with mild weakness in his hands and severe weakness below the knees. His reflexes were severely reduced or absent throughout. Sensory examination demonstrated length-dependent loss to all modalities. Electrodiagnostic evaluation demonstrated a mixed axonal and demyelinating peripheral neuropathy with ulnar conduction block. CSF demonstrated 1 white blood cell/μL and protein of 117 mg/dL. Serum protein electrophoresis and immunofixation were negative. A bone survey demonstrated a lytic lesion in the left ilium interpreted as consistent with cystic fibrous dysplasia. He was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and was treated with IV immunoglobulin (IVIg) followed by IV methylprednisolone, each for 3 months, without improvement.

Further evaluation 3 months later showed gynecomastia and cherry angiomas. Free light chain assay showed a mildly elevated lambda light chain with normal kappa to lambda ratio. His vascular endothelial growth factor (VEGF) level was normal. Positron emission tomography (PET)/CT showed intense fludeoxyglucose (FDG) uptake in the left ilium consistent with malignancy (**Figure 3-9**). Bone marrow biopsy was normal, and biopsy of the ilium lesion revealed a lambda light chain–restricted plasmacytoma. Radiation therapy to the ilium was recommended.

Comment. This case highlights that polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome should be considered in cases of treatment-unresponsive CIDP. Thorough evaluation for a monoclonal plasma cell disorder is recommended. VEGF can be normal if the patient has recently received steroids or chemotherapy.

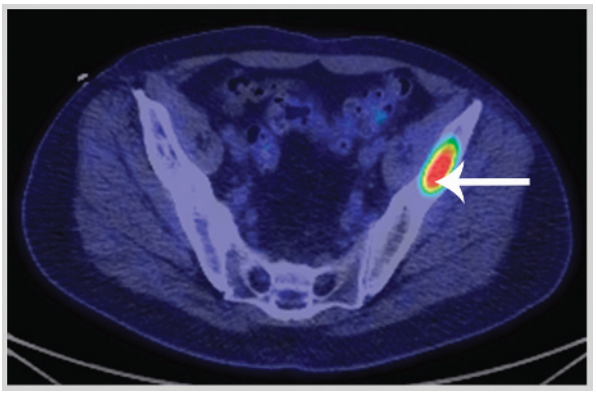

FIGURE 3-9 Positron emission tomography (PET)/CT of a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome demonstrating intense fludeoxyglucose (FDG) uptake of the left ilium (*arrow*) consistent with osteosclerotic myeloma.

with loss of temperature sensation and burning neuropathic pain and autonomic failure.[66] Orthostatic hypotension occurs in approximately one-half of patients. Gastrointestinal symptoms include postprandial vomiting or diarrhea, constipation, and gastroparesis. Erectile dysfunction is an early and frequent feature in men. Nerve conduction studies demonstrate a length-dependent sensorimotor neuropathy with axonal features. Electrodiagnostic testing can be normal in cases of purely small fiber involvement. Nerve biopsy demonstrates fiber loss, axonal degeneration, and amyloid deposition in the endoneurium and epineurium (**Figure 3-10A**). Treatment consists of stem cell transplantation in eligible patients and chemotherapy in others.

Myopathy. Myopathy is a rare presentation of AL amyloidosis that most often presents with muscle weakness

KEY POINT

- AL amyloid neuropathy causes a length-dependent neuropathy with prominent early involvement of somatic and autonomic fibers.

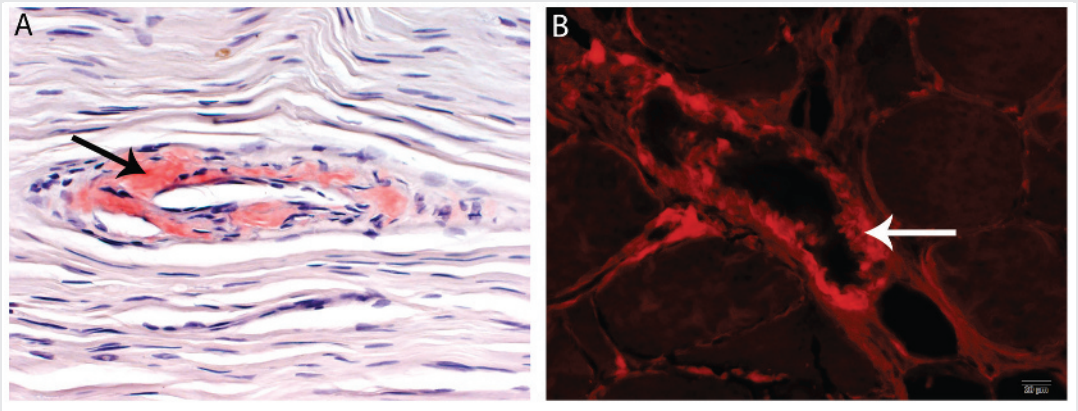

FIGURE 3-10 Patient with AL amyloidosis. *A,* Congo red preparation of sural nerve biopsy demonstrating amyloid deposition around an endoneurial vessel; *B,* Congo red preparation of muscle biopsy viewed under rhodamine optics revealing amyloid deposits within intramuscular blood vessel walls and in endomysium encasing muscle fibers.

KEY POINTS

- AL amyloid myopathy often has a normal creatine kinase.
- IgM neuropathy (distal acquired demyelinating symmetric neuropathy) often presents in older men with sensory ataxia.

with other symptoms of dysphagia, myalgia, macroglossia, jaw claudication, and hoarseness in some patients. Patients often can have a normal creatine kinase level at diagnosis, making it an unreliable marker for diagnostic purposes.[67] The myopathy is most often proximal; however, one-half also have distal weakness. EMG demonstrates myopathic potentials and fibrillation potentials in the majority of patients. Muscle biopsy demonstrates an increase in perimysial or endomysial fibrous and fatty connective tissue as well as a myopathic process with regenerating and necrotic fibers (**Figure 3-10B**). Many patients also show neurogenic findings on EMG and muscle biopsy (denervation atrophy and fiber-type grouping) indicating coexisting neuropathy.

Monoclonal Gammopathy of Undetermined Significance

Three major types of MGUS exist: IgM MGUS, non-IgM MGUS, and light chain MGUS. MGUS carries a risk of progression to a hematologic malignancy of 1% per year.[39]

Peripheral neuropathy. As many as one-third of patients with an MGUS have a peripheral neuropathy. IgM is overrepresented, occurring in 48% of patients with monoclonal gammopathy and peripheral neuropathy.[68] This type of neuropathy is often referred to as IgM neuropathy or distal acquired demyelinating symmetric (DADS) neuropathy.[69] It typically affects older men in the sixth to ninth decade. It is a distal, symmetric, sensory-predominant neuropathy often presenting with sensory ataxia. Mild distal weakness may occur, and a mild tremor is common. Less commonly, patients develop a polyradiculoneuropathy similar to CIDP. Electrodiagnostic studies demonstrate demyelinating features, with preferential involvement for the distal nerve segments causing prolonged motor distal latencies and short terminal latency indices. Sensory responses are often absent. Approximately 50% of patients have antibodies to myelin-associated glycoprotein (MAG). Its positivity can strengthen the association of IgM and peripheral neuropathy; however, no phenotypic or prognostic difference is seen. No proven effective treatments for IgM neuropathy have been found, although rituximab, IVIg, and others may be tried if the patient

has an early age of onset, severe gait imbalance, or weakness, or if the disease is rapidly progressing.

CONCLUSION

Varied neurologic complications occur in lymphoma, leukemia, and paraproteinemic disorders. These syndromes can occur as the presenting symptom of the disease, with systemic involvement, or at relapse. Early recognition is important as a delay in treatment can adversely affect patient outcome. Complications occur more commonly in non-Hodgkin lymphoma than Hodgkin lymphoma, with leptomeningeal metastases occurring in up to one-third of patients with non-Hodgkin lymphoma. Leukemia can have masslike involvement, which can lead to diagnostic uncertainty. Peripheral neuropathy is the most common complication of paraproteinemic disorders; therefore, the evaluation of peripheral neuropathy should include a serum protein electrophoresis, immunofixation, and free light chain assay.

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Rheumatology and Neurology

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ABSTRACT

Purpose of Review: This article reviews the various rheumatologic disorders that have neurologic complications and manifestations.

Recent Findings: Recent advances have improved the understanding of the true epidemiology of many rheumatologic diseases and their complications. Many years of observation have clarified findings even in rarer disorders. Classification and diagnostic criteria have been updated and validated. As newer pharmacologic agents have become available, new information regarding efficacy and toxicity has emerged.

Summary: Rheumatologic disorders are common, as can be their neurologic complications. In many instances, these complications are treatable, but clinicians' understanding of the underlying disorder, its neurologic risks, and the risk of therapy is required.

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INTRODUCTION

Rheumatologic diseases are a group of acute and chronic autoimmune disorders. Most have systemic involvement resulting in end organ damage and can include damage to the central nervous system (CNS) and peripheral nervous system (PNS), features of which can be a presenting symptom or an eventual manifestation. Additionally, newer treatment modalities can lead to iatrogenic neurologic disorders. This article reviews rheumatologic diseases that demonstrate nervous system involvement and highlights potential neurologic complications of treatment of rheumatologic disease.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS

CNS manifestations are myriad and represent pathology that can span the central neuraxis. They may result from CNS inflammation (eg, meningoencephalitis, cerebritis, myelitis), direct vasculitis or vasculopathy (eg, stroke syndromes, venous sinus thrombosis, dissection), or structural disease (eg, atlantoaxial subluxation), or may present as secondary manifestations (eg, headache, movement disorders, seizures, acute confusional state, anxiety, cognitive dysfunction, mood disorder, psychosis).

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS

PNS manifestations are also highly varied and span the PNS from spinal nerve root through muscle. They also can be primary and related to direct autoinflammatory processes (eg, inflammatory myopathy) or vasculitis (eg, vasculitic neuropathy) or secondary (eg, median neuropathy at the wrist due to compression).

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease

KEY POINT

- Rheumatologic disorders are common and can present with central or peripheral nervous system manifestations; they can also develop at any time during the disease course.

manifesting numerous presentations systemically and neurologically. Proposed diagnostic criteria were first published in 1971 and have undergone several revisions. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) revised and validated the updated American College of Rheumatology (ACR) classification criteria with the goal of improving clinical relevance and adding relevant immunologic advancements (**Table 4-1**).[1] The SLICC identified 17 criteria, and application of the criteria has resulted in fewer misclassifications, greater sensitivity, and equivalent specificity to the ACR criteria. Four criteria must be fulfilled (at least one clinical and one immunologic) or biopsy-proven lupus nephritis found in the presence of either antinuclear antibody (ANA) or anti–double-stranded DNA (dsDNA) antibodies for the diagnosis. An important clarification is that isolated clinical or immunologic findings should not be diagnosed

TABLE 4-1 Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics Classification Criteria[a,b]

▶ **Clinical Criteria**
1. Acute cutaneous lupus including
Lupus malar rash (do not count if malar discoid)
Bullous lupus
Toxic epidermal necrolysis variant of systemic lupus erythematosus
Maculopapular lupus rash
Photosensitive lupus rash
In the absence of dermatomyositis
OR
Subacute cutaneous lupus (nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus including
Classic discoid rash
Localized (above the neck)
Generalized (above and below the neck)
Hypertrophic (verrucous) lupus
Lupus panniculitis (profundus)
Mucosal lupus
Lupus erythematosus tumidus
Chilblains lupus
Discoid lupus/lichen planus overlap

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TABLE 4-1 **Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics Classification Criteria**[a,b] *Continued from page 692*

3. Oral ulcers

   Palate

   Buccal

   Tongue

   OR

   Nasal ulcers

   In the absence of other causes, such as vasculitis, Behçet disease, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)

   In the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

5. Synovitis involving two or more joints, characterized by swelling or effusion *OR* tenderness in two or more joints and 30 minutes or more of morning stiffness

6. Serositis

   Typical pleurisy for more than 1 day

   OR

   Pleural effusions

   OR

   Pleural rub

   Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day

   OR

   Pericardial effusion

   OR

   Pericardial rub

   OR

   Pericarditis by ECG

   In the absence of other causes, such as infection, uremia, and Dressler syndrome

7. Renal

   Urine protein/creatinine (or 24-hour urine protein) representing 500 mg of protein per 24 hours

   OR

   Red blood cell casts

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TABLE 4-1 **Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics Classification Criteria[a,b]** *Continued from page 693*

8. Neurologic
    - Seizures
    - Psychosis
    - Mononeuritis multiplex
        - *In the absence of other known causes such as primary vasculitis*
    - Myelitis
    - Peripheral or cranial neuropathy
        - *In the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus*
    - Acute confusional state
        - *In the absence of other causes, including toxic-metabolic, uremia, or drugs*
9. Hemolytic anemia
10. Leukopenia (<4000/mm^3 at least once)
    - *In the absence of other known causes such as Felty syndrome, drugs, or portal hypertension*
    - *OR*
    - Lymphopenia (<1000/mm^3 at least once)
        - *In the absence of other known causes such as corticosteroids, drugs, or infection*
11. Thrombocytopenia (<100,000/mm^3 at least once)
    - *In the absence of other known causes such as drugs, portal hypertension, or TTP*

▶ **Immunologic Criteria**

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody as determined by any of the following
    - Lupus anticoagulant
    - False-positive RPR
    - Medium or high titer anticardiolipin (IgA, IgG, or IgM)
    - Anti-β2 glycoprotein I (IgA, IgG, or IgM)
5. Low complement
    - Low C3
    - Low C4
    - Low CH50

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TABLE 4-1 **Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics Classification Criteria**[a,b] *Continued from page 694*

6. Direct Coombs test in the absence of hemolytic anemia

▶ **Classification Rule**

Classify a patient as having SLE if

The patient satisfies four of the criteria listed including at least one clinical and one immunologic criterion

OR

The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies

ANA = antinuclear antibody; dsDNA = double-stranded deoxynucleic acid; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; RPR = rapid plasma reagin; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura.

[a] Modified with permission from Petri M, et al, Arthritis Rheum.[1] © 2012 American College of Rheumatology. *onlinelibrary.wiley.com/doi/10.1002/art.34473/full*.

[b] Criteria are cumulative and need not be present concurrently.

KEY POINT

■ Central nervous system manifestations of neuropsychiatric lupus are more common than peripheral nervous system presentations. Headache, mood disorders, cognitive dysfunction, seizures, and cerebrovascular disease are most common.

as SLE. The SLICC expanded on the original criteria of psychosis or seizure and now include those as well as mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state.

Neuropsychiatric SLE refers to the CNS, PNS, autonomic nervous system, and psychiatric manifestations associated with SLE. These were outlined by the ACR in 1999, standardizing nomenclature and case definitions.[2] Delineated CNS and psychiatric syndromes and PNS syndromes are listed in **Table 4-2**. Neuropsychiatric SLE symptoms can present before the onset of other manifestations of SLE or at any time during the disease course, even when a patient is otherwise in remission. A 2011 meta-analysis estimated neuropsychiatric SLE prevalence among patients with SLE to be 56.3% (95% confidence interval 42.5% to 74.7%).[3] Alternative explanations for any presentation of neuropsychiatric SLE must be evaluated and excluded. A number of autoantibodies are seen in the presence of neuropsychiatric SLE, such as ANA, dsDNA, anti-ribosomal P protein, and antiphospholipid antibodies.[4]

CNS presentations can be highly varied and may represent the sequelae of any of a number of secondary causes related to SLE (eg, renal insufficiency or hypertension from renal disease, side effects or toxicity from therapy, infection) or may be a primary manifestation. They may or may not be the direct effects of inflammation itself. Cumulative prevalence estimates for CNS disease range from 13% to 92%,[4] although the true prevalence likely falls toward the upper end of this range as studies reporting lower estimates may have underreported headache, not included headache, or included syndromes only at the time of diagnosis and not on long-term follow-up.[3] The five most common CNS syndromes (pooled prevalence from prospective studies) appear to be headache (23.3%; 37% when excluding studies underreporting or not including headache), mood

TABLE 4-2 Neuropsychiatric Syndromes Observed in Systemic Lupus Erythematosus[a]

▶ **Central Nervous System Syndromes**
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Movement disorder
Myelopathy
Seizure
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
▶ **Peripheral Nervous System Syndromes**
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
Autonomic disorder
Mononeuropathy, single or multiple
Myasthenia gravis
Cranial neuropathy
Plexopathy
Polyneuropathy

[a] Modified with permission from American College of Rheumatology, Arthritis Rheum.[2] © 1999 American College of Rheumatology. *onlinelibrary.wiley.com/doi/10.1002/1529-0131(199904)42:4%3C599::AID-ANR2%3E3.0.CO;2-F/pdf*.

disorders (14.9%), cognitive dysfunction (13.9%; 23% to 60% when only including studies using formal neuropsychological testing), seizures (8.0%), and cerebrovascular disease (7.2%).[3]

PNS presentations are much rarer, with prevalences of 0 to 56% and representing 6.9% of all manifestations.[3] Peripheral neuropathy is the most common PNS complication, seen in up to 28% of patients, followed by cranial neuropathy and mononeuropathy (including mononeuritis multiplex). A distal sensory or sensorimotor neuropathy that may be symmetric or asymmetric is most common. Just as in the general population without SLE, the median and ulnar nerves are most commonly affected as isolated mononeuropathies. Cranial neuropathies can be single or multiple as well. Other PNS syndromes (eg, acute inflammatory demyelinating polyradiculoneuropathy [AIDP], autonomic dysfunction, myasthenia gravis, and plexopathies) are extremely rare, although autonomic dysfunction is probably underestimated because autonomic symptoms often require direct questioning of the patient and autonomic testing is not widely available.

Muscle disease is not included in the ACR or SLICC criteria. Inflammatory myopathy occurs in up to 8% of patients,[5] heralded by predominantly proximal weakness and muscle pain. Serum creatine kinase (CK) and aldolase levels show variable elevation. The author's personal experience and that of others shows that in patients without symptoms of muscle disease, it is important to recognize that muscle biopsies can still show inflammatory changes. The clinical implications of this are unclear.[6]

A 2015 retrospective cross-sectional study examined patients with newly diagnosed neuropsychiatric SLE who had an MRI within 6 months after the onset of neuropsychiatric symptoms.[7] Imaging abnormalities were categorized as inflammatorylike (poorly defined T2-weighted hyperintensities of medium to large size not in a specific vascular territory), large vessel

disease, and small vessel disease, with the latter subcategorized as white matter hyperintensities, recent small subcortical infarcts, lacunes, microbleeds, and atrophy. Of neuropsychiatric SLE episodes, 87% were diagnosed as CNS neuropsychiatric SLE, with headache, cerebrovascular disease, seizure, and cognitive dysfunction again being the most common manifestations. About 40% of MRIs were normal. Small vessel disease, primarily white matter hyperintensities, predominated in the remainder of patients with abnormal MRIs. Of 35 patients with headache, 17 had abnormal MRIs, all of which demonstrated only white matter hyperintensities, one also with a lacune. White matter hyperintensities also correlated with cognitive dysfunction, low CH50, and presence of lupus anticoagulant. No association with vascular risk factors was seen, and this, in conjunction with the association with inflammatory markers, may suggest an inflammatory role in pathogenesis. Lupus anticoagulant was also associated with microbleeds and trended toward an association with lacunes. Patients with large vessel disease tended to have more than one infarct, suggesting high recurrence. This also showed a trend toward association with lupus anticoagulant. Interestingly, inflammatorylike findings were rare and associated with low complement. Overall, findings are nonspecific and tend to represent vascular disease. The association with specific antibodies suggests that subsets of patients exist that may warrant heightened scrutiny for cerebrovascular disease.

The association with vascular disease does not appear to be coincidental. Atherosclerosis is increasingly recognized to have a chronic inflammatory component. Accordingly, patients with autoimmune diseases commonly experience cardiovascular compromise, and patients with SLE are no exception. Patients with SLE develop atherosclerosis prematurely independent of other vascular risk factors and elevated rates of endocarditis and other valvular abnormalities; they are also at risk of supraventricular arrhythmias. Any of these may increase the risk for cerebrovascular disease, particularly in conjunction with known autoantibodies.[8] Aggressive stroke risk factor monitoring and modification is essential in patients with SLE.

The SLICC criteria include more of the recognized diagnoses included in neuropsychiatric SLE as compared to the ACR criteria but not all of them. They tend to be rare, and none of the neuropsychiatric SLE syndromes is specific to SLE. They may occur in patients with other autoimmune disorders as well as in people without coincident autoimmune disease. When they arise, it is certainly necessary to consider SLE, but it obviously should not be diagnosed from neurologic manifestations in isolation.

KEY POINT

- Chronic inflammation is implicated in accelerated atherosclerosis; in systemic lupus erythematosus, this manifests as increased risk for cardiovascular and cerebrovascular disease independent of other vascular risk factors.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) occurs in approximately 1% to 2% of the population and is the most common inflammatory arthritis. It causes a primarily symmetric inflammatory arthropathy but also causes a number of extraarticular complications. Classification criteria were established in 1987 by the American Rheumatism Association and replaced by the 2010 Rheumatoid Arthritis Classification Criteria, as the former had insufficient sensitivity for early RA (**Table 4-3**).[9] The new criteria were designed to be applied to ''eligible'' patients (those with clinical synovitis) and can be applied retrospectively. Prior criteria achieved the

TABLE 4-3 The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis[a]

- **Target population (Who should be tested?): Patients who**
  1. Have at least one joint with definite clinical synovitis (swelling)
  2. With the synovitis not better explained by another disease
- **Classification criteria for rheumatoid arthritis (score-based algorithm: add score of categories A–D; a score of ≥6 out of 10 is needed for classification of a patient as having definite rheumatoid arthritis)**
  - A. Joint involvement
    - 1 large joint[b] (0 points)
    - 2–10 large joints[b] (1 point)
    - 1–3 small joints[c] (with or without involvement of large joints[b]) (2 points)
    - 4–10 small joints[c] (with or without involvement of large joints[b]) (3 points)
    - >10 joints (at least 1 small joint[c]) (5 points)
  - B. Serology (at least one test result is needed for classification)
    - Negative rheumatoid factor (RF) *and* negative anti-citrullinated protein antibody (ACPA) (0 points)
    - Low-positive[d] RF *or* low-positive ACPA (2 points)
    - High-positive[e] RF *or* high-positive ACPA (3 points)
  - C. Acute-phase reactants (at least one test result is needed for classification)
    - Normal C-reactive protein (CRP) *and* normal erythrocyte sedimentation rate (ESR) (0 points)
    - Abnormal CRP *or* normal ESR (1 point)
  - D. Duration of symptoms (self-reported)
    - <6 weeks (0 points)
    - ≥6 weeks (1 point)

[a] Modified with permission from Aletaha D, et al, Arthritis Rheum.[9] © 2010 American College of Rheumatology. *onlinelibrary.wiley.com/doi/10.1002/art.27584/pdf*.
[b] Large joints: shoulders, elbows, hips, knees, ankles.
[c] Small joints: metacarpophalangeal, proximal interphalangeal, second to fifth metatarsophalangeal, thumb interphalangeal, wrists.
[d] Low positive: less than upper limit of normal but greater than 3 times the upper limit.
[e] High positive: greater than 3 times the upper limit of normal.

goal of differentiating established disease from other entities, while the 2010 criteria are meant to enable classification of early disease. They include additional serologic criteria (in addition to rheumatoid factor positivity). Anti–cyclic citrullinated peptide (CCP) antibodies appear to be more specific for RA than rheumatoid factor positivity (a recent single-center study found anticitrullinated protein antibody sensitivity and specificity to be

61.8% and 89.9%, respectively, versus 64.4% and 76.5% for rheumatoid factor),[10] likely have a more highly positive likelihood ratio,[11] and carry equal weight in the new criteria to rheumatoid factor. Erythrocyte sedimentation rate and C-reactive protein elevations are weighted less heavily.

RA causes joint swelling and pain, synovitis, and erosion that can be seen on conventional radiography. Extra-articular disease occurs in 40% to 70% of patients and includes a number of systemic complications, such as rheumatoid nodules, Felty syndrome (RA, splenomegaly, and neutropenia), and, rarely, systemic vasculitis, in addition to neurologic involvement. Non–joint-related disease occurs via a number of mechanisms. Nonarthritic symptoms arise from inflammatory mediators, encasement or compression of structures near inflamed synovium or rheumatoid nodules, and several sequelae from vasculitis (addressed later in the section on vasculitides).[12]

CNS presentations are likely less common than PNS presentations, and all are increased in the setting of seropositivity and longer disease duration. Psychiatric disorders and cognitive dysfunction are increasingly recognized. Depression and anxiety occur at rates higher than in the general population and should be screened for. Cognitive impairment is associated with lower baseline education, lower income, glucocorticoid administration, and higher number of cerebrovascular disease risk factors. In the setting of any neuropsychiatric finding, medications must be reviewed and MRI of the brain obtained to exclude demyelination (treatment-related disorders are addressed in a later section). Headaches are also common and may represent a coincidental primary headache syndrome not related to RA or may be caused by intracranial pathology due to RA. A 2015 study also demonstrated a hazard ratio of 1.52 for epilepsy in patients with RA as compared to matched controls.[13] An unusual finding was that nonsteroidal anti-inflammatory drug (NSAID) use correlated with significantly reduced risk, but the clinical implications of this remain unclear given study design and a lack of corroborating studies.

Rheumatoid meningitis and meningoencephalitis are rare and can occur in patients with long-standing disease but may also very rarely be presenting manifestations.[14] Symptoms are nonspecific, as are imaging findings of pachymeningeal or leptomeningeal thickening and enhancement, although nodular lesions may mimic a neoplasm. Patients may have focal neurologic signs, cognitive dysfunction, seizures, or headache. CSF tends to appear inflammatory, with elevated mononuclear cells and protein, but has also been reported to be normal. Meningeal and brain biopsy may be required for the diagnosis, showing mononuclear cell infiltrates, often plasma cell rich, with necrosis and possible granulomata. Chronic meningeal inflammation may lead to late normal pressure hydrocephalus.[12] Rheumatoid nodules and vasculitis sparing larger vessels may also occur. Nodules alone can also cause focal symptoms and signs due to mass effect and compression. Vasculitis can cause strokelike syndromes, but patients with RA are also at increased risk for early and advanced cerebrovascular and cardiovascular disease, valvular disease, and congestive heart failure, leading to increased risk of stroke.[8] Risk factor modification is essential.

Cervical spine involvement from RA takes the form of bony erosions, atlantoaxial subluxation, subaxial subluxation, and vertical subluxation. It may take place in over 40% of patients

KEY POINT

- Rheumatoid arthritis is the most common inflammatory arthritis and affects 1% to 2% of the population. Central nervous system complications are rare but more common with seropositivity, including anti–cyclic citrullinated peptide antibodies, rheumatoid factor, antinuclear antibody, and C-reactive protein, and with longer disease duration.

KEY POINTS

- Cervical spine subluxation is a common complication of rheumatoid arthritis, with atlantoaxial subluxation being most common, leading to progressive myelopathy; surgical stabilization may be necessary to prevent progression.
- Patients with rheumatoid arthritis may develop vasculitis, which can cause a vasculitic neuropathy, including mononeuritis multiplex or a distal symmetric sensory or sensorimotor peripheral neuropathy; this is an independent predictor of mortality.

and is one of the most recognized and feared neurologic manifestations of the disease.[15] Spinal sequelae are usually a late feature of the disease due to chronic atlantoaxial arthritis. Atlantoaxial subluxation is most common, as the atlantoaxial ligaments become lax due to pannus formation at C1-C2 and bony destruction occurs, usually leading to anterior subluxation and eventually nerve root and cord compression with myelopathy. Subaxial subluxation occurs more caudally in the cervical spine and less frequently but can lead to progressive myelopathy as well. Vertical subluxation (also called cranial settling or superior migration of the odontoid) leads to the descent of the foramen magnum; apparent migration upward of the odontoid; and compression of the brainstem and cervical spine, cranial nerve dysfunction, stroke (particularly in the basilar artery distribution), hydrocephalus, and cardiac arrest. These entities should be suspected in any patient with RA and neck pain or symptoms referable to the brainstem or high cervical spine. Patients with instability may be at acute risk during intubation as well. Surgical stabilization of the spine should prevent further deterioration.

Peripheral neuropathy is common in RA and is asymptomatic in a majority of patients. Compressive mononeuropathies are the most common PNS finding in RA. They can occur from subcutaneous rheumatoid nodules, in association with severe arthropathy, or with synovitis and synovial thickening. Almost any named nerve can be susceptible anywhere along its course, including the median, ulnar, anterior or posterior interosseous, radial, sciatic, fibular (peroneal), tibial, or femoral nerves. Reduction of disease activity may be beneficial, but otherwise management is similar to that in patients without RA.

Distal symmetric sensory or sensorimotor neuropathy and mononeuritis multiplex also occur, and all may be due to rheumatoid vasculitis. The hallmark is that of a painful neuropathy, particularly in mononeuritis multiplex. A digital neuropathy may also complicate the clinical course of RA, often in concert with a distal sensory neuropathy. In the setting of vasculitis, concomitant cutaneous vasculitis, low C4 complement level, and severe neuropathy affecting more than two limbs are predictors of mortality.[16] Such patients may require more aggressive therapy. Autonomic neuropathy is likely underrecognized and may occur in isolation or in association with a somatic neuropathy.

Patients with RA also develop muscle symptoms. Type 2 fiber atrophy is common from disuse atrophy or steroid administration. Inflammatory myopathy can manifest as polymyositis, dermatomyositis, vasculitic myositis, or nodular myositis.

SJÖGREN SYNDROME

Sjögren syndrome causes chronic inflammation of exocrine glands, leading to its hallmark symptoms of dry eyes (xerophthalmia associated with keratoconjunctivitis sicca) and dry mouth (xerostomia). Periductal lymphocytosis accounts for profound loss of exocrine function, but this feature can be subtle or lacking, and extraglandular features may predominate in some patients. Likewise, dry eyes and dry mouth are relatively nonspecific, rendering the diagnosis difficult to make at times. In 2002, the American-European Consensus Group revised initial classification criteria using clinical, pathologic, and serologic criteria and specifying primary versus secondary disease and exclusion criteria (**Table 4-4**).[17] It occurs alone as primary Sjögren syndrome or in conjunction with another connective tissue

TABLE 4-4 Criteria for the Classification of Sjögren Syndrome[a]

▶ **Diagnosis of primary Sjögren syndrome requires the presence of four of the following six criteria, as long as item IV or VI is present. Diagnosis of secondary Sjögren syndrome in patients with a potentially associated disease requires the presence of item I or II and any two of items III–V.**

I. Ocular symptoms

II. Oral symptoms

III. Ocular signs (Schirmer test or ocular dye score)

IV. Histopathology in minor salivary glands

V. Salivary gland involvement shown by reduced salivary flow, abnormal sialography, or scintigraphy

VI. SSA or SSB antibody present, or both

▶ **Exclusion criteria**

Past head/neck radiation

Hepatitis C infection

AIDS

Lymphoma

Sarcoidosis

Graft versus host disease

Use of anticholinergic drugs

AIDS = acquired immunodeficiency syndrome; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

[a] Modified with permission from Vitali C, et al, Ann Rheum Dis.[17] © 2002 Annals of the Rheumatic Diseases. *ard.bmj.com/content/61/6/554.full*.

disease (eg, SLE or RA) as secondary Sjögren syndrome. The focus of this article is primary Sjögren syndrome.

In addition to the lacrimal and salivary glands, Sjögren syndrome affects other exocrine glands, such as in the skin and upper airways. It produces nonspecific generalized symptoms, such as fatigue, muscle and joint pain, and Raynaud phenomenon, and can be complicated by a small vessel vasculitis. Serologic studies may be positive for ANA, rheumatoid factor, and hypergammaglobulinemia, and there may be anemia with lymphopenia, but anti–Sjögren syndrome A (SSA) and anti–Sjögren syndrome B (SSB) antibodies are more specific but not particularly sensitive.

Neurologic involvement can include PNS and, much less commonly, CNS disease. The prevalence of neurologic involvement is debated and, depending on the study, can run from 0 to over 70%, depending upon recruitment and clinic type, criteria used, and diagnosis definition; it likely runs closer to 20%.[18] A 2011 study of 32 patients with Sjögren syndrome found neurologic involvement in 20 patients,[19] with the only distinguishing clinical feature between those with and without neurologic disease being the presence of fever in 45% of the group with neurologic disease. Neurologic findings commonly precede typical xerostomia and xerophthalmia. A 2015 review noted that anti-SSA and anti-SSB

KEY POINTS

- Sensory neuronopathy (ganglionopathy) is a classic presentation of Sjögren syndrome, manifesting with non–length-dependent sensory loss, pseudoathetosis, and ataxia due to lymphocytic inflammation of the dorsal root ganglion.
- Longitudinally extensive demyelinating lesions of the spinal cord in patients with Sjögren syndrome are considered to be reflective of primary neuromyelitis optica rather than a central nervous system complication of Sjögren syndrome itself.

antibodies appear less commonly in patients with neurologic involvement as opposed to in those without.[4]

The most common manifestation is polyneuropathy, which can be the presenting feature of primary Sjögren syndrome. A distal symmetric axonal sensory or sensorimotor neuropathy is typical and is a classic finding in Sjögren syndrome, but a minority of patients will have an asymmetric neuropathy or be asymptomatic, necessitating electrodiagnostic testing. Small and large fibers can be affected. A pure small fiber neuropathy is also common but, as in other conditions, it may require specific historical inquiry and autonomic testing to discover it. Autonomic dysfunction can include pupillary reaction abnormalities (Adie tonic pupil), orthostatic intolerance, changes in sweat volume or distribution, gastrointestinal dysmotility, and Valsalva or heart rate response to deep breathing.

A particularly important pattern to recognize is that of sensory neuronopathy (ganglionopathy), a rare disorder with a limited differential. In patients with a sensory neuronopathy, non–length-dependent involvement of large and small fiber sensory function is present, with either the acute or chronic onset of sensory loss and ataxia. Pseudoathetosis is a clinical clue, and nerve conduction studies show a non–length-dependent reduction in amplitude or loss of sensory responses (ie, upper limb responses more affected than lower limb). The level of pathology is at the level of the dorsal root ganglion rather than the nerve axon itself, likely related to lymphocytic infiltration.[4] **Case 4-1** provides an example of a sensory neuronopathy in the setting of Sjögren syndrome.

Acute mononeuritis multiplex may result from a vasculitis, although care must be taken to avoid labeling common entrapment neuropathies that may also occur at higher rates in patients with primary Sjögren syndrome as mononeuritis since treatment is much different (immune suppression or modulation versus protection and decompression). An isolated trigeminal neuropathy is also a presentation of primary Sjögren syndrome and is often purely sensory and bilateral; this is also likely a ganglionopathy.

CNS involvement in Sjögren syndrome is much less common and poorly characterized. Most frequent are encephalopathy and cognitive dysfunction, although cognitive changes may be very subtle and detectable only on neuropsychological testing. Even pseudodementia and psychiatric manifestations may occur. Aseptic meningitis is not uncommon and can recur. MRI of the brain may show nonspecific white matter changes. Focal CNS involvement leads to anatomically appropriate deficits but also seizures, movement disorders, and dyscoordination. Myelopathy is historically more common, with longitudinally extensive demyelinating lesions of the spinal cord similar to that seen in neuromyelitis optica (NMO). Aquaporin-4 antibody positivity likely represents primary and coincident NMO in the setting of primary Sjögren syndrome rather than a CNS manifestation of primary Sjögren syndrome itself; some of the historical cases may have been just that given the coexistence with optic neuritis as well.[17,20]

SYSTEMIC SCLEROSIS/ SCLERODERMA

Systemic sclerosis actually comprises several related disorders characterized by a vasculopathy of small vessels, multiorgan fibrosis, and autoantibodies. Patients generally have skin thickening (scleroderma) with or without internal

Case 4-1

A 60-year-old woman presented for evaluation of a possible peripheral neuropathy. Following lumbar spine surgery, she developed difficulty controlling her legs and her left arm. She had difficulty with balance and pain, sensory loss, and weakness in both legs and the left arm that progressed over 3 weeks. She described reduced sensation from the feet to the knees and from the left hand to the shoulder. On review of systems, she had long-standing dry eyes and dry mouth.

On examination, she had reduced sensation to light touch, pinprick, and vibratory sensation throughout the left upper limb to the shoulder and in both legs to the knees bilaterally, with reduced cold sensation to the midthighs. She had severely reduced upper limb and absent lower limb reflexes. Strength in the upper and lower limbs was normal. She had difficulty with left finger-to-nose testing with eyes closed and was unable to perform the heel-to-shin test bilaterally. She had an unsteady gait, and Romberg sign was present.

Motor nerve conduction study responses were normal, but sensory responses were unobtainable in the arms and legs. Needle examination of upper and lower limb muscles was normal. These electrophysiologic findings were consistent with a sensory neuronopathy. Antinuclear antibody and Sjögren syndrome A (SSA) antibodies were elevated. Minor salivary gland lip biopsy demonstrated inflammation, and she was diagnosed with Sjögren syndrome. She was placed on daily prednisone and then methotrexate with no improvement.

Comment. The presentation of sensory loss, incoordination, and ataxia with normal strength is consistent with a sensory neuronopathy (ganglionopathy). EMG studies showing unobtainable sensory responses with normal motor studies are compatible. This is a typical picture for Sjögren syndrome–associated sensory neuronopathy, which can be very difficult to treat.

organ pathology. Systemic sclerosis comprises diffuse cutaneous systemic sclerosis (skin involvement proximal to the elbows or knees or truncal, including the face), limited cutaneous systemic sclerosis (distal limbs or face), systemic sclerosis without skin manifestations (systemic sclerosis sine scleroderma), and localized scleroderma (morphea, linear scleroderma, and *coup de sabre* [an indented vertical line of skin on the forehead appearing as though the person was struck by a sword]). CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) is a subcategory of limited cutaneous systemic sclerosis. Systemic sclerosis may also exist in overlap with other connective tissue diseases. Classification criteria were initially established in 1980, but they were insensitive to early or limited cutaneous disease; the criteria were revised in 2013 by an American-European collaborative initiative (**Table 4-5**)[21] and have since been validated.[22] The 2013 criteria sought to include classification of early disease, apply new knowledge regarding systemic sclerosis–specific autoantibodies (anticentromere, antitopoisomerase I [also known as anti-Scl70], anti-RNA polymerase III), incorporate capillaroscopy and vascular pathology, and be applicable to daily practice.

Systemic sclerosis serology has been a topic of focus of late. Different antibodies appear to have prognostic

TABLE 4-5 American College of Rheumatology/European League Against Rheumatism Criteria for the Classification of Systemic Sclerosis[a,b]

Item	Subitem	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (*sufficient criterion*)		9
Skin thickening of the fingers (*only count the highest score*)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to metacarpophalangeal joint but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (*only count the highest score*)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nail fold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (*maximum score is 2*)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon		3
Scleroderma-related antibodies (any of anticentromere, antitopoisomerase I [anti-Scl 70], anti-RNA polymerase III) (*maximum score is 3*)	Anticentromere	3
	Antitopoisomerase I	
	Anti-RNA polymerase III	

[a] Modified with permission from van den Hoogen F, et al, Arthritis Rheum.[21] © 2013 American College of Rheumatology. *onlinelibrary.wiley.com/doi/10.1002/art.38098/full*.

[b] These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. These criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic cheiroarthropathy).

value or predict associated manifestations with varying geographic distributions.[23] In North American cohorts, anti-PM/Scl antibodies have been associated with overlap, myositis, arthritis, calcinosis, and younger age at onset. Antitopoisomerase I has been associated with interstitial lung disease, while anticentromere may be protective. Anti-U3RNP and anti-RNA polymerase III have been associated with pulmonary hypertension, while

antitopoisomerase I may be protective. Patients who are anti-RNA polymerase III positive may also have an increased risk of malignancy temporally correlated to the time of systemic sclerosis diagnosis. Furthermore, antitopoisomerase I may predict diffuse cutaneous systemic sclerosis and anticentromere may predict limited cutaneous systemic sclerosis.[24] Nonneurologic systemic involvement is variable and can be widespread. Aside from skin involvement, systemic sclerosis may also affect the lungs (pulmonary arterial hypertension, pulmonary fibrosis), gastrointestinal tract (dysmotility, particularly esophageal), kidneys (ischemia, renal crisis), heart (pericardial effusion, constrictive pericarditis, myocarditis, contraction band necrosis), thyroid (fibrosis), salivary and lacrimal glands (fibrosis), and penile vessels (erectile dysfunction not associated with autonomic dysfunction).

CNS disease has traditionally been thought to be rare or unusual in systemic sclerosis in contrast to PNS involvement, but more recent studies incorporating more sensitive testing indicate this may not be the case. A 2013 systematic review characterized neurologic involvement and systemic sclerosis subtype.[25] Localized scleroderma may have a high incidence of muscle involvement either electrophysiologically, radiographically, clinically, or pathologically (up to 90%), but this may also simply represent local extension of the cutaneous and subcutaneous pathology into the subjacent muscle rather than being an independent manifestation of the disease. As stated in the 2013 review, over 41% of those with *coup de sabre* were diagnosed with epilepsy, most commonly manifesting as complex partial seizures followed by generalized tonic-clonic seizures.[25] In systemic sclerosis, depression and anxiety are common, with a relative risk of 1.5. Headache is not infrequent, and seizures were associated but at a lower frequency than in *coup de sabre*.

Weakness and myalgia are common in systemic sclerosis, but only about 20% of patients with systemic sclerosis develop a true myopathy. Pathology may demonstrate fibrosis without inflammation or vasculopathy, although a true inflammatory myopathy is more common and is associated with anti-PM/Scl positivity. When seen in the setting of diffuse cutaneous systemic sclerosis, caution must be used in treatment decisions as corticosteroids may cause renal crisis. While inflammatory myopathy may respond to immune suppression, fibrotic myopathy usually does not. Additionally, sensorimotor peripheral neuropathy, median mononeuropathy (carpal tunnel syndrome), and trigeminal neuropathy are common findings in systemic sclerosis.

KEY POINT

- Inflammatory myopathy in the setting of systemic sclerosis is more frequent with anti-PM/Scl antibody positivity; if seen in diffuse cutaneous systemic sclerosis, corticosteroids should be avoided as their use can lead to renal crisis.

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease is an overlap syndrome associated with anti-U1RNP antibody positivity (in the absence of anti-Smith [anti-Sm] and anti-dsDNA) with features of other connective tissue diseases in various combinations. Not all features present concomitantly, and it may take years for the diagnosis to become apparent. Common overlaps include features of SLE, systemic sclerosis, Raynaud phenomenon, and sclerodactyly. **Table 4-6** lists proposed diagnostic criteria for mixed connective tissue disease.[26] Inflammatory myopathy, pathologically reminiscent of dermatomyositis more often than polymyositis, is common, and trigeminal neuropathy is a risk as in systemic sclerosis. CNS disease is rare and resembles that of SLE, although

KEY POINT

- Numerous systemic vasculitides exist, but primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy represent two forms of vasculitis isolated to the central nervous system and peripheral nervous system, respectively.

TABLE 4-6 Proposed Criteria for the Diagnosis of Mixed Connective Tissue Disease[a,b]

1. Serologic
Anti-RNP titer ≥ 1:1600
2. Clinical
Hand edema
Synovitis
Myositis
Raynaud phenomenon
Acrosclerosis

RNP = ribonuclear protein.

[a] Modified from Alarcón-Segovia D, Cardiel MH, J Rheumatol.[26] © 2016 by The Journal of Rheumatology Publishing Company Limited. *europepmc.org/abstract/med/2724251*.

[b] Diagnosis requires serologic criteria and at least three clinical criteria to be fulfilled. If clinical criteria consist of hand edema, Raynaud phenomenon, and acrosclerosis, then at least one of the other clinical criteria must be fulfilled.

isolated CNS vasculitis has been reported.[27]

VASCULITIDES

The vasculitides include a variety of disorders characterized by inflammatory invasion of blood vessel walls leading to end organ ischemic and inflammatory damage (**Figure 4-1**). They may be idiopathic or associated with immune complex deposition in patients with chronic infection (eg, hepatitis or human immunodeficiency virus [HIV]), or connective tissue disease. They are classified according to the size and type of blood vessels involved, and their nomenclature was revised in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (**Table 4-7**).[28] While most vasculitides are multisystemic, two manifest neurologically in isolation: primary angiitis of the CNS and nonsystemic vasculitic neuropathy.

Primary Angiitis of the Central Nervous System

Primary angiitis of the CNS is a rare disease. Vasculitis affects small arteries and veins less than 200 μm in diameter in the meninges and cortex with fibrinoid necrosis and, at times, granulomas. The diagnosis is difficult, as symptoms often appear gradually over several months and are nonspecific. Patients most commonly have headache or cognitive decline/encephalopathy, ischemia or hemorrhage with focal neurologic symptoms and signs, seizures, meningitis, or myelopathy. The course may relapse and remit or present with an apparent mass lesion or acute to subacute encephalopathy. Systemic symptoms should be absent; if present, a secondary CNS vasculitis is more likely.

Suspicion of primary angiitis of the CNS usually follows neuroimaging with brain MRI showing any of a number of abnormalities (**Table 4-8**).[29] Vascular imaging may show the classic ''beads on a string'' (stenosis alternating with dilation), but this is not specific for inflammatory vasculopathy, with a specificity of only about 30%.[30] It is also important to note that normal vascular imaging does not exclude primary angiitis of the CNS.[29,30]

Reversible cerebral vasoconstriction syndrome deserves special mention. It is often clinically and radiographically mistaken for primary angiitis of the CNS. Reversible cerebral vasoconstriction syndrome presents with thunderclap headache far more commonly than without, but even in those without a thunderclap headache and with vasculopathic angiography, a normal

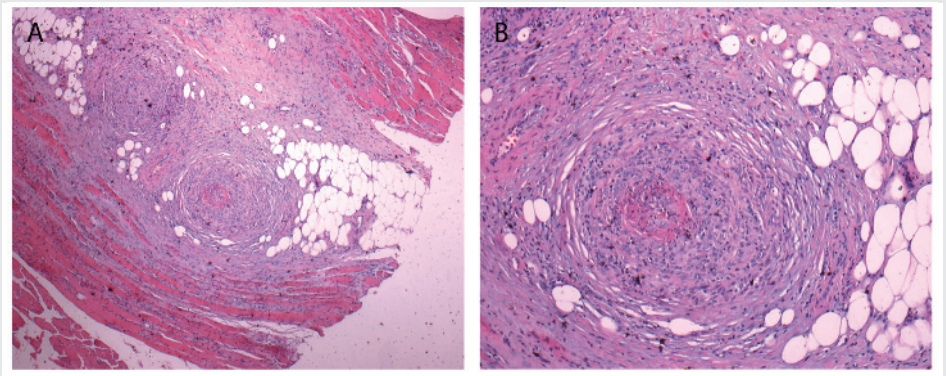

FIGURE 4-1 Vasculitis in a patient with polyarteritis nodosa and vasculitic myopathy presenting with painful proximal weakness, fever, and weight loss. *A*, Two perimysial blood vessel walls are invaded by inflammatory cells with fibrinoid necrosis and occlusion of the blood vessel lumina. *B*, Higher-power view of the rightmost vessel in *panel A*.

parenchymal brain MRI is most consistent with reversible cerebral vasoconstriction syndrome; deep or brainstem infarcts with or without abnormal CSF are most consistent with primary angiitis of the CNS.[31]

CSF analysis in primary angiitis of the CNS typically shows an elevated

TABLE 4-7 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides[a]

- ▶ **Large Vessel Vasculitis**
  - Takayasu arteritis
  - Giant cell arteritis
- ▶ **Medium Vessel Vasculitis**
  - Polyarteritis nodosa
  - Kawasaki disease
- ▶ **Small Vessel Vasculitis**
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis
    - Microscopic polyangiitis
    - Granulomatosis with polyangiitis (Wegener granulomatosis)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
  - Immune complex small vessel vasculitis
    - Anti–glomerular basement membrane disease
    - Cryoglobulinemic vasculitis
    - IgA vasculitis (Henoch-Schönlein purpura)
    - Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Continued on page 708

TABLE 4-7 **2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides**[a] *Continued from page 707*

- ▶ **Variable Vessel Vasculitis**
  - Behçet disease
  - Cogan syndrome
- ▶ **Single-organ Vasculitis**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- ▶ **Vasculitis Associated With Systemic Disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- ▶ **Vasculitis Associated With Probable Etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

IgA = immunoglobulin A.
[a] Reprinted with permission from Jennette JC, et al, Arthritis Rheum.[28] © 2013 American College of Rheumatology. *onlinelibrary.wiley.com/doi/10.1002/art.37715/full*.

protein with mild pleocytosis and normal glucose, but this is also neither sensitive nor specific. Ultimately, once CNS vasculitis is suspected and alternative causes have been excluded, a brain biopsy is necessary to confirm primary angiitis of the CNS. To maximize the diagnostic yield of biopsy, it should include areas abnormal on imaging and both leptomeninges and cortex. Although specific, not even brain biopsy is fully sensitive. It is important, however, that when not diagnostic for primary angiitis of the CNS, alternative pathologic diagnoses are not uncommon. In the end, diagnosis requires demonstration of CNS angiitis, exclusion of alternative causes or diagnoses, and limitation of the vasculitis to the CNS.[29]

Nonsystemic Vasculitic Neuropathy

Nonsystemic vasculitic neuropathy is limited to the PNS with no other end organ damage other than local

TABLE 4-8 MRI Findings in Primary Angiitis of the Central Nervous System[a]

- Normal
- Progressive confluent white matter lesions
- Cortical and subcortical T2-weighted hyperintensities
- Multiple lesions with restricted diffusion
- Large intraparenchymal hematoma
- Multiple microhemorrhages
- Small or large enhancing lesions, including masslike lesions
- Leptomeningeal enhancement

MRI = magnetic resonance imaging.
[a] Modified with permission from Powers WJ, Neurol Clin.[29] © 2015 Elsevier. *neurologic.theclinics.com/article/S0733-8619(14)00120-0/pdf*.

involvement of the skin or muscle directly contiguous to the affected nerve. It is the most common vasculitic neuropathy.[32] Systemic signs may be seen in few patients. Mononeuritis multiplex is the most common manifestation, followed by distal asymmetric polyneuropathy, distal symmetric polyneuropathy, and a pure sensory neuropathy. Cranial neuropathy, lumbosacral plexus neuropathy, and radiculopathy are rare presentations. Although clinically similar to neuropathy from systemic vasculitis, the prognosis is more favorable and progression is slower. The course may be relapsing-remitting, monophasic, or rapidly progressive, and the time course may be prolonged.[33]

As with primary angiitis of the CNS, biopsy is not particularly sensitive, about 50%.[32] Vasculitis is typically necrotizing and involves epineurial vessels, although perivascular inflammation, vessel wall thickening, and ischemic changes are suggestive. According to the Peripheral Nerve Society guidelines, pathologically definite (inflammatory infiltration of vessel walls with signs of vascular nerve injury) or clinically probable (sensory or sensorimotor involvement, a multifocal or asymmetric pattern, distal lower limb predominance, pain, an acute relapsing course, and axonal electrodiagnostic features) vasculitic neuropathy is necessary for the diagnosis, in conjunction with the absence of several exclusions (**Table 4-9**).[34] **Case 4-2** is an example of nonsystemic vasculitic neuropathy.

Systemic Vasculitides

The systemic vasculitides are classified according to the size of involved vessels. Of the vasculitides listed in **Table 4-7**, nervous system involvement is commonly recognized in Takayasu arteritis; giant cell arteritis; polyarteritis nodosa; Kawasaki disease; and the antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). Cryoglobulinemic vasculitis, Behçet disease, and Cogan syndrome also cause neurologic impairment. It should also be mentioned that vasculitis associated with systemic disease may lead to neurologic sequelae just like any other systemic vasculitis.

Takayasu arteritis and giant cell arteritis both may cause granulomatous vasculitis and are more common in women. The main distinguishing feature is that Takayasu arteritis tends to occur in those younger than 40 years of age and giant cell arteritis in those older than 50 years of age. Controversy exists over whether any distinction is arbitrary. They are both

KEY POINTS

- Biopsy is the diagnostic procedure of choice for primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy, but its sensitivity is not 100% in either case, requiring high clinical suspicion.
- The vasculitides are categorized according to the size of vessels involved, although neurologic involvement is not specific to the vessel size involved.

TABLE 4-9 Criteria for the Diagnosis of Nonsystemic Vasculitic Neuropathy[a]

1. Patient meets criteria for pathologically definite or clinically probable vasculitic neuropathy as defined by the Peripheral Nerve Society Guideline
2. Constitutional symptoms may occur
3. None of the following exclusions
   - Evidence of involvement of other organ systems likely due to vasculitis
   - Diagnostic visceral angiogram
   - Laboratory markers of systemic inflammation or connective tissue disease
     - Anti-Pr3 or myeloperoxidase
     - Mixed cryoglobulins
     - Erythrocyte sedimentation rate ≥100 mm/h
     - SSA, SSB, Smith, ribonucleoprotein, Scl-70, centromere, dsDNA, cyclic citrullinated peptide antibodies if patient satisfies diagnostic criteria for the associated connective tissue disease
   - Biopsy evidence of vasculitis in nonperipheral nerve tissue (muscle excepted)
   - Serologic, polymerase chain reaction (PCR), or biopsy evidence for vasculitis-associated infection
     - Hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus, leprosy, Lyme disease, human T-cell lymphotropic virus type 1 (HTLV-1)
   - Predisposing conditions
     - Connective tissue disease
     - Sarcoidosis
     - Inflammatory bowel disease
     - Active malignancy
     - Hypocomplementemic urticarial vasculitis
     - Cutaneous polyarteritis nodosa
     - Drugs thought to cause vasculitis

dsDNA = double-stranded deoxyribonucleic acid; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

[a] Modified with permission from Collins MP, et al, J Peripher Nerve Syst.[34] © 2010 Peripheral Nerve Society. *onlinelibrary.wiley.com/wol1/doi/10.1111/j.1529-8027.2010.00281.x/full.*

large vessel vasculitides with a predilection for the aorta and its immediate branches. Takayasu arteritis is also known as pulseless disease and commonly manifests with hypertension with renal artery stenosis, limb claudication, reduced pulses, arterial tenderness, and bruits, often preceded by systemic inflammatory symptoms. Coronary, mesenteric, and pulmonary arteries may be involved. Neurologic symptoms occur in less than 50% of patients, most commonly vague dizziness, visual obscurations, and headaches in one cohort, and, more rarely, ischemic stroke from

Case 4-2

A 55-year-old man acutely developed right hip tingling and burning pain radiating down the right lateral thigh and leg to the ankle with right footdrop. He was given a short course of steroids with improvement. Two years later, he developed identical symptoms in the left leg and acutely painful sensory loss in the medial right hand.

On examination, he had moderate left foot and mild right foot dorsiflexion, toe extension, and eversion weakness. He had reduced sensation to light touch and pinprick along the right little finger and medial hand to the wrist and in both lateral lower legs and the dorsal aspects of both feet. Muscle stretch reflexes were moderately reduced at the right knee and absent at both ankles. Nerve conduction studies and EMG demonstrated an active severe left fibular (peroneal) neuropathy, an old inactive right fibular (peroneal) neuropathy, and an active mild right ulnar neuropathy. A left superficial fibular (peroneal) nerve biopsy revealed multifocal perivascular inflammatory cell collections with epineurial and perineurial blood vessel wall invasion consistent with vasculitis. All inflammatory markers and infectious serologies were negative or normal.

He was diagnosed with nonsystemic vasculitic neuropathy and placed on prednisone and mycophenolate mofetil, and his pain resolved within 2 weeks. He regained strength and sensation over the next 2 years while tapering off of prednisone.

Comment. Nonsystemic vasculitic neuropathy can present as an acute mononeuritis multiplex. The diagnosis can be made once systemic vasculitis is excluded; in this case, histologic confirmation was obtained. Patients typically respond to immune suppression but may not recover fully.

large artery stenosis/occlusion, cardioembolism, or hypertensive complications.[35] Patients with Takayasu arteritis also are at risk for posterior reversible encephalopathy syndrome (PRES), likely also a complication of hypertension.[35,36] Giant cell arteritis is also commonly known as temporal arteritis, but it is important to note that not all patients with giant cell arteritis have temporal artery involvement. Limb ischemia, aortic aneurysm, or mesenteric ischemia also occur in giant cell arteritis, and polymyalgia rheumatica (presenting clinically with symmetric pain particularly in the shoulders but also more diffusely in the neck, back, and lower limbs with an elevated erythrocyte sedimentation rate in patients over 50 years of age) commonly coexists. Headache is present in up to about 90% of patients, and a minority may have cranial neuropathies, most commonly ophthalmoparesis. Patients are at risk for sudden vision loss due to arteritic anterior ischemic optic neuropathy, and jaw claudication, ear pain, or scalp tenderness may herald involvement of cranial arteries.[37] Headache in the setting of large vessel strokes should lead to investigation for giant cell arteritis.[38] MRI of the superficial cranial arteries and fludeoxyglucose positron emission tomography (FDG-PET) may assist with confirming a diagnosis in temporal artery biopsy–negative patients.[39,40] Of particular controversy is whether varicella-zoster virus is implicated in the pathogenesis of giant cell arteritis.[41,42] The issue is not resolved, although some do treat with both antiviral and corticosteroid therapy.

Polyarteritis nodosa is rare and affects medium more than small vessels; it is classified as a medium vessel vasculitis. It may be idiopathic or associated with chronic infection, particularly hepatitis B. It is ANCA negative. Constitutional symptoms are common, including fever, weight loss, myalgia, and arthralgia. Common organ systems involved include skin, gastrointestinal, renal (but not with glomerulonephritis), coronary, ophthalmic, and, rarely, respiratory, but the nervous system predominates, particularly the PNS.[43] In a review of polyarteritis nodosa–associated disease, 68% of patients with non–hepatitis B polyarteritis nodosa had peripheral neuropathy, compared to 85% of those with hepatitis B–related polyarteritis nodosa.[44] Mononeuritis multiplex greatly predominates, distantly followed by a symmetric polyneuropathy, and evidence exists for vasculitis in muscle and isolated mononeuropathies. CNS abnormalities are rare and poorly characterized. Hepatitis B–associated disease generally carries a poorer prognosis.

Kawasaki disease is an acute generalized pediatric medium vessel vasculitis. Neurologic involvement is relatively rare, but irritability is present in 50% of children within the 10 days before diagnosis.[45] Aseptic meningitis, meningoencephalitis, altered mental status, seizures, acute disseminated encephalomyelitis (ADEM), mononeuritis multiplex, cranial neuropathy, and stroke may occur.[46,47]

Microscopic polyangiitis was separated from polyarteritis nodosa at the first Chapel Hill Consensus Conference. It affects arterioles, capillaries, and venules without granulomata and is associated with p-ANCA/myeloperoxidase (MPO) and rarely c-ACNA/proteinase 3 (Pr-3) antibodies (exclusionary for polyarteritis nodosa).[48] Rapidly progressive glomerulonephritis and pulmonary capillaritis with alveolar hemorrhage help to distinguish it from polyarteritis nodosa but are not necessary for the diagnosis. Systemic symptoms are frequently present as in polyarteritis nodosa. Myalgia is very common, but true vasculitis of muscle is rare. Peripheral neuropathy is common, present in about 40% to 50% of patients, but its prevalence de pends upon the study population and methods. Some have found that mononeuritis multiplex is extremely common, while others have found it to occur at rates similar to a pure sensory neuropathy or symmetric polyneuropathy.[49,50] CNS involvement is reported but poorly characterized.

Granulomatosis with polyangiitis manifests as a necrotizing granulomatous inflammatory disease and vasculitis of the upper and lower respiratory tract and kidneys. c-ANCA/Pr-3 antibodies tend to be present but not universally. Symmetric polyneuropathy and mononeuritis multiplex both occur fairly commonly. Cranial neuropathies are more frequent in granulomatosis with polyangiitis than most other vasculitic conditions owing to granulomatous disease in the ear, sinus, or orbits that can lead to local nerve compression, although vasculitis also causes cranial neuropathies. The olfactory and optic nerves are most commonly affected. CNS involvement is less common and results from vasculitis of the brain or spinal cord, localized granulomatous changes, and more diffuse granulomatous development intracerebrally.[50] Cerebral vasculitis with hemorrhage, ischemic infarction, and venous thrombosis represent vascular complications. Granulomatous hypertrophic pachymeningitis is unique to granulomatosis with polyangiitis among the small vessel vasculitides, as is granulomatous infiltration of the pituitary.

Headache is a common presenting symptom for granulomatous disease in contrast to focal deficits and renal disease in vasculitic disease. Spinal cord pachymeningitis and vasculitic CNS disease are more likely to cause long-term sequelae.[51]

Eosinophilic granulomatosis with polyangiitis is characterized by allergic rhinitis with nasal polyps and sinusitis, followed by asthma with hypereosinophilia and, finally, systemic vasculitis. Pathology includes small vessel necrotizing vasculitis, eosinophilic infiltration of affected tissues, and extravascular granulomas. p-ANCA/MPO antibodies are frequently found, particularly in the setting of glomerulonephritis. PNS abnormalities predominate over CNS abnormalities. Mononeuritis multiplex or an asymmetric sensorimotor polyneuropathy develops acutely or subacutely, is exquisitely painful, and is very frequently the presenting feature. Leukotriene antagonist administration may represent a risk factor for the development of neuropathy, but other than developing within 150 days of administration, the neuropathies associated with leukotriene antagonists show no significant differences from those unassociated with them.[52] Cranial neuropathy and myositis are rare, but myalgia is common. Ischemic stroke or hemorrhage of the brain or spinal cord is rare.

Cryoglobulinemic vasculitis results from cold-dependent immune complex deposition in small vessel walls and is associated with the presence of cryoglobulins, cold-precipitable monoclonal or polyclonal immunoglobulins. Type I cryoglobulinemic vasculitis consists of monoclonal cryoglobulins. Type II harbors mixed monoclonal and polyclonal populations, and type III is mixed polyclonal. ''Essential'' cryoglobulinemia is unassociated with an underlying disease process, while secondary forms are associated with chronic conditions such as infection, inflammatory disorders, or hematologic malignancies. Mixed types II and III tend to be associated with neurologic disease, most commonly a painful peripheral neuropathy. Mixed cryoglobulinemia occurs in chronic hepatitis C infection, although a minority of patients develop neuropathy. The skin and kidneys are also commonly affected. The neuropathy is most commonly a distal sensory polyneuropathy, less commonly mononeuritis multiplex. Rare reports of PRES and inflammatory myopathy as presentations exist.[53,54]

Behçet disease is a rare systemic relapsing vasculitis affecting various vessel sizes. Systemic findings include oral and genital ulcers, uveitis, skin lesions, arthritis, gastrointestinal involvement, large vessel vasculopathy, and neurologic manifestations (neuro-Behçet disease). Multiple diagnostic criteria have been formed, most recently via a revision of the International Criteria for Behçet's Disease collaborative (**Table 4-10**).[55] International consensus recommendations have also been developed specifically for neuro-Behçet disease but await validation (**Table 4-11**).[56] In essence, neuro-Behçet disease should be suspected in the presence of oral or genital ulcers, uveitis, or other features of Behçet disease. Neuro-Behçet disease should be considered in any focal or multifocal CNS parenchymal inflammatory syndrome, particularly those in which headaches, motor features, and cognitive or behavioral symptoms predominate; headache is the most common presentation in neuro-Behçet disease. Common localizations include the brainstem and basal ganglia, but the hemispheres and spinal cord may be involved. CNS

KEY POINT

- The presence of mixed cryoglobulinemia in the setting of peripheral neuropathy should prompt a search for hepatitis C infection, although a minority of patients with hepatitis C will develop neuropathy.

KEY POINT

- Antiphospholipid antibodies are prothrombotic and can cause false-positive Venereal Disease Research Laboratory and rapid plasma reagin tests; they also occur in systemic lupus erythematosus and are associated with other, nonstroke-related neurologic manifestations.

TABLE 4-10 International Criteria for Behçet Disease[a,b]

Sign/Symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurologic manifestations	1
Vascular manifestations	1
Positive pathergy test (optional)	1[c]

[a] Modified with permission from Davatchi F, et al, J Eur Acad Dermatol Venereol.[55] © 2013 The Authors, European Academy of Dermatology and Venereology. *onlinelibrary.wiley.com/doi/10.1111/jdv.12107/full*.

[b] Score ≥4 indicates a Behçet disease diagnosis.

[c] Pathergy test is optional, and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted, one extra point may be assigned for a positive result.

disease may be asymptomatic, relapsing and remitting, or progressive. Alternatively, neuro-Behçet disease may manifest as increased intracranial pressure due to cerebral venous thrombosis. PNS involvement manifests with peripheral neuropathy, mononeuritis multiplex, or inflammatory myopathy but is quite rare.

Cogan syndrome is a rare variable vessel vasculitis primarily of young adults. It causes interstitial keratitis with vestibulocochlear dysfunction leading to hearing and vision loss and vertigo; in atypical disease, ocular inflammation is present but not interstitial keratitis, or the eye and vestibular disease occur more than 2 years apart. Typical systemic symptoms may be present as in polyarteritis nodosa, most commonly headache, arthralgia, and fever. The vasculitis can be systemic as well. The diagnosis is made on clinical grounds as no specific serologic or radiologic tests exist. A 2012 review of the literature defined several neurologic manifestations: ischemic stroke, venous sinus thrombosis, encephalopathy, meningoencephalitis, cranial neuropathy, polyneuropathy, mononeuritis multiplex, autonomic neuropathy, and myopathy.[57]

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid antibodies are common in patients with SLE but may be seen in a number of other disorders, including many of the other connective tissue diseases, vasculitides, HIV or other viral infections, Lyme disease, or syphilis; they also may be seen in isolation. They can cause false-positive Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) serologic tests for syphilis (but not the fluorescent treponemal antibody absorption test). Antiphospholipid antibodies are prothrombotic and significantly associated causally with deep venous thrombosis, pulmonary embolism, intracardiac thrombus, and stroke (arterial and venous). Antiphospholipid antibody syndrome is characterized by persistently elevated antibody titers at least 12 weeks apart and one or more arterial or venous thrombotic events or pregnancy loss. When in isolation, it is termed primary antiphospholipid antibody syndrome. In patients with SLE and antiphospholipid antibodies, nonstroke-related neurologic manifestations are also more likely than in patients without antiphospholipid antibodies. Patients with primary antiphospholipid antibody syndrome may develop a number of these complications as well, including migraine, cognitive dysfunction, seizures, depression, myelitis, and chorea or

TABLE 4-11 International Consensus Recommendation Criteria for Neuro-Behçet Disease Diagnosis[a]

- **Definite neuro-Behçet disease meets all of the following three criteria**
  1. Satisfies the (current accepted) International Study Group criteria for Behçet disease
  2. Neurologic syndrome (with objective neurologic signs) recognized to be caused by Behçet disease and supported by relevant and characteristic abnormalities seen on either or both
     a. Neuroimaging
     b. CSF
  3. No better explanation for the neurologic findings
- **Probable neuro-Behçet disease meets one of the following two criteria in the absence of a better explanation for the neurologic findings**
  1. Neurologic syndrome as in definite neuro-Behçet disease, with systemic Behçet disease features but not satisfying the International Study Group criteria
  2. A noncharacteristic neurologic syndrome occurring in the context of International Study Group criteria–supported Behçet disease
- **Recognized neurologic syndromes**

  Parenchymal syndrome (one or more of the following presentations at first/subsequent attack[s] or progression)

  Brainstem: symptoms and signs of brainstem involvement, including ophthalmoparesis, cranial neuropathy, cerebellar or pyramidal dysfunction

  Multifocal (diffuse): variable combination of brainstem signs and symptoms, cerebral or spinal cord involvement

  Myelopathy

  Cerebral: symptoms and signs suggestive of cerebral hemispheric involvement, including encephalopathy, hemiparesis, hemisensory loss, seizures and dysphasia, and mental changes including cognitive dysfunction and psychosis

  Optic neuropathy

  Nonparenchymal syndromes

  Cerebral venous thrombosis

  Intracranial hypertension syndrome (pseudotumor cerebri)

  Acute meningeal syndrome
- **Characteristic MRI findings in neuro-Behçet disease**

  Parenchymal neuro-Behçet disease

  Nature of the lesions

  Acute/subacute lesions are hypointense to isointense on T1-weighted images, commonly enhance on postcontrast T1-weighted images, are hyperintense on T2-weighted and FLAIR images, are hyperintense on diffusion-weighted images, and show a restricted ADC on ADC map

Continued on page 716

TABLE 4-11 **International Consensus Recommendation Criteria for Neuro-Behçet Disease Diagnosis**[a] *Continued from page 715*

In the chronic phase, smaller lesions might be seen, usually nonenhancing, but might resolve completely; evidence of atrophy may be seen, especially in the brainstem; nonspecific white matter lesions can also be seen
Location: depends on the clinical presentation
The brainstem is the typical predilection site, lesions usually involving the pons, might extend upward to involve midbrain, basal ganglia, and the diencephalon
With cerebral presentation, multiple small white matter lesions without a clear predisposition for periventricular regions can be seen; isolated cerebral hemisphere lesions can be seen, which need differentiation from lesions such as tumors, abscesses, and congenital cysts
Single or multiple inflammatory lesions of variable length involving the cervical or thoracic cord can be seen, mostly in the presence of brainstem, basal ganglia, or cerebral lesions; isolated spinal cord lesions are rare.
Nonparenchymal neuro-Behçet disease
Magnetic resonance venography or CT venography show evidence of cerebral sinus or vein thrombosis
Normal appearances are seen in intracranial hypertension syndrome
Meningeal enhancement is seen in acute meningeal syndrome, especially on contrast-enhanced T1-weighted images
▶ **Characteristic CSF finding**
Inflammatory changes involving one or more of:
Increased cells
Increased protein
High IL-6
▶ **Specific conditions to be excluded**
CNS infections
CNS neoplasms
Neurologic complications of therapies for Behçet disease

ADC = apparent diffusion coefficient; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FLAIR = fluid-attenuated inversion recovery; IL-6 = interleukin 6; MRI = magnetic resonance imaging.

[a] Modified with permission from Kalra S, et al, J Neurol.[56] © 2013 The Authors. *link.springer.com/article/10.1007/s00415-013-7209-3*.

other movement disorders, although a direct correlation can be difficult to establish.[58]

IgG4-RELATED DISEASE

IgG4-related disease is a recently described entity characterized by fibrosis and sclerosis, elevated IgG4 concentrations in the serum, and IgG4-positive plasma cell rich inflammatory exudates. It was initially found in association with autoimmune pancreatitis but now is recognized to occur as a systemic inflammatory disease.

Pathologic diagnosis is based on a consensus statement published in 2012.[59] Several reports exist of neurologic involvement, most commonly pachymeningitis, but also involvement of orbital tissues, the cavernous sinus, cranial nerves, pituitary gland, nerve roots, and neuropathy.

TREATMENT COMPLICATIONS

Treatment-related myopathy is a well-known complication of a number of medications used to treat rheumatologic disorders. Corticosteroids can cause weakness, and toxicity is characterized by type 2 muscle fiber atrophy at any time in the course of therapy and at just about any dose. Chloroquines (such as hydroxychloroquine) cause a vacuolar myopathy, often with cardiomyopathy and peripheral neuropathy. Cyclosporine has rarely been associated with myopathy and penicillamine with myositis and myasthenia gravis. All of these tend to be reversible with removal of the offending agent.

More recently, the discovery of biologic agents and tumor necrosis factor α (TNFα) inhibitors represents a significant development in the treatment of inflammatory disorders. TNFα inhibitors have rapid onset, prevent structural damage, and are efficacious. With their increasing use, several possible neurologic adverse events have been reported. They are rare occurrences but of unknown frequency. Some researchers have estimated the development of demyelinating disease to be as high as 30%, but others have found that the rate of development is no higher than that of the general population.[60] It is also understood that ''autoimmunity begets autoimmunity,'' and inflammatory disorders tend to cooccur. Regardless, most reported complications are those of CNS or PNS demyelination, including overt multiple sclerosis, optic neuritis, transverse myelitis, AIDP, Miller Fisher syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with conduction block, and a nondemyelinating axonal sensorimotor polyneuropathy. Other reported associations include neurosarcoidosis, small fiber neuropathy, antiphospholipid antibody syndrome with CNS lupus, and encephalitis.[61–63] A 2013 review of the US Food and Drug Administration (FDA) Adverse Event Reporting System found that following the administration of etanercept, infliximab, or adalimumab, peripheral neuropathy was the most commonly reported adverse event, followed by CNS/spinal demyelination.[64] An interesting outcome of this report is that following application of the Naranjo algorithm, a causality assessment score used to rate the strength of association between a medication and a potential adverse event, 71.3% of reported events were categorized as ''possible,'' and none were ''definite.'' A 2014 review confirmed the predominance of peripheral neuropathy.[62] If suspected to be the cause of a peripheral neuropathy, the TNFα inhibitor should be withheld. Reported treatment has most commonly included IV immunoglobulin (IVIg), but corticosteroids and plasma exchange have also been used. The author's personal experience is that any neuropathy should be characterized electrophysiologically and alternative causes investigated. Once other causes are excluded, the TNFα inhibitor should be discontinued and the peripheral neuropathy will tend to respond to IVIg or plasma exchange, often with complete resolution. In the setting of preexisting demyelinating disease, many clinicians avoid TNFα inhibitors.

Leflunomide inhibits dihydroorotate dehydrogenase and, as such, inhibits pyrimidine synthesis and has

KEY POINTS

- Pachymeningitis is a classic presentation of IgG4-related disease but requires biopsy confirmation with specific pathologic criteria met for the diagnosis.
- Tumor necrosis factor α inhibitor administration may be complicated by demyelination of the central nervous system, peripheral nervous system, or both.

antiproliferative activity. It has been approved for use in RA since 1998 and has shown utility in a variety of autoimmune diseases. A distal symmetric sensorimotor peripheral neuropathy has been reported in some series to occur in as many as 10% of patients, but when alternative risk factors of peripheral neuropathy are excluded (eg, diabetes mellitus, other neurotoxic medications, vasculitis, connective tissue diseases), Metzler and colleagues found the incidence to be closer to 1.4%.[65,66] Nonetheless, preexisting risk factors should be considered and patients on leflunomide should be periodically assessed clinically for neuropathy.

CONCLUSION

Rheumatologic disorders are common, and many manifest with neurologic complications. Likewise, many present with a neurologic symptom or syndrome, and an understanding of the different disorders is necessary to assist with diagnosis and, ultimately, management. Thus it is important for neurologists to work in conjunction with rheumatologists when evaluating and managing patients with these disorders.

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Renal Disease and Neurology

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ABSTRACT

Purpose of Review: Neurologic dysfunction is prevalent in patients with acute and chronic renal disease and may affect the central nervous system, peripheral nervous system, or both. Neurologic manifestations may result directly from the uremic state or as a consequence of renal replacement therapy. Early recognition of neurologic dysfunction may provide opportunities for intervention and reduced morbidity.

Recent Findings: Advances in the understanding of neurologic complications of renal disease and its treatments have led to more widespread recognition and earlier identification of encephalopathy syndromes such as cefepime neurotoxicity and posterior reversible encephalopathy syndrome (PRES), dramatic reductions in the incidence of dialysis disequilibrium syndrome and dialysis dementia, and improved survival in disorders such as von Hippel-Lindau disease and thrombotic thrombocytopenic purpura.

Summary: This article summarizes the conditions that affect both the renal and the nervous systems, the effects of renal failure on the nervous system, and the neurologic complications of dialysis.

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INTRODUCTION

The link between neurologic and renal disease can be divided into two major categories: conditions that affect both the kidney and the nervous system and neurologic sequelae of renal disease. Conditions affecting both the kidney and nervous system may be genetic or acquired, and, while renal failure commonly affects the nervous system, the reverse is not true (renal failure rarely results from neurologic disease). Central and peripheral neurologic complications are seen in the majority of patients with renal failure. Central nervous system (CNS) sequelae include cognitive deficits, cerebrovascular complications, and uremia (encephalopathy, movement disorders, and seizures), while peripheral sequelae include primarily neuropathy and myopathy. Many of these effects are more pronounced when renal failure is acute. Additional neurologic complications result from the use of dialysis in the management of renal failure. This article focuses on conditions that affect both the renal and nervous systems, the effects of renal failure on the nervous system, and the neurologic complications of dialysis.

INHERITED DISEASES AFFECTING BOTH THE KIDNEY AND THE NERVOUS SYSTEM

A number of genetically determined disorders affect both the renal and nervous systems. These disorders are summarized in **Table 5-1**, and the more common genetically determined disorders are discussed here.

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease has an estimated prevalence of 1 per 400 to 1 per 1000[1] and is

characterized by the development of renal cysts and various extrarenal manifestations. Renal function is often maintained despite continued cyst growth until the fourth to sixth decades of life. Hypertension is present in about half of patients with normal renal function and affects all patients by the time end-stage renal disease develops. Pain is common and may result from renal hemorrhage, passage of stones, urinary tract infections, and,

TABLE 5-1 Genetically Determined Disorders Affecting Both the Renal and Nervous Systems

Disease Type and Disease/ Syndrome	Inheritance	Genetic Mutation	Renal Manifestations	Neurologic Manifestations
Glomerular disease				
Alport syndrome	X-linked dominant, autosomal recessive, autosomal dominant	*COL4A3*, *COL4A4*, or *COL4A5* (abnormal collagen type IV chains)	Glomerular/tubular basal membrane injury, hemorrhagic nephritis	Progressive symmetric sensorineural hearing impairment
Fabry disease	X-linked	*GLA*	Proteinuria, chronic kidney disease, Fanconi syndrome, renal sinus cysts, hypertension	Small fiber peripheral neuropathy, cerebrovascular complications
Pierson syndrome	Autosomal recessive	*LAMB2*	Congenital nephrotic syndrome	Anomalies of the retina and neuromuscular junction
Proximal tubular disease				
Proximal (type 2) renal tubular acidosis	Autosomal recessive	*SLC4A4*	Severe hypokalemic, hyperchloremic, metabolic acidosis	Impaired psychomotor and cognitive function, opacification of the basal ganglia
Lowe syndrome	X-linked recessive	*OCRL1*	Renal tubular acidosis and progressive renal impairment, Fanconi syndrome	Neonatal hypotonia, peripheral neuropathy, psychomotor delay, seizures
Hartnup disease	Autosomal recessive	*SLC6A19*	Gross aminoaciduria	Cerebellar ataxia
Loop of Henle disease				
Bartter syndrome	Autosomal recessive	*NKCC2*, *ROMK*, or *CLCNKB*	Impaired potassium, calcium, and magnesium reabsorption	Developmental delay

Continued on page 724

TABLE 5-1 **Genetically Determined Disorders Affecting Both the Renal and Nervous Systems**
Continued from page 723

Disease Type and Disease/ Syndrome	Inheritance	Genetic Mutation	Renal Manifestations	Neurologic Manifestations
Distal tubular disorders				
Gitelman syndrome	Autosomal recessive	*SLC12A3*	Hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria	Intermittent muscle weakness and tetany
Distal (type 1) renal tubular acidosis	Autosomal dominant	*SLC4A1*	Nephrocalcinosis, nephrolithiasis, mild to moderate hypokalemia	Periodic paralysis
	Autosomal recessive	*ATP6V0A4, ATP6V1B1*	Hyperchloremic metabolic acidosis, moderate to severe hypokalemia, nephrocalcinosis	Periodic paralysis, sensorineural hearing loss
Parenchymal disease				
Polycystic kidney disease	Autosomal dominant	*PKD1* or *PKD2*	Progressive renal failure due to continued cyst enlargement, hypertension, hematuria, nephrolithiasis, acute or chronic flank/abdominal pain	Saccular cerebral aneurysms, dolichoectasia; rare subdural hemorrhage or CSF hypotension
Von Hippel-Lindau disease	Autosomal dominant	*VHL* tumor suppressor gene	Renal cysts, renal cell carcinoma	Retinal and central nervous system hemangioblastomas, ataxia, syringobulbia, syringomyelia
Joubert syndrome	Autosomal recessive	Genetic heterogeneity	Renal cysts, chronic kidney disease	Vermian hypoplasia, ataxia, psychomotor delay, hypotonia, nystagmus

CSF = cerebrospinal fluid.

rarely, renal cell carcinoma, but some patients develop chronic flank pain without an identifiable cause other than the cysts themselves. Extrarenal cysts can develop in the liver, seminal vesicles, pancreas, and arachnoid membrane. Arachnoid membrane cysts are usually asymptomatic, but they can increase the risk of subdural hematomas. Patients with autosomal dominant polycystic kidney disease have an increased frequency of spinal meningeal diverticula, which can rarely present with a CSF leak leading to intracranial hypotension.

Other neurologic manifestations include saccular cerebral aneurysms, cervicocephalic artery dissections, and dolichoectasia. The incidence of cerebral aneurysms is around 6% in patients with no family history of autosomal dominant polycystic kidney disease and 16% in those with a positive family history, compared with 2% to 3% in the general population. The average age at rupture is lower than in the general population (41 years versus 51 years).[2] While 71% of patients have hypertension at the time of rupture, most have preserved renal function. A global interdisciplinary expert panel recently convened and did not recommend widespread screening for intracranial aneurysms.[2] Their rationale was that screening yields mostly small aneurysms with a low risk of rupture and that prophylactic repair of an unruptured aneurysm may be risky. They advised the following indications for screening in patients with a good life expectancy: family history of intracranial aneurysm or subarachnoid hemorrhage, previous intracranial aneurysm rupture, high-risk professions (eg, airline pilots), or patient anxiety despite adequate information. This is similar to the recommendation published in recent American Heart Association/American Stroke Association guidelines stating that screening is appropriate in patients with autosomal dominant polycystic kidney disease and a family history of intracranial aneurysm.[3] If screening is pursued, time-of-flight MRI without gadolinium enhancement is the method of choice.[2] Coil embolization may be safe and effective for those patients with intracranial aneurysms in autosomal dominant polycystic kidney disease; however, a concern about the development of contrast-induced nephropathy exists in patients with chronic kidney disease stage 5 or a serum creatinine level higher than 2.0 mg/dL.[4]

Von Hippel-Lindau Disease

Von Hippel-Lindau disease is an autosomal dominant syndrome that results from a mutation in the *VHL* tumor suppressor gene. It is not rare, occurring in about 1 in 36,000 live births.[5] Affected individuals are at risk of developing benign and malignant tumors, including retinal and CNS hemangioblastomas, clear cell renal cell carcinomas, pheochromocytomas, pancreatic neuroendocrine tumors, and endolymphatic sac tumors. Neurologic manifestations include retinal and CNS hemangioblastomas, ataxia, syringobulbia, and syringomyelia. Hemangioblastomas of the CNS are the most common tumor in von Hippel-Lindau disease, affecting 60% to 80% of patients. The frequency and age at onset of neurologic lesions are listed in **Table 5-2**. These tumors are benign but cause significant morbidity through local mass effect, edema, and associated cyst formation. Management largely consists of surgical resection of symptomatic tumors, those tumors at risk of metastasizing, or tumors causing hormonal symptoms (pheochromocytomas).[6] Early detection through presymptomatic screening of at-risk individuals may enhance overall outcome. Before widespread screening, median lifespan was less than 50 years; however, routine screening, improvements in treatment, and increased awareness of the disease have improved prognosis and reduced tumor-related morbidity. The main causes of death are complications of renal cell carcinoma and cerebellar hemangioblastomas (**Figure 5-1**[7]).[5,8]

KEY POINTS

- Neurologic manifestations of autosomal dominant polycystic kidney disease include saccular cerebral aneurysms, cervicocephalic artery dissections, and dolichoectasia.
- Screening for intracranial aneurysms in autosomal dominant polycystic kidney disease is recommended in patients with a family history of intracranial aneurysm or subarachnoid hemorrhage, previous intracranial aneurysm rupture, high-risk professions (eg, airline pilots), or patient anxiety despite adequate information.
- Neurologic manifestations of von Hippel-Lindau disease include retinal and central nervous system hemangioblastomas, ataxia, syringobulbia, and syringomyelia.
- Early detection of tumors through presymptomatic screening of at-risk individuals may enhance overall outcome in patients with von Hippel-Lindau disease.

TABLE 5-2 Frequency, Age at Onset, and Associated Neurologic Sequelae of Central Nervous System Hemangioblastomas[a]

Location	Frequency in Patients	Age of Onset (Years) (Data Reported as Mean [Range])	Signs and Symptoms (%) in Patients Undergoing Resection
Retinal	25–60%	25 (1–67)	N/A[b]
Craniospinal			
Supratentorial	<1%	Unknown	Unknown
Brainstem	10–25%	32 (12–46)	Hypesthesia (55%), gait ataxia (22%), dysphagia (22%), hyperreflexia (22%), headaches (11%), dysmetria (11%)
Cerebellum	44–72%	33 (9–78)	Gait ataxia (64%), dysmetria (64%), headaches (12%), diplopia (8%), vertigo (8%), emesis (8%)
Spinal cord	13–50%	33 (12–66)	Hypesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%), incontinence (14%)
Lumbosacral nerve roots	<1%	Unknown	Unknown

N/A = not applicable.
[a] Modified with permission from Lonser RR, et al, Lancet.[5] © 2003 Elsevier. *sciencedirect.com/science/article/pii/S0140673603136434.*
[b] Typically treated with laser photocoagulation or cryotherapy.

Alport Syndrome

The estimated prevalence of X-linked Alport syndrome is 1 per 10,000, whereas that of autosomal recessive Alport syndrome is 1 per 50,000.[9] Changes in collagen type IV chains result in injury to the glomerular and tubular basal membranes, eyes, and cochlea, resulting in hemorrhagic nephritis, progressive symmetric sensorineural hearing impairment, and ocular changes that do not typically affect vision. Boys present with microscopic hematuria by the age of 10, and end-stage renal disease usually develops between the ages of 16 and 35 years. Females have earlier-onset renal disease.

Gitelman Syndrome

Gitelman syndrome is an autosomal recessive disorder that presents with a characteristic set of metabolic abnormalities, including hypokalemia, metabolic alkalosis, hyperaldosteronism, and hyperplasia of the juxtaglomerular apparatus (the source of renin in the kidney), with resultant hyperreninemia. In a report from the Framingham Heart Study, the prevalence of Gitelman syndrome was 1 in 40,000. Gitelman syndrome is observed in older children and adults and typically presents with fatigue, severe muscle cramps of the arms and legs, and intermittent episodes of muscle weakness and tetany associated with hypokalemia and hypomagnesemia.

Fabry Disease

Fabry disease, also called Anderson-Fabry disease, is an X-linked inborn error of glycosphingolipid metabolism and the second most prevalent lysosomal storage disorder after Gaucher disease, ranging from 1 per 40,000 to

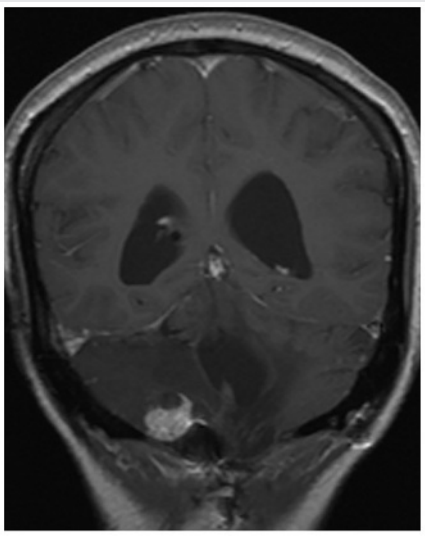

FIGURE 5-1 Hemangioblastoma in von Hippel-Lindau disease. Coronal MRI shows a cystic hemangioblastoma with a solid enhancing mural nodule.

Reprinted with permission from Leung RS, et al, Radiographics.[7] © 2008 RSNA. *pubs.rsna.org/doi/abs/10.1148/rg.281075052*.

1 per 117,000 males in white populations.[10] The classic form occurs in males who have less than 1% α-galactosidase A enzyme activity, in whom the onset occurs in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesia). These symptoms are precipitated by illness, fever, stress, exercise, or heat and result from a small fiber neuropathy. Other early features include hypohidrosis, vascular cutaneous lesions (angiokeratomas), corneal and lenticular opacities, and proteinuria. Renal function gradually deteriorates to end-stage renal disease by the third to fifth decades. In middle age, most patients develop cardiovascular or cerebrovascular disease, which may manifest as transient ischemic attacks, cerebral infarctions, or, as illustrated in **Case 5-1**, dolichoectasia. Additional neurologic manifestations include cramp-fasciculation syndrome without peripheral neuropathy, hearing impairment, vascular dementia, and aseptic meningitis.

The adult neurologist will most likely encounter these patients in the workup for neuropathy and stroke. Features that should trigger specific testing for Fabry disease include patient-reported lack of sweating; intermittent episodes of severe pain in the extremities (acroparesthesia); cutaneous vascular lesions (angiokeratomas); or stroke, left ventricular hypertrophy, or chronic kidney disease of unknown etiology in young adulthood. Measurement of leukocyte α-galactosidase A activity is the standard enzymatic test at most laboratories in classically affected males; however, in males with atypical presentations and in females, additional testing may be necessary.[11]

Consensus on the recommended use of enzyme replacement therapy does not exist; however, trials comparing enzyme replacement therapy to placebo show significant improvement in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life.[12] The long-term effects on risk of morbidity and mortality have not been established.[12]

ACQUIRED CONDITIONS AFFECTING BOTH THE KIDNEY AND THE NERVOUS SYSTEM

Vasculitides, connective tissue disorders, and plasma cell dyscrasias, by their nature, involve more than one organ system, and several affect both the renal and nervous systems. Plasma cell dyscrasias and neurologic manifestations are briefly summarized here (**Table 5-3**).[8,13] For more information on vasculitides and connective tissue disorders, refer to the article "Rheumatology and Neurology" by Elliott L. Dimberg, MD, FAAN,[14] in this issue of *Continuum*.

KEY POINT

- By middle age, most patients with Fabry disease develop cardiovascular or cerebrovascular disease, which may manifest as transient ischemic attacks, cerebral infarctions, or dolichoectasia.

Case 5-1

A 42-year-old man with no significant past medical history presented for evaluation of progressive bilateral symmetric lower extremity weakness over a period of 3 weeks. Over the past several days, he had noticed worsening slurred speech and difficulty swallowing. On review of systems, he reported a history of episodic pain in his legs since he was about 13 years of age.

On examination, his blood pressure was 156/90 mm Hg. He had prominent dysarthria, spastic paraparesis, and diffuse hyperreflexia. Babinski signs were present bilaterally. His serum creatinine was 3.2 mg/dL, and a lipid panel was normal. Fabry disease was suspected because of his age, gender, history of acroparesthesia beginning in his teenage years, and the new finding of renal disease. α-Galactosidase A enzyme activity level was severely reduced, consistent with suspected Fabry disease. An MRI of the brain did not show any restricted diffusion but demonstrated a large vertebrobasilar aneurysm with intramural thrombus and severe dolichoectasia of the vertebrobasilar system (**Figure 5-2**).

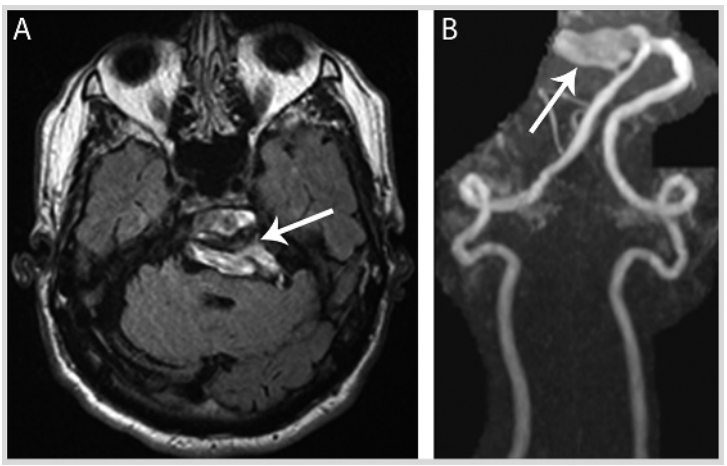

FIGURE 5-2 Imaging of the patient in Case 5-1 showing vertebrobasilar aneurysm with intramural thrombus in Fabry disease. *A*, Axial T2 fluid-attenuated inversion recovery (FLAIR) image showing a large vertebrobasilar aneurysm with intramural thrombus producing significant anterior mass effect on the medulla (*arrow*). *B*, Three-dimensional time-of-flight magnetic resonance angiogram (MRA) showing bilateral vertebral artery dolichoectasia and large basilar artery aneurysm (*arrow*).

Comment. Dolichoectasia frequently accompanies Fabry disease, particularly in the posterior circulation, and may be related to weakening of the vessel wall due to glycosphingolipid deposition and hypertension. The patient's neurologic symptoms and signs were attributed to progressive mass effect on the medulla and pons from the dolichoectatic vessel.

TABLE 5-3 Vasculitides, Connective Tissue Disorders, and Plasma Cell Dyscrasias With Renal and Neurologic Manifestations

Disease Type and Disease/Syndrome	Renal Manifestations	Neurologic Manifestations
Vasculitides		
Polyarteritis nodosa	Renal insufficiency, renal infarctions, ruptured renal artery aneurysms, minimal proteinuria, possibly modest hematuria	Peripheral neuropathy (mononeuropathy multiplex), central nervous system (CNS) involvement (encephalopathy, subarachnoid hemorrhage, chorea)
ANCA-associated vasculitides Granulomatosis with polyangiitis (Wegener granulomatosis) Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Asymptomatic hematuria; subnephrotic proteinuria; focal necrotizing, often crescentic, pauci-immune glomerulonephritis	Mononeuritis multiplex, sensory neuropathy, cranial nerve abnormalities, CNS mass lesions, external ophthalmoplegia, sensorineural hearing loss; meningeal disease is most commonly associated with granulomatous inflammation of the CNS
Connective tissue disorders		
Rheumatoid arthritis	Rare focal glomerulonephritis, possible membranous nephropathy, rheumatoid vasculitis	Carpal tunnel syndrome, radiculopathy, cervical myelopathy, CNS vasculitis, rheumatoid nodules located within the CNS, meningitis
Sjögren syndrome	Interstitial nephritis (variable abnormalities in tubular function, including Fanconi syndrome, distal renal tubular acidosis, nephrogenic diabetes insipidus, hypokalemia); less commonly membranoproliferative glomerulonephritis or membranous nephropathy	Peripheral neuropathy (predominantly axonal sensory and sensorimotor polyneuropathies) cranial neuropathies, autonomic neuropathy, radiculoneuropathies, focal or diffuse brain lesions, transverse myelopathy, longitudinally extensive myelopathy, subacute aseptic meningitis, chorea, optic neuritis, cognitive dysfunction
Systemic lupus erythematosus	Glomerulonephritis, less commonly hypertension	Cognitive dysfunction, peripheral neuropathy, headache, thromboembolic events (often associated with lupus anticoagulant or antiphospholipid antibodies) that may result in strokes or seizures; less commonly movement disorders, cranial neuropathies, myelitis, meningitis

Continued on page 730

TABLE 5-3 **Vasculitides, Connective Tissue Disorders, and Plasma Cell Dyscrasias With Renal and Neurologic Manifestations** *Continued from page 729*

Disease Type and Disease/Syndrome	Renal Manifestations	Neurologic Manifestations
Plasma cell dyscrasias		
Cryoglobulinemia (varied types and etiologies)	Varied depending on type and etiology: isolated proteinuria or hematuria, membranoproliferative glomerulonephritis, nephrotic syndrome, renal failure	Varied depending on type and etiology: multiple mononeuropathy, sensory and motor neuropathy; hyperviscosity syndrome (blurring or loss of vision, headache, vertigo, nystagmus, dizziness, sudden deafness, diplopia, ataxia, confusion, disturbances of consciousness, stroke, or coma)
Monoclonal gammopathies of undetermined significance	Occasional proteinuria and amyloid deposition	Progressive demyelinating neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Multiple myeloma	Renal failure due to light chain cast nephropathy, hypercalcemia, light chain amyloidosis, or light chain deposition disease	Thoracic or lumbar radiculopathy; less commonly spinal cord compression from an extramedullary plasmacytoma, peripheral neuropathy, intracranial plasmocytomas, leptomeningeal myelomatosis, encephalopathy due to hyperviscosity
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome (osteosclerotic myeloma)	Acute and chronic renal failure, renal hemangiomas, rare proteinuria	Peripheral neuropathy (mandatory for diagnosis), cerebral infarction
Waldenström macroglobulinemia	Rare proteinuria, nephrotic syndrome, renal failure	Peripheral neuropathy, encephalopathy, or cerebral infarction due to hyperviscosity syndrome, myelopathy

ANCA = antineutrophil cytoplasmic antibody.

The thrombotic microangiopathies, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, involve both renal and nervous systems. Thrombotic thrombocytopenic purpura usually presents in previously healthy individuals as a severe microangiopathic hemolytic anemia and thrombocytopenia but may also present in patients with other autoimmune disorders such as systemic lupus erythematosus. Diagnostic evaluation includes a complete blood cell count, peripheral smear, serum chemistry, creatinine, lactate

dehydrogenase, bilirubin, haptoglobin, coagulation testing, direct antiglobulin test, and ADAMTS13 activity and inhibitor testing. Severely reduced ADAMTS13 activity (less than 10%) is a hallmark of acquired thrombotic thrombocytopenic purpura; however, it should not be used in isolation for diagnosis or to guide initiation or discontinuation of therapy. In the presence of delayed recognition, the pentad of thrombocytopenia, fever, acute renal failure, microangiopathic hemolytic anemia, and neurologic findings will develop and result in death; however, since use of therapeutic plasma exchange has become routine, the presence of the full pentad has become rare.[15,16] Neurologic and gastrointestinal manifestations remain common. Renal insufficiency may be present, but renal failure rarely occurs. Neurologic manifestations may include confusion, headache, transient focal neurologic deficits, seizures, stroke, or coma.[15] Initial treatment consists of prompt initiation of plasma exchange without waiting for the results of ADAMTS13 activity levels or inhibitor testing. Expert consensus and observational studies also support the use of glucocorticoids in addition to plasma exchange as an initial therapy, while rituximab is typically reserved for patients with severe disease, major neurologic symptoms, or thrombocytopenia refractory to plasma exchange.[17]

Hemolytic uremic syndrome is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure caused by diarrheal infection due to Shiga toxin–producing bacteria, complement deficiency, or pneumococcal infection.[15,18] Renal involvement ranges from microscopic hematuria and proteinuria to severe renal failure. Neurologic involvement may include seizures, coma, stroke, pyramidal or extrapyramidal syndromes, dysphasia, and cortical blindness.[18] Both thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have been associated with posterior reversible encephalopathy syndrome (PRES). Management of hemolytic uremic syndrome is primarily supportive, but some benefit may be derived from eculizumab, a monoclonal antibody to complement factor C5 that blocks complement activation.[19] Plasma infusion and exchange have been used in the treatment of some patients with little evidence.[18]

Renal and neurologic manifestations can also be seen in a variety of infections, including those caused by bacterial (eg, streptococcus), mycobacterial, rickettsial, tuberculous, protozoal (eg, malaria), and viral (eg, human immunodeficiency virus [HIV], dengue, hantavirus, cytomegalovirus, and varicella-zoster virus) pathogens.

RENAL FAILURE AND THE NERVOUS SYSTEM

Renal failure itself can lead to a number of neurologic complications through the development of acid-base imbalances, electrolyte disturbances, or toxin accumulation. These sequelae are reviewed in the following sections.

Acid-Base and Electrolyte Disturbances

Normal acid-base balance depends on the maintenance of a constant pH between 7.35 and 7.45 through renal production and excretion of bicarbonate and pulmonary elimination of carbon dioxide. If a primary change in bicarbonate is not compensated for by the lungs, a metabolic acid-base disorder develops; conversely, if a primary change in carbon dioxide is not compensated for by the kidneys, a respiratory acid-base disorder develops. Acidosis and alkalosis both

KEY POINTS

- In the presence of delayed recognition of thrombotic thrombocytopenic purpura, the pentad of thrombocytopenia, fever, acute renal failure, microangiopathic hemolytic anemia, and neurologic findings will develop and lead to death; however, since the use of therapeutic plasma exchange has become routine, the presence of the full pentad has become rare.
- Hemolytic uremic syndrome is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in which seizures, coma, stroke, pyramidal or extrapyramidal syndromes, dysphasia, and cortical blindness may occur.
- Acidosis and alkalosis both can present with neurologic signs, predominantly altered consciousness.

can present with neurologic signs, predominantly altered consciousness.[20] Because carbon dioxide easily crosses the blood-brain barrier, respiratory acid-base disorders can have marked effects on cerebral blood flow. A decrease in brain pH causes vasodilation and increased cerebral blood flow; an increase in brain pH causes vasoconstriction and a decrease in cerebral blood flow. Both acute kidney injury and chronic kidney disease predispose to metabolic acidosis and electrolyte disturbances. Metabolic acidosis negatively affects cerebral neuronal metabolism and impairs normal brain function by increasing the affinity of ammonia for glutamate dehydrogenase (resulting in oxidative deamination of glutamate and excess ammonia cycling between neurons and astrocytes) and activation of acid-sensing ion channels (resulting in an influx of sodium and calcium into cells, leading to membrane depolarization, cellular injury, and death) among other mechanisms.[21] **Table 5-4** summarizes the major acid-base imbalances and their neurologic manifestations, while **Table 5-5** summarizes the major electrolyte disturbances and their corresponding neurologic manifestations.

Uremia

Renal failure (acute or chronic) that is sufficient to prevent adequate clearance of nitrogenous waste products

TABLE 5-4 Major Acid-Base Disturbances and Their Corresponding Neurologic Manifestations

Acid-Base State	Neurologic Manifestations	Mechanisms
Respiratory alkalosis	Lightheadedness, syncope, seizures, acral and circumoral paresthesia, muscle cramps, hyperreflexia, tetany, Chvostek sign	Reduced cerebral blood flow → vasoconstriction → cerebral ischemia
Respiratory acidosis	Signs and symptoms of increased intracranial pressure: nocturnal or early morning headaches, disorientation, visual disturbances, papilledema, altered consciousness; when severe, coma, loss of brainstem reflexes, upper motor neuron findings reflecting brain herniation	Hypoventilation → vasodilatation → increased cerebral blood flow → increased intracranial pressure
Metabolic alkalosis	Headache, lethargy, neuromuscular excitability, encephalopathy, seizures, weakness, tetany, seizures	Increased protein binding of ionized calcium (Ca^{++}) → hypocalcemia; hypokalemia
Metabolic acidosis	Lethargy, altered consciousness; numerous other neurologic manifestations are etiology specific (eg, methanol toxicity, ethylene glycol toxicity, salicylate toxicity, diabetic ketoacidosis, alcoholic ketoacidosis)	Increasing affinity of ammonia for glutamate dehydrogenase → oxidative deamination of glutamate and excess ammonia cycling between neurons and astrocytes → activation of acid-sensing ion channels → influx of sodium and calcium into cells → membrane depolarization, cellular injury and death; other mechanisms

TABLE 5-5 Major Electrolyte Disturbances and Their Corresponding Neurologic Manifestations[a]

Electrolyte Disturbance	Definition	Neurologic Manifestations	Caution
Hyponatremia[b]	Serum sodium <135 mmol/L; osmolality <285 mmol/L	Muscle cramps, hyporeflexia, cerebral edema, increased intracranial pressure, encephalopathy, seizures	Central pontine myelinolysis with rapid correction
Hypernatremia[b]	Serum sodium >145 mmol/L; osmolality >295 mmol/L	Weakness with hyperreflexia, rigidity, tremor, chorea, myoclonus, encephalopathy, seizures	Cerebral edema, seizures, and coma with rapid correction
Hypokalemia	Serum potassium <3.5 mmol/L	Weakness with normal reflexes, ascending weakness (sparing cranial nerves), paresthesia	Cardiac arrhythmias; hypocalcemic tetany with concurrent hypocalcemia
Hyperkalemia	Serum potassium >5 mmol/L	Weakness with hyporeflexia, ascending weakness (sparing cranial nerves), burning paresthesia	Cardiac arrhythmias especially without coadministration of calcium
Hypocalcemia	Serum calcium <8.2 mg/dL; ionized calcium <4.4 mg/dL	Tetany, trismus, opisthotonus, encephalopathy, seizures, Chvostek sign, Trousseau sign	Digitalis toxicity in patients on digoxin with rapid or aggressive correction
Hypercalcemia	Serum calcium >10.5 mg/dL	Encephalopathy, myoclonus, rigidity, proximal weakness, hyperreflexia	Furosemide may worsen hypercalcemia in presence of heart failure
Hypomagnesemia	Serum magnesium <0.6 mmol/L	Tetany with Chvostek and Trousseau signs, encephalopathy, seizures, hyperreflexia, tremor, chorea, myoclonus with startle	Weakness with rapid or aggressive correction
Hypermagnesemia	Serum magnesium >2 mmol/L	Acute flaccid areflexic paralysis with respiratory insufficiency (may mimic a midbrain syndrome)	Ischemic heart disease, arrhythmias, preeclampsia, or bronchial constriction with rapid or aggressive correction
Hypophosphatemia	Serum phosphorus <0.8 mmol/L	Acute areflexic paralysis with diaphragmatic, pharyngeal, facial, and extraocular muscle weakness preceded by perioral paresthesia	Hypocalcemia-related complications with rapid or aggressive correction

[a] Modified with permission from Espay AJ, Handb Clin Neurol.[20] © 2014 Elsevier. *sciencedirect.com/science/article/pii/B9780702040863000230*.

[b] Hyponatremia and hypernatremia are concerning to neurologists insofar as they change plasma osmolality (sodium is a major osmotically active solute in the extracellular compartment). Hypoosmolality results in osmotic flow of water from plasma and interstitial fluid into the cells, resulting in cytotoxic edema and reduced cellular function. The hypertonic hyperosmolarity of hypernatremia results in cellular dehydration and reduced cellular function.

KEY POINTS

- Neurologic manifestations of the uremic state include both central nervous system complications (eg, lethargy, encephalopathy, seizures, acute movement disorders, and coma) and peripheral nervous system complications (eg, neuropathy and myopathy).
- Symptoms of uremia are usually alleviated by dialysis or renal transplantation.

results in a constellation of signs and symptoms referred to as uremia. Neurologic manifestations of the uremic state include both CNS complications (eg, lethargy, encephalopathy, seizures, acute movement disorders, and coma) and peripheral nervous system complications (eg, neuropathy and myopathy). Before the widespread use of renal replacement therapy (dialysis), uremia was almost invariably fatal. A direct correlation between the absolute serum levels of blood urea nitrogen (BUN) or creatinine and the development of uremia does not exist. While one patient may become markedly symptomatic with a serum BUN of 60 mg/dL, another may tolerate a BUN of 130 mg/dL without developing symptoms. A major factor in this discrepancy is the rapidity of rise of the BUN, and other factors, such as the age of the patient, may play a role. Symptoms of uremia are usually alleviated by dialysis or renal transplantation.

Encephalopathy. Uremic encephalopathy syndrome is composed of a wide array of symptoms ranging from fatigue, apathy, emotional lability, perceptual errors, irritability, and impaired cognition to lethargy, sleep impairment, delirium, delusions, hallucinations, generalized tonic-clonic seizures, and fluctuating level of consciousness progressing to coma. The symptoms often proceed insidiously and are frequently mild in chronic renal failure, with family members observing poor concentration, forgetfulness, and personality changes. In acute renal failure and in decompensated chronic kidney disease, the severity correlates with the extent and rapidity of accumulation of uremic toxins.[8] Neuroimaging is not necessary to make the diagnosis but may be useful to exclude other causes of encephalopathy or if focal neurologic deficits develop. Typical EEG changes in uremic encephalopathy include diffuse slowing, frontal intermittent rhythmic theta, paroxysmal bilateral diffuse high-voltage delta, and triphasic waves. The pathophysiology of uremic encephalopathy is complex but is thought to result from accumulation of uremic neurotoxins, hormonal disturbances, alterations in intermediary metabolism, and imbalances of excitatory and inhibitory neurotransmitters.

Movement disorders. Involuntary motor disturbances associated with uremic encephalopathy include varying degrees of tremor, fasciculations, asterixis, and multifocal myoclonus.[22] These movements are typically arrhythmic or asynchronous but may appear more rhythmic, in which case an EEG may be required to differentiate them from seizures. These abnormal movements occurring in the setting of uremia have sometimes been referred to as the twitch-convulsive syndrome.[23] Resolution of the acute kidney injury or dialysis to remove the uremic toxins is the definitive treatment. Less commonly, chorea or parkinsonism may develop and can be associated with radiographic changes in the basal ganglia.[22,24]

Seizures. Seizures in patients with renal failure may result directly from uremic toxins in association with uremic encephalopathy or from electrolyte disturbances (**Table 5-5**), PRES, or cefepime or other drug neurotoxicity. Seizures may also occur as a result of intracerebral hemorrhage or cerebral infarction or in the setting of dialysis disequilibrium syndrome or dialysis dementia (discussed later in this article).

Up to one-third of patients with uremic encephalopathy may develop seizures[25] which can be focal or

generalized, convulsive or nonconvulsive (**Case 5-2**). The use of cefepime in the setting of renal failure may result in neurotoxicity, which commonly presents with reduced consciousness, encephalopathy, and myoclonus. Seizures are an uncommon but important manifestation of cefepime neurotoxicity, as nonconvulsive status epilepticus may be an easily overlooked and treatable cause of encephalopathy in patients with renal failure. Cefepime neurotoxicity occurs more often when the dose is not adjusted for renal function but can still occur when the drug is renally dosed.[26]

Renal insufficiency also predisposes patients to PRES, which is accompanied by seizures in 60% to 75% of patients. A diagnosis of PRES should be considered when acute neurologic symptoms develop in patients with renal failure, blood pressure fluctuations, autoimmune disorders, use of cytotoxic drugs, or eclampsia.[27]

Certain considerations regarding the administration of antiseizure drugs in the setting of renal insufficiency are important. If a highly water-soluble anticonvulsant is used, such as levetiracetam, topiramate, or gabapentin, supplemental dosing is required after dialysis as these drugs have lower protein binding, resulting in removal during dialysis. Antiepileptic drugs that are highly protein bound, such as phenytoin, valproic acid, and carbamazepine, are less prone to dialysis-related changes in serum concentration and therefore are preferred for the treatment of seizures that complicate end-stage renal disease.[28] As levetiracetam is a commonly used and effective antiepileptic drug that has limited drug interactions, it is also acceptable in dialysis patients; however, an additional dose should be administered immediately postdialysis.

Peripheral nervous system complications. The same nitrogenous waste products that lead to the development of encephalopathy cause nerve injury in 60% to 100% of patients with end-stage renal disease.[29] While polyneuropathy may result from uremia alone, it may also develop in diseases that involve the kidney, such as diabetes mellitus, vasculitis, connective tissue diseases, and plasma cell dyscrasias. Uremic polyneuropathy may be painless or

KEY POINTS

- The use of cefepime in the setting of renal failure may result in neurotoxicity, which commonly presents with reduced consciousness, encephalopathy, and myoclonus and less commonly with nonconvulsive status epilepticus.
- A diagnosis of posterior reversible encephalopathy syndrome should be considered when acute neurologic symptoms develop in patients with renal failure, blood pressure fluctuations, autoimmune disorders, use of cytotoxic drugs, or eclampsia.
- Polyneuropathy may result from uremia alone, or it may develop in diseases that involve the kidney, such as diabetes mellitus, vasculitis, connective tissue diseases, and plasma cell dyscrasias.

Case 5-2

A 61-year-old man with a past medical history notable for obesity-hypoventilation syndrome and chronic hemodialysis–dependent renal failure was evaluated for multiple stereotyped spells that began 6 days previously, were occurring daily, and seemed to be increasing in frequency. His wife described these episodes as a sudden change in behavior in which he stopped talking, had fluttering of the eyes but maintained eye opening, and did not respond to her. Following the episodes, he appeared confused. He had no associated abnormal movements, except perhaps some quivering of the lips. No precipitating factors were noted, and he was not on any medications known to cause seizures.

Neurologic examination was normal apart from tangential speech and poor thought content. Laboratory evaluation was remarkable for a creatinine of 4.1 mg/dL and a blood urea nitrogen of 98 mg/dL. A noncontrast head CT and MRI were performed and were unremarkable. Because of suspected focal seizures with dyscognitive features, continuous EEG monitoring was initiated, which showed left temporal intermittent rhythmic delta activity and recurrent electrographic seizures of left temporal onset (**Figure 5-3**).

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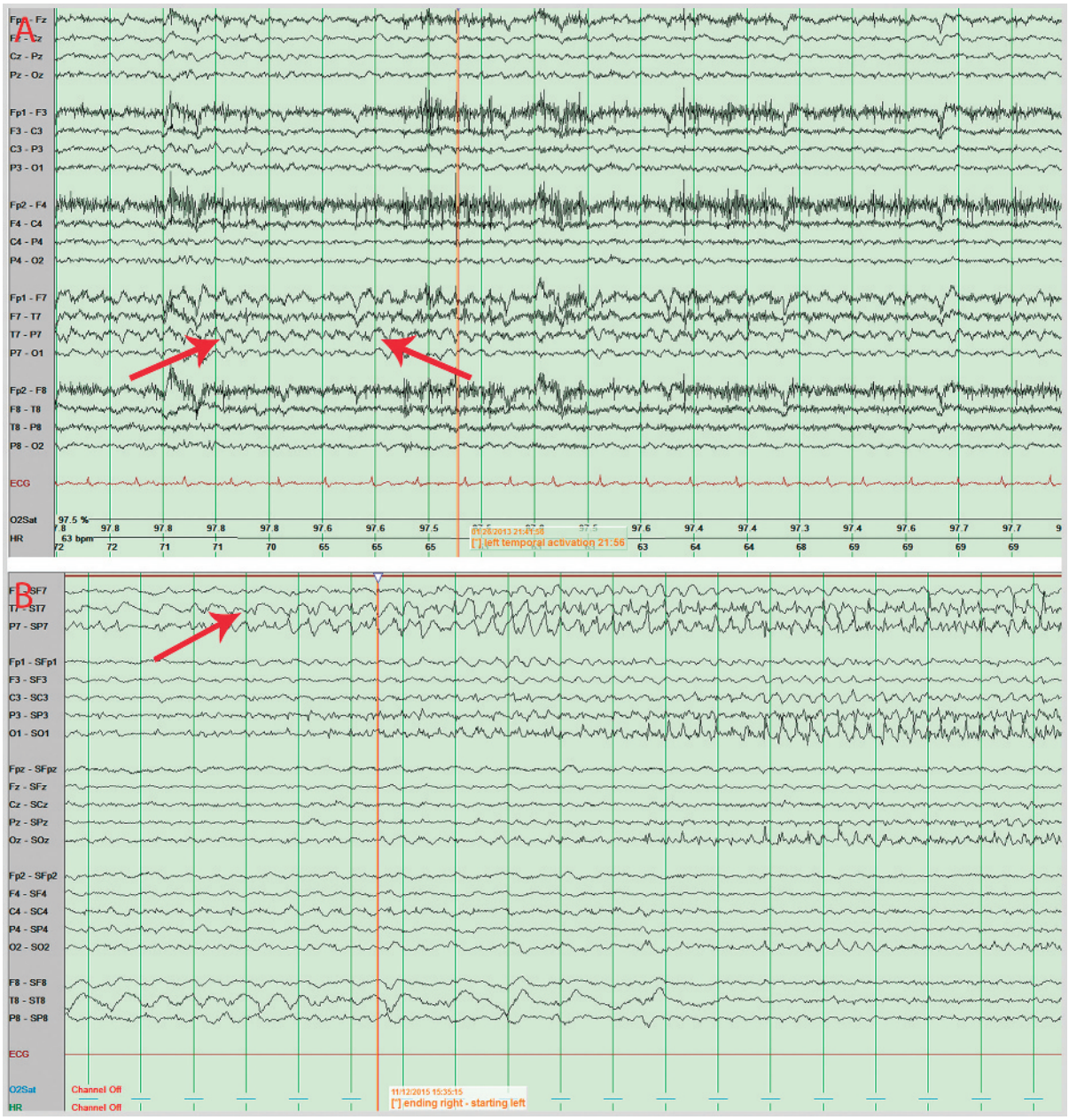

FIGURE 5-3 EEG of the patient in **Case 5-2** showing focal seizure in uremic encephalopathy. *A*, Bipolar montage EEG showing left temporal intermittent rhythmic delta activity (*arrows*). *B*, Laplacian montage EEG showing a seizure of left temporal onset (*arrow*).

Comment. Generalized or focal seizures may develop in patients with uremic encephalopathy and should be considered when patients have abrupt changes in mental status, abnormal movements, or a progressive decline in the level of consciousness. Treatment consists of initiation of an antiepileptic drug in patients with chronic kidney disease with seizures who are expected to be at continued risk for uremic encephalopathy. If status epilepticus develops despite initiation of an anticonvulsant, dialysis may be required to stop the seizures.

may present initially with pruritus and burning dysesthesia of the feet, impaired temperature and vibratory sense of the feet, loss of ankle jerks, and weakness of foot dorsiflexion. Later, weakness and muscle wasting develop. Autonomic involvement has also been reported, with symptoms including postural hypotension, impaired sweating, esophageal dysfunction, diarrhea, constipation, hyperhidrosis, incontinence, or impotence.[22,29] Uremic neuropathy is classically a length-dependent, distal, axonal, sensorimotor, large fiber neuropathy; however, cases of pure motor and pure sensory neuropathy have been reported.[8] Isolated mononeuropathies may also occur, presumably due to an increased susceptibility to compression and ischemia. The most common of these are ulnar, median, and femoral neuropathies, but the optic, facial, trigeminal, and, rarely, vestibulocochlear nerves may also be affected.[30] Uremic neuropathy can stabilize or improve during dialysis.

Myopathy can also develop as a result of uremia, with progression mirroring the decline of renal function. Estimates of its prevalence are challenging, as clear definitions have not been established. When defining uremic myopathy as a functional alteration of skeletal muscle in patients undergoing dialysis, it occurs in up to 50% of patients on hemodialysis.[31] The clinical presentation is similar to that of primary hyperparathyroidism and osteomalacia. Patients have proximal limb weakness and muscle wasting with bone pain and tenderness. Proposed mechanisms include uremic toxins, altered vitamin D metabolism, carnitine deficiency, insulin resistance, ischemia, and malnutrition.[32] Uremic myopathy also improves with renal transplantation.

Cerebrovascular complications. Cerebrovascular disease is a common cause of morbidity and mortality in patients with chronic kidney disease as chronic kidney disease predisposes to ischemic and hemorrhagic strokes, progressive white matter lesions, and cerebral microbleeds independently of vascular risk factors.[33,34] Among patients on dialysis, the relative risk of hospitalization for ischemic or hemorrhagic stroke is estimated to be fourfold to tenfold higher than that of patients without chronic kidney disease.[35] Atherosclerosis and thromboembolic disease are the primary causes of ischemic stroke in renal failure; however, intradialytic hypotension may account for rare cases. Atherosclerosis is generally relatively diffuse compared with the general population, possibly because of the combined effects of traditional atherogenic risk factors and specific factors related to renal failure (ie, accumulation of guanidino compounds, hyperhomocysteinemia, oxidative and carbonyl stress, and disturbances of calcium-phosphate metabolism). Anemia, a common sequela of chronic kidney disease, is also an independent risk factor for stroke.[36] Hemorrhagic stroke in chronic kidney disease is most commonly hypertensive in origin and therefore most often affects the basal ganglia, cerebellum, or brainstem. Qualitative platelet dysfunction resulting from the uremic state may also play a role. While uncommon, patients with nephrotic syndrome are at risk for the development of venous sinus thrombosis, which presents clinically with venous infarctions with hemorrhagic conversion.[37]

DIALYSIS

Dialysis itself may lead to, or worsen, neurologic complications of renal failure, although advancements in our knowledge of renal replacement therapy have decreased their frequency. The

KEY POINTS

- Uremic neuropathy is classically a length-dependent, distal, axonal, sensorimotor, large fiber neuropathy.
- Uremic myopathy presents with proximal limb weakness and muscle wasting with bone pain and tenderness, and the progression mirrors the decline of renal function.
- The relative risk of hospitalization for ischemic or hemorrhagic stroke among patients on dialysis is estimated to be fourfold to tenfold higher than that of patients without chronic kidney disease.

KEY POINTS

- Dialysis disequilibrium syndrome presents with a variable constellation of symptoms, including headache, irritability, blurred vision, nausea, muscle cramps, encephalopathy, and seizures. It may be prevented or alleviated by adding osmotically active solutes to the dialysate and slowing the rate, increasing the frequency, and shortening the duration of dialysis.
- Poor-quality sleep, which has been associated with restless legs syndrome and snoring, has been documented in the majority of patients with end-stage renal disease.

following sections provide an overview of these complications.

Dialysis Disequilibrium Syndrome

The self-limiting dialysis disequilibrium syndrome presents with a variable constellation of symptoms, including headache, irritability, blurred vision, nausea, muscle cramps, encephalopathy, and seizures. Focal deficits have been reported.[38] It typically develops toward the end of dialysis and subsides over several hours, but severe forms have been reported to last for days. The risk of developing dialysis disequilibrium syndrome seems to be higher with initiation of dialysis or if the patient skips dialysis treatments, because of the increased azotemia in those patients. Several theories have been put forth to explain the syndrome. Osmotic shifts in the brain may be related to more rapid clearing of urea from the blood than brain, leading to cerebral edema (the reverse urea hypothesis). An alternative hypothesis is the idiogenic osmole hypothesis, which proposes that newly formed brain osmoles produce an osmotic gradient between brain and plasma during rapid dialysis.[39] Still others have suggested that cerebral edema is caused by increased production of organic acids, leading to intracellular acidosis in the cerebral cortex.

Adding osmotically active solutes to the dialysate and slowing the rate, increasing the frequency, and shortening the duration of dialysis may prevent development of the syndrome.[30] Dialysis disequilibrium syndrome has become much less common, primarily because of increased awareness of the complication and preventive measures. It is, therefore, now a diagnosis of exclusion, with other disorders such as intracranial bleeding or systemic infection being sought first when patients become obtunded during dialysis.[8]

Dialysis Dementia

Dialysis dementia is a subacute-onset progressive condition manifesting as apathy, personality changes, dysarthria, dysphasia, ataxia, myoclonus, seizures, dementia, and, eventually, immobilization and mutism that typically progresses to death within 6 months.[22] It was common before 1980 when patients were dialyzed with an aluminum-containing dialysate used to bind dietary phosphate. This has since been reduced to an aluminum concentration of less than 20 mcg/L, and the use of aluminum-free phosphate binders largely prevents the development of this complication; however, patients on dialysis remain twice as likely as age-matched healthy controls to develop cognitive impairment, primarily due to a vascular type dementia.[40]

Sleep Disturbance

A number of sleep disorders may be encountered in patients on renal replacement therapy, including insomnia, obstructive sleep apnea, restless legs syndrome (RLS), and excessive daytime sleepiness. Subjective sleep complaints have been reported in up to 80% of patients with end-stage renal disease, and one study documented poor-quality sleep in 75% of patients.[41] Poor-quality sleep was associated with RLS and snoring.[41] Patients may be more predisposed to RLS and periodic limb movements because of iron deficiency, accumulation of uremic toxins, a central dopaminergic disturbance, or uremic polyneuropathy. In patients with secondary RLS associated with end-stage renal disease who are on hemodialysis, insufficient evidence exists to support or refute the use of IV iron dextran.[42]

Wernicke Encephalopathy

Patients on chronic renal replacement therapy (hemodialysis or peritoneal dialysis) are at risk of developing Wernicke encephalopathy due to a combination of reduced oral intake and increased loss of the water-soluble vitamin thiamine (**Case 5-3**). This can develop at the initiation of dialysis but is more common in patients on chronic dialysis, and it must be considered as a potential cause of acute or subacute encephalopathy in this population. Rapid

Case 5-3

A 48-year-old woman with chronic renal failure secondary to autosomal dominant polycystic kidney disease presented to the hospital as she had become progressively more confused and disoriented. Initially, the confusion was transient, but similar episodes occurred the next day and by the third day had become persistent. Her family insisted that she seek medical evaluation when she developed gait instability. She had been on hemodialysis for approximately 1 year and in that time lost 70 pounds unintentionally. Her heart rate was 105 beats/min, and her pulse was bounding. Blood pressure was 120/80 mm Hg. She was inattentive and oriented only to person and location. She had severe restriction of gaze in all directions, intermittent nystagmus, decreased reflexes, and both gait and standing ataxia. Chest x-ray showed bilateral infiltrates and an enlarged heart.

Comment. This patient had symptoms and signs consistent with severe thiamine deficiency, including both wet beriberi (high-output cardiac failure and depressed reflexes suggestive of a peripheral neuropathy) and Wernicke encephalopathy (encephalopathy, oculomotor abnormalities, and ataxia). She was started on 500 mg IV thiamine, infused over 30 minutes 3 times a day for 2 consecutive days, followed by 250 mg IV once a day for an additional 5 days, in combination with other B vitamins. The oculomotor abnormalities resolved within several days, while the gait instability and confusion gradually resolved over 9 days. During that time, an MRI of the brain was performed and demonstrated T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities extending along the most dorsal brainstem in a symmetric fashion, the mammillary bodies, and in the periaqueductal gray matter, extending into the bilateral medial thalami and involving the tectum (**Figure 5-4**).

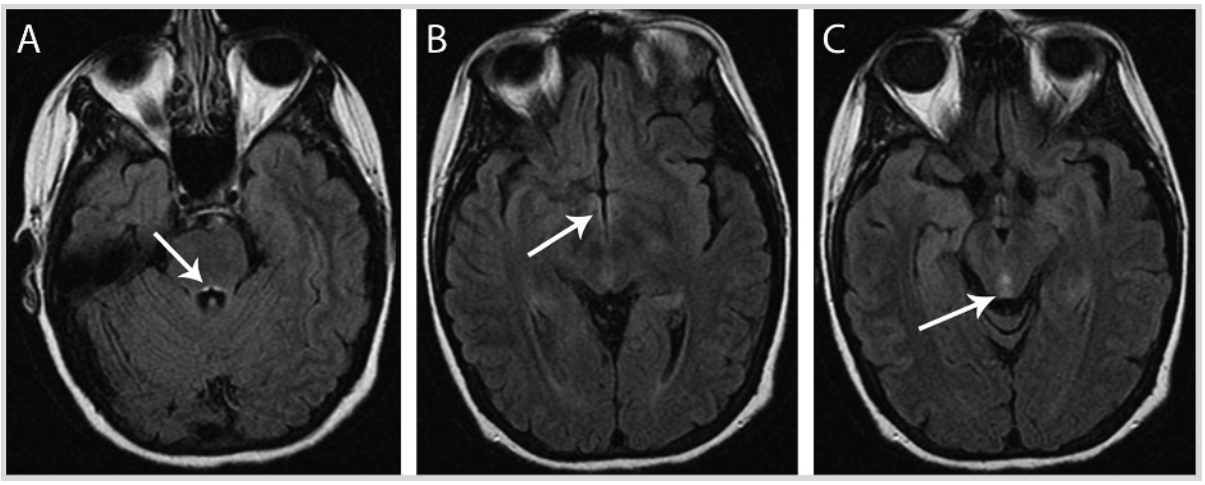

FIGURE 5-4 Imaging of the patient in **Case 5-3** with Wernicke encephalopathy. Axial fluid-attenuated inversion recovery (FLAIR) images showing increased FLAIR signal along the abducens nuclei regions (*A*, *arrow*), mammillary bodies (*B*, *arrow*), and the tectum of the midbrain and periaqueductal gray matter (*C*, *arrow*).

KEY POINTS

- End-stage renal disease is a risk factor for Wernicke encephalopathy due to a combination of reduced oral intake and increased loss of the water-soluble vitamin thiamine during dialysis.
- Patients who are dependent on dialysis are at higher risk for the development of subdural hematoma than the general population due to trauma, uremia-related coagulation disturbances, use of anticoagulants for dialysis, and use of rapid ultrafiltration and hypertonic dialysate.
- Mononeuropathies, particularly median neuropathy at the wrist, may be seen in association with dialysis.

recognition and initiation of treatment may minimize long-term neurologic deficits.

Subdural Hematomas

Subdural hematomas occur at a rate of 34.7 per 10,000 person-years in patients undergoing hemodialysis and 21.5 per 10,000 person-years in patients undergoing peritoneal dialysis, and 60% are associated with trauma.[43] Potential explanations for nontraumatic subdural hematomas include uremia-related coagulation disturbances, use of anticoagulants for dialysis, and use of rapid ultrafiltration and hypertonic dialysate. Routine education on fall prevention is advised for patients undergoing dialysis, and those who have had a subdural hematoma may benefit from peritoneal dialysis or heparin-free dialysis.

Headache

Headaches that develop during at least half of hemodialysis sessions and resolve within 72 hours of dialysis are considered to meet criteria for hemodialysis-related headache according to the International Headache Society.[44] They are thought to result from water and electrolyte shifts during dialysis and resolve with renal transplantation.

Neuropathies

Peripheral mononeuropathies may be seen in association with dialysis, particularly median neuropathy at the wrist but also ulnar neuropathy. Carpal tunnel syndrome results from compression of the median nerve at the wrist and is characterized by numbness of the first three digits, with weakness and atrophy of the thenar muscles when severe. Patients on dialysis may be predisposed to developing this condition because of β_2-microglobulin–associated amyloid deposition or vascular access placement (explaining a higher prevalence on the side of vascular access for dialysis). β_2-Microglobulin–associated amyloidosis is observed in up to 90% of patients on long-term dialysis.[45] Motor and sensory dysfunction arising in the distribution of multiple peripheral nerves within hours of fistula construction suggests that an ischemic monomelic neuropathy has developed. It results from shunting of blood away from the distal regions of the arm leading to peripheral nerve ischemia. Patients with diabetes mellitus or severe peripheral vascular disease are predisposed to developing this complication.[46] Both anterior and posterior ischemic optic neuropathies have also been reported and are related to dehydration, hypotension, and anemia.[47,48]

Nephrogenic Systemic Fibrosis

In earlier years, gadolinium-based contrast agents were used liberally, even in patients with impaired renal function. In 2006, it was noted that some gadolinium-based contrast media were responsible for a "very late" adverse reaction (defined as occurring more than 7 days after exposure to the agent) that came to be called *nephrogenic systemic fibrosis*.[49–51] Earlier, this condition was called *nephrogenic fibrosing dermopathy*. The name was changed to nephrogenic systemic fibrosis after reports noted that, in addition to the skin, the liver, lungs, muscle, and heart may be involved. Dural calcification has also been reported.[52] Typically, nephrogenic systemic fibrosis begins with subacute-onset distal swelling, with subsequent induration that progresses proximally and is associated with erythema, pain, contractures, and limited mobility. The disease severity is variable and not necessarily related to dose of administered agent.[51] No cases of nephrogenic systemic

fibrosis have been reported in patients with a glomerular filtration rate higher than 60 mL/min. Patients at most risk include those with a glomerular filtration rate lower than 30 mL/min, those on dialysis, and those with acute renal failure.[51] In North America, the condition seems to have been eliminated by not using gadolinium-based contrast agents in patients with significantly reduced renal function.

CONCLUSION

This article illustrates the many clinical interrelationships between neurology and the kidney and highlights how primary renal dysfunction can be associated with a broad range of neurologic disorders that contribute to the morbidity and mortality of renal failure. Important advances have been made in recognition and understanding of several of these conditions, in some cases resulting in a reduced incidence of the complication. Neurologists and nephrologists should be familiar with the neurologic complications that develop in these patients because familiarity may provide opportunities for early intervention or even prevention.

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Gastroenterology and Neurology

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ABSTRACT

Purpose of Review: Just as gastrointestinal dysfunction may develop in the setting of neurologic disease, neurologic dysfunction may become evident in the setting of gastrointestinal disease. This article describes the range of neurologic features that have been described in three primary gastrointestinal diseases: celiac disease and gluten-related disorders, inflammatory bowel disease, and Whipple disease. Particular emphasis is placed on the controversial and evolving clinical picture of neurologic dysfunction in disorders of gluten sensitivity.

Recent Findings: Gluten-related disorders, including both the traditional autoimmune-based celiac disease and the more recently recognized nonautoimmune, nonallergic gluten sensitivity, have been the source of much attention in both medical and lay publications. The possible association between Crohn disease and neurologic disorders also is receiving attention. The recognition that, although Whipple disease is an exceedingly rare disorder, a surprising percentage of the population may be asymptomatic stool carriers of the causative organism makes it important to always be cognizant of the disorder.

Summary: The range of neurologic dysfunction in gastrointestinal diseases is broad and spans the spectrum from peripheral to central processes. Peripheral neuropathy, myopathy, myelopathy, cerebrovascular events, epilepsy, encephalopathy, and cerebellar dysfunction have all been described. Neurologists should be aware of the possibility that an underlying gastrointestinal disease process may be present in and responsible for the neurologic dysfunction that has prompted referral of an individual for evaluation.

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INTRODUCTION

The disciplines of neurology and gastroenterology have much more in common than often is realized. Much of gastrointestinal function is controlled by the enteric nervous system, a complex network of neurons that lines virtually the entire gastrointestinal tract and contains approximately 100 million neurons, a number comparable to the number of neurons in the spinal cord.[1] The neurons of the enteric nervous system employ a complex array of neurotransmitters that carry out its sensory, integrative, and motor functions. Although closely integrated with the central nervous system (CNS) via the autonomic nervous system, the enteric nervous system generates and controls many gastrointestinal functions independently, causing it sometimes to be labeled the *mini-brain*. The similarities in function between the enteric nervous system and CNS are mirrored in the setting of dysfunction in that gastrointestinal dysfunction may appear in neurologic diseases and neurologic dysfunction may become evident in gastrointestinal disease processes. It is this latter category of interaction that is addressed in this article. This article focuses on three distinct processes with which neurologic complications

have been particularly associated: celiac disease and gluten-related disorders, inflammatory bowel disease, and Whipple disease. For more information on the interface between gastroenterology and neurology, such as malabsorption syndromes and hepatic disease processes, refer to the articles "Nutrients and Neurology" by Neeraj Kumar, MD,[2] and "Liver Disease and Neurology" by Robert N. Schwendimann, MD, FAAN, and Alireza Minagar, MD, FAAN,[3] respectively, in this issue of *Continuum*.

CELIAC DISEASE AND NONCELIAC GLUTEN SENSITIVITY

What is now known as celiac disease was probably first described by Aretaeus of Cappadocia in the second century but given its modern name and description by Samuel Gee in 1887; it was first linked to wheat protein ingestion in 1952 by Willem Dicke, who had noted improvement of his patients with celiac disease during periods of bread shortage in the Netherlands during World War II and who later developed the gluten-free diet for the treatment of celiac disease.[4]

In recent years, it has been recognized that not all individuals displaying sensitivity to gluten ingestion develop the intestinal involvement that defines celiac disease and that the pathogenesis of involvement also is heterogeneous. This recognition has prompted the formation of a new consensus-based nomenclature and classification system for a spectrum of what are now termed *gluten-related disorders*.[5] Gluten-related disorders are now divided into three categories, each characterized by a different mode of pathogenesis (**Figure 6-1**).

Allergic Gluten-related Disorders

The first category, wheat allergy, is a classic allergic disorder in which IgE antibodies to wheat proteins trigger the release of histamine and other mediators from basophils and mast cells.[6] The most widely recognized form of wheat allergy is bakers' asthma, which is a respiratory allergy. Diagnosis is based on skin testing

KEY POINT

- The enteric nervous system contains approximately 100 million neurons, about the same number as the spinal cord.

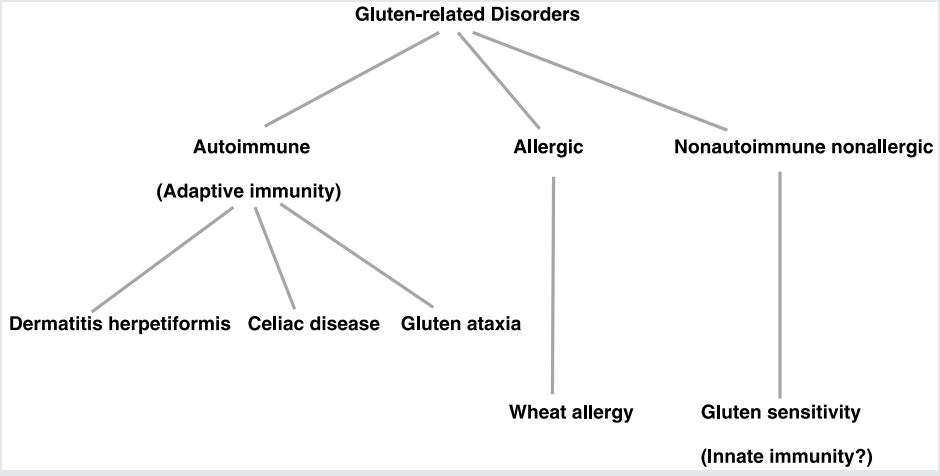

FIGURE 6-1 Classification of gluten-related disorders. Gluten-related disorders can be divided into three categories (autoimmune, allergic, and nonautoimmune nonallergic), each with a different mode of pathogenesis.

KEY POINTS

- Wheat allergy and other allergic gluten-related disorders are characterized by the presence of IgE antibodies.
- Celiac disease is an autoimmune enteropathy involving the adaptive immune system.
- The classic clinical features of celiac disease are diarrhea, malabsorption, weight loss, and gassy distension.

and the demonstration of specific IgE antibodies.[5]

Autoimmune Gluten-related Disorders

The second category, typified by celiac disease, is an autoimmune enteropathy involving the adaptive immune system in which individuals display the presence of gliadin-related IgA antibodies, such as antiendomysial and anti–tissue transglutaminase, along with evidence of damage to the small intestinal mucosa, characterized by the triad of villous atrophy, crypt hyperplasia, and increased epithelial lymphocytes. The classic clinical characteristics of celiac disease include the constellation of diarrhea, malabsorption, weight loss, and gassy distension (**Table 6-1**). The prevalence of celiac disease in the American population was estimated to be 0.71% but actually may be much higher.[7] Genetic factors are evident: 90% to 95% of individuals with celiac disease express genes encoding human leukocyte antigen (HLA)-DQ2 or HLA-DQ8.[8] The pathology of autoimmune gluten-related disorders, however, is not always limited to the gastrointestinal tract.

Dermatitis herpetiformis, characterized by a vesicular rash and cutaneous IgA deposits, is considered to be a dermatologic manifestation of celiac disease because enteral pathology, antiendomysial and anti–tissue transglutaminase antibodies, and gluten sensitivity also are evident.[9] A variety of other extraintestinal manifestations of celiac disease, such as osteoporosis and anemia, also occur. Neurologic manifestations have been described in the setting of celiac disease and are discussed in detail later in this article. In particular, the place of the entity now labeled *gluten ataxia* is addressed.

TABLE 6-1 Celiac Disease

▶ **Enteric Pathologic Features**
Villous atrophy
Crypt hyperplasia
Increased epithelial lymphocytes
▶ **Gastrointestinal Clinical Features**
Diarrhea
Malabsorption
Weight loss
Gassy distension
▶ **Neurologic Clinical Features That Have Been Described**
Peripheral neuropathy
Epilepsy
Headache
Other
Myopathy
Myelopathy
Myoclonus ataxia
Restless legs syndrome
Chorea
Paroxysmal nonkinesigenic dystonia
Pseudotumor cerebri

Nonallergic, Nonautoimmune Gluten-related Disorders

In the past decade, recognition has grown that there are individuals who experience apparent reactions to gluten, typically characterized by chronic diarrhea and abdominal pain, that seemingly are not characterized by either allergic or autoimmune mechanisms, thus constituting a third category of gluten-related dysfunction, which has now been christened *gluten sensitivity* (or *nonceliac gluten sensitivity*).[10]

Several double-blind placebo-controlled trials have documented improvement in symptoms of these individuals with the dietary exclusion of gluten.[11] The concept of gluten sensitivity also has exploded into the popular psyche and fostered a burgeoning industry for gluten-free foods that some have estimated will extend to 15% to 25% of consumers and reach $6.6 billion annually in the United States by 2017.[10] Gluten sensitivity is not accompanied by anti–tissue transglutaminase autoantibodies and small intestinal pathology typically is not evident,[12] but individuals do display a positive response to eliminating gluten from the diet. It has been suggested, although not proven, that the innate immune system, without involvement of the adaptive immune system, may play a role in the development of gluten sensitivity.[13] Individuals who have been identified as having gluten sensitivity may experience gastrointestinal symptoms similar to celiac disease, but extraintestinal symptoms, including neuropsychiatric, are more common.[5]

NEUROLOGIC MANIFESTATIONS OF GLUTEN-RELATED DISORDERS

A surprisingly broad array of neurologic disorders has been described in the various gluten-related disorders. Distinct differences between the groups in the character of the neurologic manifestations are emerging.

Allergic Gluten-related Disorders

Neurologic dysfunction is not part of the clinical presentation of wheat allergy in any of its modes of presentation.

Autoimmune Gluten-related Disorders

Neurologic dysfunction is not part of the clinical picture of dermatitis herpetiformis but is well described in the setting of celiac disease.

Celiac disease. Although nutritional deficiency secondary to malabsorption often is blamed for the development of neurologic dysfunction in the setting of celiac disease, immunologic mechanisms may be a more probable explanation in many instances. Cooke and Smith[14] provided the first detailed description of neurologic dysfunction in adult celiac disease, but many other reports have followed.

Some reports place neurologic dysfunction as occurring in up to 22.5% of individuals with celiac disease, although most describe a range of 6% to 13%.[15,16] The list of reported neurologic manifestations is extensive and includes peripheral neuropathy, myopathy, epilepsy, myelopathy, myoclonus ataxia, multiple sclerosis, neuromyelitis optica (NMO), headache, restless legs syndrome, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), chorea, paroxysmal nonkinesigenic dystonia, autonomic imbalance, pseudotumor cerebri, and others. Many of these descriptions are anecdotal case reports, but for some neurologic manifestations, more extensive (and sometimes more confusing) information is available.

Peripheral neuropathy. In one retrospective review, peripheral neuropathy accounted for 17% of the neurologic abnormalities present in a group of patients with celiac disease.[17] Another group of investigators identified chronic axonal sensorimotor neuropathy in 23% of 26 patients with celiac disease and abnormalities on neurophysiologic testing in 31%, despite the affected individuals being on gluten-free diets.[18] Sural nerve biopsy, when performed, may demonstrate the presence of axonal injury. In a large study using nationwide data on 28,232 patients with biopsy-proven celiac disease, a 2.5-fold increase in the development of peripheral neuropathy was seen compared with controls.[19] In most individuals

KEY POINTS

- Gluten sensitivity disorders are not accompanied by anti–tissue transglutaminase antibodies and typically do not display small intestinal pathology.
- The innate immune system may be involved in gluten sensitivity disorders.
- Allergic gluten-related disorders do not display neurologic manifestations.
- Neurologic dysfunction may appear in up to 22.5% of persons with celiac disease.
- Individuals with celiac disease have a 2.5-fold increased risk of developing peripheral neuropathy.

KEY POINT

- Purkinje cell loss and lymphocytic infiltration in the cerebellum has been described in gluten ataxia.

in that study, the specific type of neuropathy was not documented, but in those for whom it was, an increased risk of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), autonomic neuropathy, and mononeuritis multiplex was present. In another study, peripheral neuropathy accounted for 30% of the neurologic manifestations of celiac disease in a group of 228 patients; a sensorimotor axonal length-dependent symmetric neuropathy was evident in 80% of the affected individuals, and a sensory ganglionopathy was present in 20%.[20]

Epilepsy. Whether an association exists between celiac disease and epilepsy has been a focal point for controversy. Some investigators have reported an increased prevalence of celiac disease in persons with epilepsy, but others have not.[21] A syndrome consisting of epilepsy, bilateral occipital calcification, and celiac disease has been described, primarily (but not exclusively) by Italian investigators.[22] Another syndrome, consisting of the combination of refractory celiac disease, ataxia, and cortical myoclonus sometimes progressing to epilepsy and even myoclonic status epilepticus, also has been described.[23]

Headache. In children and adolescents with recurrent headache, the prevalence of celiac disease is almost twice that expected in the comparable general population.[24] In a study of 90 adults with migraine, 4.4% were diagnosed with celiac disease, compared with only 0.4% of blood donor controls.[25] Abnormalities of regional cerebral blood flow and headache severity both improved with institution of a gluten-free diet.

Gluten ataxia. Ataxia is the neurologic complication that has received the most interest and attention in the setting of celiac disease and gluten-related disorders. Although first described in 1966,[14] the current concept of gluten ataxia has largely been developed and shaped by Hadjivassiliou and colleagues.[15] In 1996, they published the first of an ongoing series of reports that delineated the presence of antigliadin antibodies in individuals with sporadic adult-onset ataxia of unknown etiology and proposed the name *gluten ataxia* for the condition. Subsequently, they have collected a series of approximately 800 patients with adult-onset progressive ataxia and documented the presence of serologic evidence of gluten sensitivity in 23% (148 of 635) of the individuals tested.[5]

The clinical characteristics of gluten ataxia are not particularly distinctive or diagnostic. Both gait and limb ataxia are evident in most individuals; dysarthria and nystagmus also are often present. The mean age at onset of symptoms is 53,[15] although the range of symptom onset extends from 30 to 60 years of age.[26] Cerebellar atrophy and white matter abnormalities are often evident on MRI. Autopsy examination in several affected individuals has demonstrated Purkinje cell loss and lymphocytic infiltration within the cerebellum and posterior columns of the spinal cord.[27] The classic gastrointestinal symptoms of celiac disease are present in only a minority of individuals with gluten ataxia. In fact, gastrointestinal symptoms become evident in less than 10% of patients,[28] and evidence of classic celiac disease is found on duodenal biopsy in only 25% to 33% of individuals with gluten ataxia.[15,29]

Although gluten ataxia is considered to be an autoimmune disorder like celiac disease itself, the most frequent antibodies identified are not the anti–tissue transglutaminase 2 or antiendomysial antibodies typically

seen in celiac disease but rather anti–tissue transglutaminase 6 antibodies that appear to be directed against cerebellar Purkinje cells. Measurement of anti–tissue transglutaminase 6 antibodies is not readily available, but antigliadin antibodies (IgG or IgA) are present in approximately 23% to 47% of individuals with gluten ataxia, compared with approximately 12% of healthy controls.[5,15] The presence of these antigliadin antibodies in a significant percentage of the general population diminishes their usefulness as a screening tool for gluten ataxia, but at the present time their presence is the best screening aid to suggest further investigation. However, many laboratories no longer perform this test since the newer assays (eg, anti–tissue transglutaminase 2, antiendomysial, deamidated gliadin antibodies) are superior for diagnosing celiac disease in which enteric involvement is present. However, the newer assays typically are negative in patients without enteropathy. Therefore, the best screening approach might be to include all available serologic testing (anti–tissue transglutaminase 2, anti–tissue transglutaminase 6, antiendomysial, deamidated gliadin, and antigliadin) in individuals suspected of having gluten-related disorders.[20]

Some, although not all, individuals diagnosed with gluten ataxia respond favorably to a gluten-free diet, as illustrated in **Case 6-1**. When a diagnosis is made and a gluten-free diet initiated early, patients are more likely to show a response; patients with long-standing symptoms may have sustained irreversible damage.[5] IV immunoglobulin (IVIg) therapy also may be effective in reducing cerebellar ataxia in some individuals with antigliadin antibodies.[30]

One additional note regarding the classification of gluten ataxia seems in order. Despite the publication of the consensus on nomenclature and classification of gluten-related disorders,[5] the proper classification of gluten ataxia continues to be an issue for researchers and authors. Some authors still define gluten sensitivity/nonceliac gluten sensitivity as "the clinical term used to describe [gastrointestinal] and/or extraintestinal symptoms associated with gluten ingestion that resolve with gluten exclusion when [celiac disease] and [wheat allergy] have been properly ruled out,"[11] which is slightly different from the definition used by the authors of the consensus. Other authors assert that "gluten ataxia is better classified as nonceliac gluten sensitivity than as celiac disease,"[26] despite the fact that the consensus publication clearly lists gluten ataxia as a disorder distinct from celiac disease but still an autoimmune disorder, in contrast to gluten sensitivity (or nonceliac gluten sensitivity), which is considered to be nonautoimmune and nonallergic in origin. This apparent nomenclatorial fuzziness will not be solved here, but rather awaits further study and better diagnostic tools. Nevertheless, it is important to be aware of it when reviewing the literature.

KEY POINTS

- Anti–tissue transglutaminase 6 antibodies have been described in gluten ataxia.
- Patients with gluten ataxia may respond to a gluten-free diet.

Nonautoimmune, Nonallergic Gluten-related Disorders

The concept that individuals can experience neurologic and other symptoms related to gluten that are of neither allergic nor conventional autoimmune origin is receiving increasing attention but remains controversial. The term *gluten sensitivity* is usually applied to these disorders.

Gluten sensitivity. The spectrum of neurologic symptoms and dysfunction described in the setting of gluten sensitivity is broad and differs in some respects from that described in celiac

KEY POINT

- Various neuropsychiatric symptoms may be present in individuals with gluten sensitivity.

Case 6-1

A 55-year-old man first noted the onset of progressive gait unsteadiness at age 50. Over time, the ataxia gradually became more prominent, dysarthria developed, and incoordination of the upper extremities also emerged. His family history was negative. Neurologic examination demonstrated nystagmus, dysarthria, impaired upper extremity coordination, and gait ataxia. No parkinsonian features were evident, nor was autonomic dysfunction present. Extensive laboratory studies looking for treatable causes of sporadic adult-onset ataxia were negative, including antiendomysial and anti–tissue transglutaminase antibody titers. However, antigliadin antibodies were present. On a gluten-free diet, the patient showed gradual partial resolution of his cerebellar dysfunction.

Comment. In patients being evaluated for adult-onset progressive ataxia without any obvious family history, the possibility of gluten ataxia should be considered. In these individuals, antiendomysial and anti–tissue transglutaminase antibodies will typically be negative and intestinal pathology also absent. However, the presence of antigliadin antibodies points toward a diagnosis of gluten ataxia, which may be responsive to institution of a gluten-free diet, especially if initiated early in the course of the disorder.

disease. In one study of 334 patients with gluten sensitivity, the most frequent neurologic manifestations were peripheral neuropathy, ataxia, and encephalopathy.[20] Of these, peripheral neuropathy was the most common, present in 54% of those with neurologic manifestations. Less frequently appreciated problems included myopathy, myelopathy, stiff person syndrome, chorea, myoclonic ataxia, and epilepsy. A variety of vague neuropsychiatric symptoms has been described in the setting of gluten sensitivity, including a "foggy mind," tiredness, fatigue, headaches, loss of balance, and numbness.[11] Psychiatric dysfunction may also be part of the clinical picture. Depression has been described in individuals with gluten sensitivity.[31] An association between schizophrenia and celiac disease, with improvement in symptoms when placed on a gluten-free diet, was championed by Dohan as early as the 1960s,[32] and again described more recently with gluten sensitivity.[33] An increased prevalence of anti–tissue transglutaminase 6 antibodies has been demonstrated in individuals with schizophrenia, which might signify that such individuals may be better categorized as having an autoimmune gluten-related disorder rather than gluten sensitivity.[34]

INFLAMMATORY BOWEL DISEASE

Crohn disease (regional enteritis, granulomatous colitis) and ulcerative colitis are the most widely recognized members of the inflammatory bowel disease family. Both are characterized by a dysregulated mucosal immune response to antigens normally present within the intestinal lumen and thus are considered to be autoimmune disease processes.[35,36] Genetic factors also are active, as exemplified by the identification of the *NOD2/CARD15* gene, which is involved in the immune detection of bacterial products, as a susceptibility gene for Crohn disease.[37] Although grouped together as inflammatory bowel diseases, Crohn disease and ulcerative colitis are distinct disease processes that

display definite differences in their clinical features and pathologic profiles (**Table 6-2**). Neurologic dysfunction has been described in both. The pathogenesis probably is diverse, with immune, prothrombotic, and nutritional deficiency mechanisms all playing a role. Neurologic complications of the medical management of these disorders are another potential source of dysfunction. Because reported studies often include patients with both disorders, the two are grouped together in the discussion that follows, rather than discussed separately.

Clinical Features

Urgent, bloody diarrhea is the clinical hallmark of ulcerative colitis. It follows a course marked by exacerbations and remissions. It is characterized by diffuse inflammation of the mucosa and superficial submucosa of the colon, Unlike Crohn disease, the pathology in ulcerative colitis remains confined to the colon, although the distance it extends proximally from the rectum can vary widely.

Abdominal pain and nonbloody less urgent diarrhea, often accompanied by weight loss, characterize Crohn disease. Unlike ulcerative colitis, the pathology in Crohn disease extends deeply and often transmurally, leading to scarring and stricture formation that can result in fistula formation and partial intestinal obstruction. Noncaseating granulomas may be present. Also in marked contrast to ulcerative colitis, Crohn disease is not confined to the colon and may involve the entire gastrointestinal tract, although it most frequently involves the distal small intestine and proximal colon. Both disorders typically follow a course of exacerbations and remissions.

A broad range of extraintestinal involvement may occur in individuals

TABLE 6-2 Inflammatory Bowel Disease

▶ **Pathologic Features**
Ulcerative colitis
Diffuse inflammation of the mucosa and submucosa
Limited to the colon
Crohn disease
Deep, often transmural, inflammation
Noncaseating granulomas may be present
Scarring and stricture formation
Fistula formation
Partial intestinal obstruction
May involve the entire gastrointestinal tract
From mouth to anus
▶ **Gastrointestinal Features**
Ulcerative colitis
Exacerbations and remissions typical
Urgent, bloody diarrhea
Nausea and anorexia
Weight loss
Abdominal pain usually not prominent
Crohn disease
Exacerbations and remissions typical
Nonbloody, less urgent diarrhea
Weight loss
Abdominal pain prominent
Anal and perianal lesions and fistulas
Intestinal stricture formation

KEY POINT

- The pathology of ulcerative colitis is confined to the colon; Crohn disease may involve the entire gastrointestinal tract.

KEY POINTS

- The reported presence of neurologic dysfunction in inflammatory bowel disease ranges from 0.25% to 37.5%.
- Peripheral neuropathy is the most frequent manifestation of neurologic involvement in inflammatory bowel disease.

with inflammatory bowel disease, including various musculoskeletal, mucocutaneous, ocular, hepatobiliary, pancreatic, pulmonary, renal, and hematologic manifestations, with a reported frequency ranging from 6% to 47%.[38] Some of the extraintestinal manifestations, such as involvement of joints, skin, mouth, and eyes, correlate with active colonic inflammation and may develop in both Crohn disease and ulcerative colitis. Others, such as gallstones and renal calculi, are the consequence of small intestinal involvement and, thus, primarily limited to Crohn disease.

Neurologic Manifestations

In comparison with many of the systemic manifestations of inflammatory bowel disease, neurologic involvement is less frequent. The frequency with which neurologic involvement occurs is not entirely clear. Lossos and colleagues reported the presence of neurologic involvement in 3% of 638 persons they studied with either ulcerative colitis or Crohn disease.[39] However, in other reports, the prevalence ranges from 0.25% to 37.5%.[40] Neurologic impairment may appear during periods of disease activity or during disease quiescence. Neurologic involvement may take the form of peripheral neuropathic, neuromuscular, myelopathic, cerebrovascular, encephalopathic, or other manifestations (**Table 6-3**).[41]

Peripheral neuropathy. The peripheral nervous system is the most frequent site of neurologic dysfunction in ulcerative colitis and Crohn disease, present in 31.5% of patients who were neurologically affected in one study.[39] An extensive array of peripheral neuropathic processes has been described in the setting of inflammatory bowel disease. The frequency with which they occur has been the subject of some disagreement, with estimates ranging from 0% to 39%.[42] Both axonal and demyelinating processes occur

TABLE 6-3 Neurologic Dysfunction in Inflammatory Bowel Disease

▶ **Peripheral Nervous System**
Axonal sensorimotor neuropathy
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
Mononeuropathy
Brachial plexopathy
Mononeuritis multiplex
Multiple compressive neuropathies
Neuropathy due to nutritional deficiency
Cranial neuropathies
Acute sensorineural hearing loss
Melkersson-Rosenthal syndrome
▶ **Muscle and Myoneural Junction**
Myopathy
Myasthenia gravis
▶ **Central Nervous System**
Cerebrovascular disease
Arterial thromboembolic infarction
Dural and cortical venous thrombosis
Vasculitis
Myelopathic disease
Seizures
Diffuse encephalopathy
Cerebral vasculitis

and may be either acute or chronic. Mononeuropathy, brachial plexopathy, mononeuritis multiplex, multiple compressive neuropathies, and cranial neuropathies also have been described.

Gondim and colleagues, in an initial retrospective study of 18 patients with Crohn disease and 15 with ulcerative colitis who had developed peripheral neuropathy with no other identifiable etiology, found the neuropathy to be demyelinating in nature in slightly under 30% of the patients, small or large fiber axonal sensory in about 30%, and large fiber axonal sensorimotor in approximately 40%.[43] In a nested case-control study within an ongoing prospective cohort study, the same research group reported that the risk of developing a large fiber neuropathy was 5 times that of the control group for patients with ulcerative colitis and 7.4 times greater for patients with Crohn disease.[44] In another report from the same study, 12.4% of the 121 patients with either Crohn disease or ulcerative colitis had small fiber neuropathy and 19.8% had large fiber damage.[45]

The pathophysiologic basis for peripheral neuropathy in the inflammatory bowel diseases likely is multifactorial. Nutritional factors, particularly vitamin B_{12} deficiency secondary to impaired absorption, are responsible in some instances; an autoimmune basis is likely in others. Both axonal and demyelinating neuropathies may respond to immunotherapy; the response is more consistent and robust in patients with demyelinating neuropathy.[43]

More localized peripheral neuropathic processes may also appear; two processes involving cranial nerves are particularly noteworthy. Melkersson-Rosenthal syndrome is characterized by the clinical constellation of recurrent facial nerve palsy, intermittent orofacial swelling, and fissuring of the tongue (lingua plicata) and has been reported in the setting of Crohn disease. The fact that the pathology of both includes noncaseating granuloma formation has led some to suggest that Crohn disease and Melkersson-Rosenthal syndrome may be part of the same pathologic spectrum.[46] In ulcerative colitis, acute sensorineural hearing loss, presumably on an autoimmune basis, has been described. The presumption of an autoimmune basis for the hearing loss is based, in part, upon reported responses to steroid administration. Chronic subclinical hearing loss may also develop in ulcerative colitis.

Neuromuscular dysfunction. Myopathy accounted for 16% of the cases of neurologic dysfunction in the context of inflammatory bowel disease in the series compiled by Lossos and colleagues.[39] A variety of processes have been reported, including dermatomyositis, polymyositis, rimmed vacuole myopathy, and granulomatous myositis. Localized myopathic involvement, such as orbital myositis and gastrocnemius myalgia syndrome, also has been described. Myopathic involvement most likely is autoimmune in origin and primarily, although not exclusively, appears during periods of gastrointestinal disease activity. Anecdotal reports of the development of both ocular and generalized myasthenia gravis in the setting of Crohn disease and ulcerative colitis exist; however, the occurrence is rare.

Myelopathy. Chronic, slowly progressive myelopathy is yet another neurologic manifestation of inflammatory bowel disease, accounting for 5 of 19 of the patients with neurologic involvement in the series of Lossos and colleagues.[39] An association between multiple sclerosis and inflammatory bowel disease has been reported. In a large epidemiologic study using the US Department of Defense Military Health System database, both

KEY POINT

- Cerebrovascular events, both arterial and venous, are uncommon but potentially devastating neurologic manifestations of inflammatory bowel disease.

ulcerative colitis and Crohn disease were more common in the multiple sclerosis cohort than in the non–multiple sclerosis cohort, with elevated event risk ratios of 2.0 and 1.9, respectively.[47] Myelopathy as a consequence of spinal epidural abscess secondary to fistula formation or abdominal abscess has been the object of multiple case reports.[39,48,49] Transverse myelitis has been reported in an individual with ulcerative colitis and Jo-1 antibody (antisynthetase) syndrome, but whether this was causal or coincidental is uncertain.

Cerebrovascular disease. In one large study, vascular complications were documented in 1.3% of 7199 patients with either Crohn disease or ulcerative colitis.[50] Most of these did not involve the nervous system, but cerebrovascular events did account for almost 10% of the total vascular complications (9 of 92 patients). Cerebrovascular disorders have been reported in 0.12% to 4% of individuals with inflammatory bowel disease.[41] Elevations of factors V and VIII and fibrinogen along with decreased antithrombin III have been noted, suggesting that hypercoagulability is responsible for the thromboembolic events. Elevations of anticardiolipin antibodies, thrombopoietin levels, and homocysteine levels also have been documented in individuals with ulcerative colitis and Crohn disease. Although these elevations do not necessarily correlate with increased risk of thromboembolic events, such events are known to occur, as illustrated in **Case 6-2**.

Both arterial and venous events may occur in patients with inflammatory bowel disease. Younger persons seem to be at greater risk for arterial thrombosis. Both large artery and lacunar infarcts have been described. Responses to both immunosuppressive therapy (corticosteroids and azathioprine) and anticoagulation suggest that both hypercoagulable and autoimmune processes may be operative in different individuals, but additional factors, such as dehydration or immobility, may play a role in some individuals.[41,51] Cerebral vasculitis, presumably on an autoimmune basis, has been identified in both Crohn disease and ulcerative colitis; the development of cerebral vasculitis does not correlate with the severity of bowel involvement.[52]

Cerebral venous sinus thrombosis (both dural and cortical) may occur in 0.5% to 7.5% of individuals with inflammatory bowel disease, most often during periods of disease activity.[53,54] Headache is the most frequent clinical feature, although focal signs, seizures, and encephalopathy also are reported.[54] A hypercoagulable state is presumed to be present, but thrombophilic risk factors are not always identified.[54]

Seizures and encephalopathy. Seizures may occur as a complication of the medical and surgical management of inflammatory bowel disease. Whether they occur as a complication of the disease process itself is less clear.[41] All types of seizures have been reported, including status epilepticus.

Diffuse encephalopathy with altered consciousness may develop in individuals with ulcerative colitis or Crohn disease. Both cerebral vasculitis and nutritional deficiencies, including both vitamin B_{12} and thiamine deficiencies, have been identified as being responsible.

Posterior reversible encephalopathy syndrome (PRES) has been reported in the setting of acute exacerbation of ulcerative colitis[55] and following sepsis in Crohn disease.[56] PRES may be related to immunosuppressive treatment rather than to the disease process itself.

Other neurologic manifestations. Restless legs syndrome was documented to be present in 30% of 272 patients

Case 6-2

A 28-year-old right-handed graduate student who had been a healthy two-sport athlete in high school with a negative past medical history except for a diagnosis of psoriasis began to experience increasingly prominent abdominal and back pain, along with intermittent diarrhea. Repeated visits to the student health clinic resulted in a diagnosis of irritable bowel syndrome, but his symptoms did not improve when treatment was instituted; progressive weight loss that eventually reached 40 pounds ensued. Recurrent leg and foot cramping also became increasingly prominent. He was referred for further gastroenterology evaluation, and subsequent colonoscopy and biopsy confirmed a diagnosis of Crohn disease. Shortly thereafter, he developed flulike symptoms with a fever of 40°C (104°F) and began to experience shortness of breath with hemoptysis. He then developed left hemiparesis and hemisensory deficit, which resolved within 1 hour but prompted hospitalization. MRI of the brain was normal, but lung scan demonstrated multiple pulmonary emboli. Further workup identified deep venous thrombosis in the legs, and laboratory studies demonstrated the presence of antiphospholipid antibodies, but no conclusive determination could be made whether the transient episode of neurologic dysfunction was due to an embolic source or to the hypercoagulable state.

Comment. Crohn disease can be accompanied by a hypercoagulable state with the presence of antiphospholipid antibodies, which leads to an increased risk for peripheral vascular and cerebrovascular events. In a young person who experiences a cerebrovascular event, the possibility of inflammatory bowel disease should be considered in the differential diagnosis, especially if the individual also has a history of gastrointestinal symptomatology.

with Crohn disease, compared with 9% of a spousal control group.[57] The presence of restless legs syndrome did not correlate with current iron deficiency, although patients with a history of iron deficiency anemia had a higher likelihood of having restless legs syndrome than individuals without such a history. Migraine is frequently present in patients with ulcerative colitis or Crohn disease but has been the subject of few actual studies.[58] Sleep disturbances and fatigue also are common.

The potent medications used to manage inflammatory bowel disease can sometimes produce varied and serious neurologic adverse effects.[41] Monoclonal antibodies directed against tumor necrosis factor-α (eg, infliximab, adalimumab), in particular, have been linked to such problems. The list of neurologic adverse effects that have been associated with these drugs in individuals with inflammatory bowel disease and in others is large. Both AIDP and CIDP have been described, as has Miller Fisher syndrome, multifocal motor neuropathy with conduction block, axonal sensory neuropathy, and mononeuritis multiplex.[40] Use of the anti-α4 integrin antibody drug natalizumab in patients with inflammatory bowel disease has been limited because of the risk of producing progressive multifocal leukoencephalopathy; however, a newer agent, vedolizumab, does not appear to confer the same risk.[59] Older drugs, such as sulfasalazine, also can produce neurologic complications, primarily in the form of peripheral neuropathy.

KEY POINTS

- Whipple disease is a multisystem disorder and not simply a gastrointestinal disease.
- Whipple disease is caused by *Tropheryma whippleii*, an Actinobacteria that may dwell in the soil.
- Postmortem examination demonstrates central nervous system involvement in over 90% of patients with Whipple disease, many of whom have no neurologic symptoms.
- Oculomasticatory myorhythmia develops in 20% of patients with Whipple disease and is pathognomonic for the disorder.

WHIPPLE DISEASE

Initially described as a chronic gastrointestinal disorder, Whipple disease is now recognized as a multisystem disorder in which joint, dermatologic, lymphatic, cardiac, pulmonary, ocular, and neurologic involvement may occur (**Table 6-4**).[60] Diarrhea, weight loss, and abdominal pain constitute the classic gastrointestinal features of Whipple disease. However, migratory polyarthritis, generalized lymphadenopathy, anemia, fever, generalized malaise, chronic cough, pseudoaddisonian skin pigmentation, congestive heart failure, hypotension, pericardial friction rub, splenomegaly, focal glomerulitis, uveitis, retinitis, and a variety of neurologic manifestations may also develop.[60,61]

The mean age of symptom onset in Whipple disease is 55.[62] It is much more frequent in men than in women, although the male to female ratio has dropped in recent years from 8:1 down to 4:1 to 5:1.[60] The reported prevalence of Whipple disease is approximately three per million.[63] The organism responsible for Whipple disease, *Tropheryma whippleii*, is an Actinobacteria and may be a soil-dwelling organism, which might explain the apparent increased incidence of infection in farmers.[62] Although Whipple disease is very rare, the number of individuals in the general population in France who were asymptomatic stool carriers of *T. whippleii* was a surprising 4% and was even higher in sewage workers (12% to 26%) and homeless people (13%); in other studies in countries in Africa, the carrier rate was 10% to 17% in adults and up to 75% in children.[64] It also is now recognized that *T. whippleii* infection can produce an acute self-limited gastroenteritis.[62] All of this would seem to indicate that exposure alone is not sufficient to produce Whipple disease, but host factors also are important.

TABLE 6-4 Neurologic Features of Whipple Disease

▶ **Cognitive Impairment**
▶ **Psychiatric Dysfunction**
▶ **Hypothalamic Dysfunction**
Sleep disturbances
Hyperphagia
Polydipsia/polyuria
▶ **Oculomasticatory Myorhythmia/ Oculofacioskeletal Myorhythmia**
▶ **Seizures**
▶ **Ataxia**

Neurologic features. CNS involvement is common in Whipple disease. Postmortem examination reveals CNS involvement in over 90% of patients with Whipple disease, and clinical involvement becomes evident in 10% to 43%.[60,65] Neurologic dysfunction may be the presenting feature in approximately 5% of persons with Whipple disease.[65]

The most frequently occurring neurologic changes in Whipple disease are neuropsychiatric in character, with cognitive, psychiatric, or behavioral changes evident in up to 71% of individuals.[66] Vertical gaze impairment develops in approximately 50% of patients,[66] and cerebellar ataxia is apparent in up to 45% of patients.[67] Hypothalamic involvement also may occur. Peripheral neuropathy has been reported in Whipple disease but may be due to nutritional deficiencies as a consequence of malabsorption, rather than to direct involvement (**Table 6-4**).[66]

Approximately 20% of individuals with CNS Whipple disease develop

oculomasticatory myorhythmia (see video from Revilla and colleagues[68] for an example of oculomasticatory myorhythmia), a unique type of involuntary movement that appears to be pathognomonic for Whipple disease.[69] Pendular convergence nystagmus with concurrent slow, rhythmic synchronous contractions of the masticatory muscles, invariably accompanied by a supranuclear vertical gaze paresis, are the hallmarks of oculomasticatory myorhythmia. Involvement of the extremities may also be evident, prompting use of the term oculofacioskeletal myorhythmia.

Disordered sleep may become evident in CNS Whipple disease. Both severe insomnia and hypersomnia have been described, presumably secondary to thalamic or hypothalamic involvement.[70] Spinal segmental myoclonus involving the trunk and arms has also been reported in a patient with Whipple disease.[71] Episodic uncontrollable sleepiness, including multiple episodes of falling asleep in the shower, that persisted for up to 48 hours with worsened myoclonus while asleep also occurred in this individual. Sudden sleep attacks have also been reported by others.

Obstructive hydrocephalus, presenting with headache and vomiting initially but later with additional neurologic features, also has been reported in the setting of Whipple disease, presumably secondary to ependymal accumulations of bacteria producing an inflammatory stenosis of the sylvian aqueduct.[72]

The diagnosis of Whipple disease has classically been based on the identification of periodic acid-Schiff (PAS)-positive inclusions in macrophages present in duodenal biopsy specimens. The development of *T. whippleii*–specific immunochemistry and polymerase chain reaction (PCR) analysis has proven to be very useful in confirming the diagnosis.[62] Because of the presence of asymptomatic CNS involvement in approximately 50% of persons in whom Whipple disease has been diagnosed, PCR assessment of CSF is recommended in all diagnosed individuals.[62]

Prompt diagnosis of Whipple disease is important, but because it is so rare, it is difficult to know when to initiate testing for the disorder. However, individuals with chronic abdominal pain and diarrhea of undetermined etiology who also develop neurologic and other systemic features should be considered for testing, especially if the neurologic features include neuropsychiatric and oculomotor dysfunction.

Current treatment recommendations include a 2-week induction treatment period with IV ceftriaxone followed by a 12-month course of oral trimethoprim-sulfamethoxazole.[62] A prolonged clinical remission rate of over 90% has been reported with this regimen. The prolonged course of trimethoprim-sulfamethoxazole, which crosses the blood-brain barrier, is intended to treat potential or identified CNS involvement. This is especially important since CNS relapses have a poor prognosis and high mortality rate.

KEY POINT

- Prolonged 1-year antibiotic treatment of Whipple disease is necessary to prevent relapse.

CONCLUSION

Just as gastrointestinal dysfunction can arise in the setting of neurologic diseases, neurologic dysfunction can appear in the setting of gastrointestinal disease processes, of which this article has highlighted several important examples. In celiac disease, a broad array of neurologic manifestations has been described. Gluten ataxia appears to be a separate disorder within the realm of autoimmune gluten-related disorders, since there may be no associated gastrointestinal pathology. In recent years, the concept of gluten-related disorders has been greatly expanded

and the term *gluten sensitivity* coined to categorize disorders that often consist of somewhat vague neurologic or neuropsychiatric symptoms responsive to institution of a gluten-free diet. Much remains to be learned about these controversial disorders, but it is important for neurologists to be aware of their presence. Neurologic dysfunction also may develop in the setting of inflammatory bowel disease. As with the gluten-related disorders, a variety of neurologic manifestations have been described and may appear both during periods of active gastrointestinal symptomatology and during periods of symptom quiescence. Whipple disease is now recognized as a multisystem disorder, and CNS involvement with neurologic manifestations is an important part of the clinical picture. Although it is a rare disorder, continued awareness of its potential neurologic manifestations is important for the neurologist because Whipple disease is a disorder for which effective treatment is readily available.

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Liver Disease and Neurology

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ABSTRACT

Purpose of Review: Neurologists often encounter patients with acute and chronic liver disease and must be aware of how these diseases can affect the nervous system. This is particularly true when evaluating patients with alterations in cognition and level of consciousness. Wilson disease, while uncommon, is a treatable condition with many neurologic and psychiatric symptoms. Neurologic disorders associated with liver disease may affect not only the brain, but also the spinal cord and peripheral nervous system. This article reviews the association of liver disease and the nervous system and provides new information regarding diagnostic and therapeutic approaches to evaluating patients with liver diseases.

Recent Findings: Early recognition of hepatic encephalopathy may be possible using a combination of clinical suspicion and various neuropsychological studies. Management of severe hepatic encephalopathy from acute liver failure is important to neurologists involved in neurocritical care. Next-generation genetic testing may aid in the diagnosis of patients suspected of having Wilson disease. The relationship of numerous neurologic findings from hepatocerebral degeneration and from viral hepatitis is more widely recognized.

Summary: It is important for neurologists to recognize the neurologic symptoms that may occur in patients with acute and chronic liver failure, Wilson disease, and viral hepatitis to inform prompt diagnostic and management decisions.

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INTRODUCTION

Liver disease, both acute and chronic, is a worldwide cause of hospitalization that causes significant morbidity and mortality. Chronic liver disease has many causes but is most frequently related to alcoholism, infectious (viral) causes, exposure to toxins (eg, acetaminophen), and nonalcoholic liver disease; these conditions lead to liver fibrosis, structural changes in hepatic cytoarchitecture, and, ultimately, cirrhosis. In the United States, liver disease is the 12th leading cause of death.[1] The neurologic and psychiatric effects of Wilson disease should be recognized as early as possible since proper treatment can prevent significant progression of the disease. Hepatocerebral degeneration can produce symptoms very similar to Wilson disease and should be recognized by consulting neurologists. Hepatitis C has become a common cause of hepatic disease and may affect large numbers of the general population. Numerous neurologic symptoms may be associated with chronic hepatitis C infection. Emerging forms of viral hepatitis that in the past have affected populations in undeveloped countries are recognized more frequently in developed countries.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is typically defined as "brain dysfunction caused by liver insufficiency and/or portosystemic

shunting''[2]; it manifests as a wide spectrum of neurologic and psychiatric abnormalities ranging from subclinical alterations to coma. This problem can be related to acute liver failure (type A), portosystemic shunting in the absence of intrinsic liver disease (type B), or chronic disease from cirrhosis and portal hypertension (type C).[3] The most useful scale to determine the stage of hepatic encephalopathy is the West Haven criteria, which divide hepatic encephalopathy into four grades (**Table 7-1**).[3] Another classification system endorsed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) divides the stages of hepatic encephalopathy into normal, covert (minimal hepatic encephalopathy), and overt encephalopathy (**Table 7-1**).[4]

Portal hypertension results in shunting of blood from the portal veins into the systemic circulation. As a result, toxins that are usually cleared by the liver become elevated in the systemic circulation and may cross the blood-brain barrier. Elevated ammonia and glutamate levels and changes in glutamine metabolism in the liver have been strongly implicated in the etiology of hepatic encephalopathy. In the brain, Alzheimer type II astrocytes play a role in detoxification of ammonia, converting glutamate to glutamine by glutamine synthetase. Glutamine accumulation within the cell acts as an osmotic agent that subsequently leads to astrocyte swelling, oxidative failure, and mitochondrial malfunction.[5]

The major challenge to neurologists is in identifying the patient with minimal or covert hepatic encephalopathy, which occurs in 20% to 80% of patients with cirrhosis.[3] Proper identification of these individuals may lead to early therapy that can prevent the progress of the encephalopathy and affect the long-term prognosis of the liver disease. Laboratory studies that typically are helpful in patients with more advanced stages of encephalopathy may be of little help in the patient who is cognitively normal or who manifests only minimal hepatic encephalopathy. Blood ammonia levels may be normal in this group of patients. Imaging studies likewise are of little help.

The EEG has been used in the diagnosis of encephalopathies of various etiologies. Frontal slowing in the delta range of 1 Hz to 3 Hz and the presence of triphasic waves has been associated with hepatic encephalopathy, although these patterns are not specific for hepatic encephalopathy (**Case 7-1**). Various grading systems have been proposed based on the degree of slowing, which worsens as the stage of the encephalopathy progresses. The use of computerized EEG analysis can more accurately detect subtle changes in EEG rhythms and is helpful in identifying patients who manifest minimal encephalopathy. Despite the frequent use of EEG as a diagnostic tool in evaluating hepatic encephalopathy, it is of limited use in evaluating patients with minimal disease. However, EEG is useful for following a patient's progress; alterations of EEG patterns are indicative of increased risk of overt encephalopathy and death.[6]

Critical flicker fusion has been described in studies as a technique in which pulses of light that gradually decrease in frequency are presented to subjects. The person is asked to respond when the impression of fused light changes to flickering light. Several trials are given, and the mean of the trials is expressed as critical flicker fusion. This value is reported to be of prognostic value with regard to the development of overt encephalopathy and mortality.[7]

KEY POINTS

- Hepatic encephalopathy has a wide spectrum of neurologic and psychiatric symptoms ranging from subclinical alterations to coma.
- Hepatic encephalopathy can be caused by acute liver failure, portosystemic shunting with intrinsic liver disease, or chronic liver disease related to cirrhosis and portal hypertension.
- The West Haven criteria for staging of clinical symptoms are a useful way to determine the severity of hepatic encephalopathy. Simpler scales divide hepatic encephalopathy into covert and overt forms.
- Laboratory studies that typically are helpful in patients with more advanced stages of encephalopathy may be of little help in the patient who is cognitively normal or who manifests only minimal hepatic encephalopathy.
- The presence of triphasic waves on EEG recording may be seen in numerous types of metabolic encephalopathies.

TABLE 7-1 West-Haven Criteria for Clinical Manifestations of Hepatic Encephalopathy[a]

West Haven Criteria	International Society for Hepatic Encephalopathy and Nitrogen Metabolism	Description	Suggested Operative Criteria
Unimpaired		No encephalopathy and no history of hepatic encephalopathy	Tested and proven to be normal
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiologic alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations
Grade 1	Covert	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impairment of addition or subtraction; altered sleep rhythm	Despite being oriented in time and space, patient seems to have some cognitive-behavioral decay with respect to the standard on clinical examination or to the caregiver
Grade II	Overt	Lethargy or apathy; disorientation for time; obvious personality change; inappropriate behavior; dyspraxia; asterixis	Disoriented for time (at least three of the following are wrong: day of the month, day of the week, month, season, or year) with or without the other mentioned symptoms
Grade III	Overt	Somnolence to semistupor; responsive to stimuli; confused; gross disorientation; bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) with or without the other mentioned symptoms
Grade IV	Overt	Coma	Does not respond even to painful stimuli

[a] Modified with permission from American Association for the Study of Liver Diseases, European Association for the Study of the Liver.[3] © 2014 The American Association for the Study of Liver Diseases. *aasld.org/sites/default/files/guideline_documents/hepaticencephenhanced.pdf.*

Case 7-1

A 56-year-old woman with an extensive history of alcohol consumption and a 25 pack-year smoking history presented to a local emergency department with her son because of persistent worsening of her mental status. Her son noticed that she was progressively less attentive and had depressed psychomotor speed.

Examination revealed she was mildly disoriented, with decreased attention speed, mild dysarthria, and bilateral symmetric upper extremity tremor. She had a wide-based gait with no ability to do tandem gait. A comprehensive metabolic panel showed decreased albumin (2.8) with mildly elevated alanine aminotransferase, aspartate aminotransferase, total bilirubin (2.1), alkaline phosphatase, and γ-glutamyl transpeptidase (also known as γ-glutamyl transferase). Her international normalized ratio (INR) was 1.7. Serum ammonia was slightly elevated, while serum and urinary copper concentrations were normal. EEG showed diffuse mixed-frequency slow-wave activity, with a suggestion of triphasic waves anteriorly. Brain MRI showed cerebellar atrophy and symmetric bilateral T1-hyperintense lesions in the globus pallidus. Abdominal ultrasound showed ascites. A diagnosis of hepatic failure was made, and she was treated for minimal hepatic encephalopathy with lactulose and rifaximin, which resulted in significant improvement of her neuropsychiatric status.

Comment. Patients with hepatic cirrhosis at early stages present with minimal hepatic encephalopathy, which consists of an unremarkable neurologic examination along with abnormal neuropsychological test findings. The salient neurobehavioral disorder is executive dysfunction, with deficits in vigilance, working memory, response inhibition, and mental orientation. Minimal hepatic encephalopathy significantly compromises the patient's quality of life and interferes with activities of daily living; however, proper treatment may improve quality of life.

Other tests that have been evaluated in the diagnosis of minimal hepatic encephalopathy include continuous reaction time tests, inhibitory control tests, computerized test batteries, the psychometric hepatic encephalopathy score, and the repeatable battery for the assessment of neuropsychological status. While these various scales may be useful in evaluating patients with minimal encephalopathy, they should not be considered as a replacement of more standard neuropsychological testing.[6,7]

Asterixis, a form of negative myoclonus, is recognized by the lack of ability to actively keep a position followed by occurrence of irregular lapses of posture of different body parts. Clinically, asterixis is elicited by extending the patient's arms while dorsiflexing the wrists and fanning the fingers to visualize the flap of the patient's wrist. It presents at early stages of hepatic encephalopathy and may be observed in other metabolic encephalopathies. The pathophysiology of asterixis remains unknown.

Serum ammonia levels are typically elevated in patients with a higher grade of encephalopathy. Measurement of serum ammonia levels is not useful in screening for hepatic encephalopathy in patients with known chronic liver disease since levels do not correlate with the severity of the encephalopathy.[8] Brain imaging, including MRI, is generally of little use in this group of patients, although patients with chronic liver dysfunction may demonstrate regions

KEY POINT

- Brain imaging is generally of little use in the diagnosis of hepatic encephalopathy, although patients with chronic liver disease may show T1-weighted hyperintensities in the basal ganglia thought to represent accumulations of manganese.

of T1 shortening involving the globus pallidus and substantia nigra, with occasional involvement of the subthalamic nucleus, tectal plate, and hypothalamus, felt to be related to manganese deposition (**Figure 7-1**[9]).[1,3]

Hepatic encephalopathy can be precipitated by numerous factors, including infections; conditions that lead to nitrogen overload, such as gastrointestinal bleeding and uremia; overuse of diuretics; use of sedatives and hypnotics; constipation; and electrolyte imbalance.

Treatment of hepatic encephalopathy is usually directed toward reducing the production and absorption of ammonia in the intestine. Various antibiotics (including rifaximin and neomycin), lactulose, and nutritional therapies such as probiotics may be effective. Liver transplantation is considered the definitive treatment.[5]

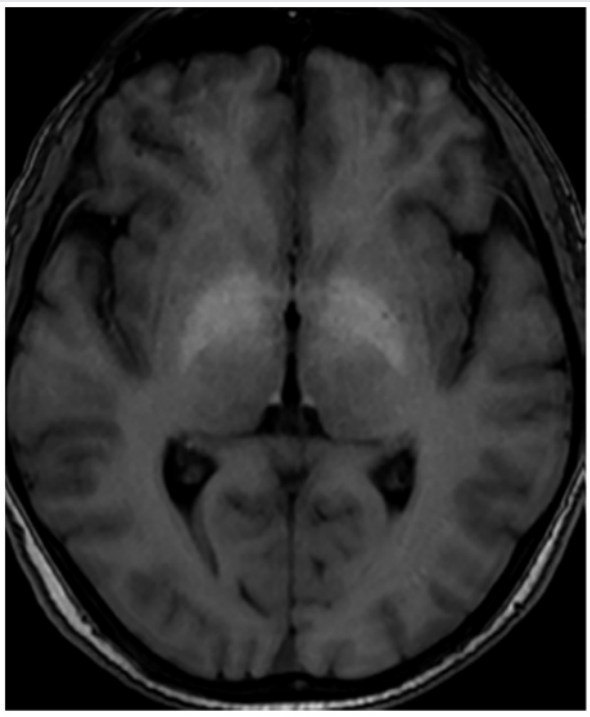

FIGURE 7-1 MRI in a patient with chronic liver disease. Axial T1-weighted MRI demonstrating bilaterally symmetric pallidal hyperintensity, thought to be related to manganese deposition.

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ACQUIRED NON-WILSONIAN HEPATOCEREBRAL DEGENERATION

Acquired non-Wilsonian hepatocerebral degeneration can occur in any patient with chronic liver failure. This condition was described by van Woerkem in 1914 and later described by Victor and Adams in 1965.[10] This clinical entity can be confused with the clinical picture seen in Wilson disease. While irreversible, progressive neurologic symptoms can be arrested following liver transplantation. Clinical symptoms are numerous, but patients may show signs and symptoms that can include parkinsonism, cognitive decline, ataxia, apathy, somnolence, myelopathy, dystonia, cranial dyskinesias, and chorea (**Case 7-2**).[1,11,12] Acquired hepatocerebral degeneration is associated with T1-weighted hyperintensities caused by manganese deposition in the basal ganglia and atrophic changes in the cerebral cortex, basal ganglia, and cerebellum on MRI.[1,12–14] It should be noted, however, that these findings may be seen in any patient with chronic liver disease, with or without clinical signs of hepatocerebral degeneration. Manganese toxicity is believed to play a role in the MRI findings and in the pathogenesis of this condition. This syndrome can usually be differentiated from Wilson disease as it begins in an older age group, is not genetic in nature, and does not have the laboratory findings seen in Wilson disease. Patients do not have evidence of Kayser-Fleischer rings.[12,13]

The toxic effects of manganese are currently thought to contribute to the

Case 7-2

A 53-year-old man was admitted to the hospital for evaluation of progressive gait difficulty, stiffness, and recurrent falls for the past 6 to 9 months. He reported a history of chronic liver disease over the past 3 years. He denied a history of heavy alcohol intake in the past. Screening for an infectious etiology was negative. He had no family history of either liver or neurologic disease. He had been evaluated for cirrhosis and portal hypertension 18 months previously. Esophagoscopy at that time showed grade 4 giant fundal varices that were resected. Following surgery, he had episodes of somnolence and confusion lasting for 24 hours. These symptoms were treated with enemas and bowel washes. In addition to gait problems leading to recurrent falls, he also recently developed dysarthria and dysphagia, confusion, and asterixis.

His neurologic examination showed dysarthria, bradykinesia, and bilateral hand tremor. Tone was increased in all four extremities, with hyperreflexia and extensor plantar responses. He had impairment of attention, vigilance, and memory. Slit-lamp examination of his eyes revealed no evidence of Kayser-Fleischer rings. Liver function tests showed mild elevation of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transpeptidase. Serum ceruloplasmin and copper levels were normal. EEG showed mild slowing of background rhythms. MRI of his brain showed bilateral symmetric hyperintensities in the globus pallidus on T1-weighted images.

Based on the patient's history and clinical findings, a diagnosis of acquired hepatocerebral degeneration was made. Attempts at treating his symptoms with dopamine agonists were not successful. Liver transplantation resulted in a mildly improved clinical state.

Comment. The development of symptoms of a movement disorder along with a history of portal hypertension and recurrent symptoms of hepatic encephalopathy should alert the neurologist to the possibility of acquired hepatocerebral degeneration.

KEY POINT

- Manganese toxicity is believed to be a major factor in the development of symptoms of acquired hepatocerebral degeneration that may mimic many of the symptoms of Wilson disease.

development of acquired hepatocerebral degeneration. Higher levels of manganese may be present in patients with cirrhosis and in those with portosystemic shunts that have developed spontaneously or were created surgically for management of esophageal varices. Attempts to lower manganese levels have not been helpful in reversing symptoms in these patients. Liver transplantation appears to be the best treatment in hopes of reversing symptoms. Therefore, in patients with acquired hepatocerebral degeneration, liver transplantation should be strongly considered as the main mode of treatment.

A manganese storage disease associated with mutations in the manganese transporter gene *SLC30A10* has also been reported recently.[15] Affected patients may manifest dystonia beginning in childhood and adolescence or an asymmetric parkinsonian picture with postural instability in adulthood. Patients with the mutation also develop hepatic cirrhosis and clinical symptoms similar to patients with Wilson disease. Laboratory investigations reveal increased serum manganese levels, polycythemia, low ferritin, and increased total iron-binding capacity. Basal ganglia hyperintensities are seen on T1-weighted MRI. Patients with extrapyramidal symptoms typically do not respond well to treatment with levodopa or penicillamine. Repeated treatments with calcium disodium ethylenediaminetetraacetic acid infusions lead to an increase in urinary

KEY POINT

- Hepatic myelopathy must be differentiated from numerous other causes of myelopathy. Liver transplantation may result in some improvement of symptoms.

manganese excretion, and early treatment can improve both parkinsonian and dystonic symptoms.[16]

HEPATIC MYELOPATHY

Another rare neurologic manifestation of chronic liver disease is hepatic myelopathy, which is typically associated with portosystemic shunts that occur either spontaneously or are surgically created (transjugular intrahepatic portosystemic shunt).[17] Clinical symptoms of spastic paraparesis develop insidiously, with slowly progressive weakness and spasticity in the lower extremities. Patients may be left wheelchair dependent as the paraparesis progresses. The upper extremities are not usually affected. Sensory involvement is usually absent, although some reports of posterior column dysfunction exist. A small fiber distal neuropathy has also been described, although this may be related to various underlying causes of liver disease. On neurologic examination, patients show evidence of spasticity, hyperreflexia, and bilateral extensor plantar responses.[18]

Symmetric loss of myelin, primarily in the lateral corticospinal tracts, has been described histologically. Demyelination in the anterior corticospinal tracts, posterior columns, and spinocerebellar tracts has also been described. As the disease progresses, axonal loss is also seen, leading to irreversible neurologic dysfunction.

Hepatic myelopathy seems to be closely related to portosystemic shunting of blood, which may allow ammonia or other nitrogenous breakdown products to bypass the liver and cause damage to the spinal cord. Although hepatic myelopathy is typically associated with repeated bouts of hepatic encephalopathy, it may occur in the absence of hepatic encephalopathy. Some possibility exists that hepatic myelopathy could be related to nutritional disorders or some other metabolic process. Conditions that might cause a metabolic myelopathy (eg, vitamin B_{12}, copper, or vitamin E deficiency) should be considered in the differential diagnosis of hepatic myelopathy.[17]

The diagnosis of hepatic myelopathy is one primarily of exclusion, although it should be considered in the presence of liver dysfunction. The differential diagnosis is very broad and includes all of the conditions that might cause a spastic paraparesis. MRI of the spinal cord is necessary to exclude a compressive myelopathy or other intrinsic/extrinsic cord disease. Usually, imaging studies of the spinal cord in hepatic myelopathy are normal. Brain MRI has been reported to show abnormalities of intracerebral corticospinal tracts; T1 hyperintensities in the globus pallidus and putamen attributable to manganese deposition have also been described in patients with hepatic myelopathy.[17]

Early diagnosis may lead to earlier treatment that can arrest the progression of hepatic myelopathy, although response to treatment is poor. Liver transplantation has been reported to be effective in some cases.[19]

ACUTE LIVER FAILURE

Fulminant hepatic failure has been defined as ''a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of preexisting liver disease.''[20,21] Liver failure of this type results in abnormal liver function tests and elevated serum ammonia levels. High serum ammonia levels are a marker for more severe encephalopathy and development of cerebral edema.[8] Coagulopathy and multiorgan failure also commonly occur in acute liver failure. Mortality may be as high

as 50%. Acute liver failure is more common in developing countries, where viral hepatitis (A, B, and E) is the most likely cause. In the United States and Western Europe, acute liver failure is usually caused by drugs, especially acetaminophen.[11,20]

Encephalopathy has a key prognostic importance in acute liver failure. The prognosis is generally poor in both covert and overt encephalopathy. Efforts to prevent the development of encephalopathy should begin as soon as the diagnosis of acute liver failure is made. In cases of acetaminophen toxicity, administration of *N*-acetylcysteine may be beneficial. The use of therapies that may lessen encephalopathic symptoms in chronic liver disease, such as rifaximin and neomycin, are ineffective in acute liver failure. The use of lactulose may result in electrolyte abnormalities and dehydration and worsen the underlying condition.[20] Treatment for possible circulatory problems and hypotension may require attempts to increase the blood volume and the use of vasopressor drugs. Monitoring of myocardial and adrenal function is necessary. Aggressive efforts are needed to prevent the development of cerebral edema that leads to increased intracranial pressure. If increased intracranial pressure develops, the chances of survival without liver transplantation is poor.[22]

The pathogenesis of encephalopathy in acute liver failure is poorly understood but is most likely related to systemic and local inflammation as well as circulating ammonia. Attempting to lower serum levels is essential in managing hepatic encephalopathy and preventing cerebral edema. Early initiation of continuous renal replacement therapy and induction of hypothermia may help to lower elevated ammonia levels. Correction of hypokalemia and metabolic alkalosis are also beneficial. It is also important to prevent infection and maintain cerebral perfusion. The risk of increased intracranial pressure can be minimized by lowering cerebral ammonia metabolism and by the use of osmotic agents such as mannitol and hypertonic saline. Controlled hyperventilation following endotracheal intubation may be helpful as well. Hypothermia is recommended, although no evidence exists that hypothermia affects outcomes. Efforts should be made to maintain a core body temperature of 35°C (95°F) to 36°C (96.8°F) and to reduce fever when present.[22,23] Liver transplantation is often necessary to save patients with acute liver failure.

KEY POINTS

- Viral hepatitis is a common cause of acute liver failure in developing countries, while in the United States the toxic effect of acetaminophen is the most common cause.
- Aggressive efforts to prevent the development of cerebral edema leading to increased intracranial pressure are necessary to increase the chances of survival in acute liver failure.

WILSON DISEASE

Wilson disease is a rare disease, first described in 1912 by S.A. Kinnear Wilson.[24] This hereditary disease is associated with both neurologic and hepatic symptoms and is very important to neurologists since its early recognition and diagnosis can lead to treatment and prevention of what may become a progressive degenerative disease. Wilson described in great detail the neuropathology of this disease, including degeneration of the putamen and globus pallidus. He recognized various symptoms that reflected involvement of the extrapyramidal systems, such as tremor, dystonia, changes in cognitive functioning, pathologic laughter, and sialorrhea. He stated that the disease appeared to be familial but did not believe it was hereditary. He blamed the condition on the presence of a toxic agent.[24] Wilson, however, did not describe the ocular findings known today as Kayser-Fleischer rings. This finding was described by Dr Benhard Kayser (1902)[25] and

KEY POINTS

- Wilson disease is caused by mutation of the gene *ATP7B* on chromosome 13q14 coding for the protein ATP7B. Next-generation sequencing of this gene may be less time consuming and more cost effective than older techniques in assessing the presence of this genetic abnormality.
- Kayser-Fleischer rings may be absent in patients with Wilson disease who do not have evidence of neurologic involvement.

Dr Bruno Fleischer (1903),[26] who thought it was caused by deposition of silver. The association of abnormal copper metabolism and Wilson disease was first described by Cumings[27] in 1948. Following this, trials of treatment for Wilson disease using the chelating agents dimercaprol and penicillamine were performed successfully.

Today, the genetic cause for Wilson disease has been found. The disease is an autosomal recessive condition caused by the mutations of the *ATP7B* gene on chromosome 13q14. This gene codes for the protein ATP7B, which enables incorporation of copper into apoceruloplasmin to form ceruloplasmin. Abnormally low levels of ceruloplasmin result because of the defective ATP7B protein. Since ceruloplasmin levels are low, hepatic copper levels increase until the liver can no longer store more. Copper subsequently spills out, leading to pathologic effects on other organ systems. More than 500 mutations of this gene have been found.[16] Genetic testing has been helpful in diagnosing this disorder, but the high number of mutations has greatly limited its use. Older techniques for gene analysis have been expensive and time consuming.[28] A 2016 report, however, indicates that the use of next-generation sequencing may prove to be a reliable method for diagnosing Wilson disease that will save both time and money.[29]

Wilson disease is a rare condition reported to have a prevalence of 30 cases per 1 million. The incidence is higher in Germany, Japan, and Austria and highest in Costa Rica.[30] Higher incidence may be related to consanguinity and a possible founder effect.[16]

Symptoms of Wilson disease can be neurologic, hepatic, or psychiatric. Onset is typically in the second or third decade, although neurologic symptoms beginning as late as age 70 have also been described.[16] Typical symptoms at the time of onset include movement disorders, such as dystonia or parkinsonian symptoms. A classic wing-beating tremor may also be present. Dysarthria is also common with these movement abnormalities. Tremors may be present at rest and with action/intention. They are often jerky and may be associated with dystonia. Dystonia is seen in one-third of patients and may be generalized, segmental, focal, or multifocal. Dysarthria and slow tongue movements may be associated with facial grimacing or risus sardonicus, a condition that was pictured in Wilson's original article.[24] A parkinsonian picture of bradykinesia, gait abnormalities, and impairment of rapid alternating movements may also be typical. Usually a dystonic, ataxic, or parkinsonian syndrome is present. More likely, a combination of these features exists. These symptoms may also be associated with cognitive decline and behavioral changes, such as irritability, disinhibition, and changes in personality.[16,31]

Wilson disease may present with only laboratory abnormalities of hepatic function, but clinical signs and symptoms of acute or chronic liver disease are more likely. Symptoms of hepatic encephalopathy can also be present early in the course of the disease.

Kayser-Fleischer rings are caused by copper deposition in the Descemet membrane and are best seen with slit-lamp examination. The presence of Kayser-Fleischer rings is common when patients have neurologic involvement and are practically pathognomonic for Wilson disease, particularly in the presence of low ceruloplasmin levels. Another ocular finding is the presence of sunflower cataracts that are caused by copper deposition in the anterior and

posterior capsule of the lens, although this finding is much less common than Kayser-Fleischer rings.[16,31]

The diagnosis of Wilson disease is based on history and clinical findings and may be aided using a system of scoring on various other tests. This system of scoring was developed in 2001 and uses both clinical and laboratory findings (**Table 7-2**).[16] In Wilson disease, serum ceruloplasmin is typically decreased by half of the lower value of the normal range. Under normal circumstances, the ATP7B protein activity leads to incorporation of six copper molecules into apoceruloplasmin, generating ceruloplasmin. However, in the pathophysiology of

TABLE 7-2 Scoring System for Wilson Disease Diagnosis Developed by Attendees at the International Wilson Disease Meeting in Leipzig, Germany, in 2001[a]

Typical Clinical Symptoms and Signs		Other Tests	
Kayser-Fleischer rings		**Liver copper** (in absence of cholestasis)	
Present	2	>5 times upper limit of normal (>250 mcg/g)	2
Absent	0	50–250 mcg/g	1
Neurologic symptoms[b]		Normal (<50 mcg/g)	-1
Severe	2	Rhodanine-positive granules[c]	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 times upper limit of normal	1
Normal (>0.2 g/L)	0	>2 times upper limit of normal	2
0.1–0.2 g/L	1	Normal, but >5 times upper limit of normal after D-penicillamine	2
<0.1 g/L	2	**Mutation analysis**	
Hemolytic anemia		Detected on both chromosomes	4
Present	1	Detected on one chromosome	1
Absent	0	No mutations detected	0
TOTAL SCORE		Evaluation:	
4 or more		**Diagnosis established**	
3		**Diagnosis possible, more test needed**	
2 or less		**Diagnosis very unlikely**	

[a] Reprinted with permission from Bandmann O, et al, Lancet Neurology.[16] © 2015 Elsevier. *thelancet.com/journals/laneur/article/PIIS1474-4422(14)70190-5/abstract*.
[b] Or typical abnormalities on brain MRI.
[c] If no quantitative liver copper available.

KEY POINTS

- Routine serum copper level is not particularly helpful in screening for Wilson disease since it measures total serum copper, which is bound to ceruloplasmin. Perhaps the best single screening test for Wilson disease is the 24-hour urinary copper measurement.
- With early diagnosis and treatment, symptoms of Wilson disease can be controlled. Treatment typically is with drugs such as penicillamine, trientine, and other chelating agents. Oral zinc can also be used to inhibit absorption of copper in the gastrointestinal tract.

Wilson disease, the defective and malfunctioning ATP7B protein cannot incorporate copper molecules into apoceruloplasmin, which, in turn, results in low levels of ceruloplasmin. Urinary copper levels are increased to over 100 mcg/24 h in adults and more than 40 mcg/24 h in children. Routine serum copper level is not particularly helpful since it measures total serum copper, which is bound to ceruloplasmin. Perhaps the best single screening test for Wilson disease is the 24-hour urinary copper measurement. Free serum copper levels may not be available routinely but are usually greater than 200 mcg/L. Hepatic copper in patients with Wilson disease is greater than 250 mcg/g dry weight. Kayser-Fleischer rings may be absent in patients who have only hepatic disease but are typically present in those with neurologic involvement. Families of patients with Wilson disease should also be screened for Kayser-Fleischer rings and have copper and ceruloplasmin studies and, if possible, genetic testing to identify presymptomatic individuals.[16,31]

Neuroimaging findings may also aid in the diagnosis of Wilson disease. Characteristic T2-weighted hyperintensities are seen in the basal ganglia and ventrolateral thalamus. T1-weighted signal changes have also been described in the putamen, caudate, globus pallidus, thalamus, and midbrain.[32] The face of the giant panda sign is described as a classic MRI finding seen on T2-weighted images in Wilson disease (**Figure 7-2**[33]). This finding is caused by high signal in the tegmentum, hypointensity in the superior colliculus, and sparing of the red nucleus and pars reticulata. However, this pattern was seen in only 14.3% of patients in a 2010 study.[34]

Treatment of Wilson disease is a lifelong endeavor because serum copper levels cannot be controlled by limiting copper intake alone. Use of chelating agents, such as penicillamine

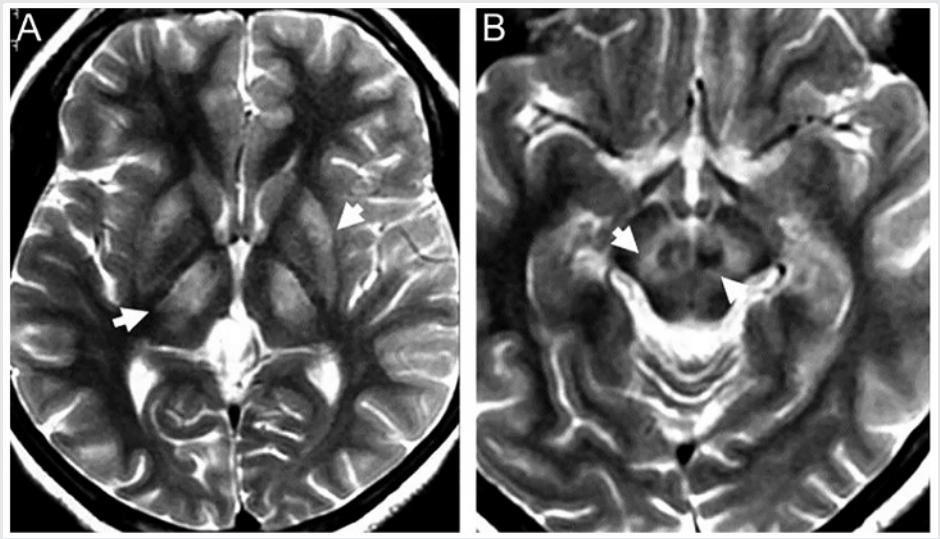

FIGURE 7-2 T2-weighted axial MRI demonstrates (*A*) symmetric hyperintense signals in the putamen, posterior internal capsule, and thalami (*arrows*), (*B*) ''face of the giant panda'' in midbrain with high signal in tegmentum and normal red nuclei (*arrows*).

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and trientine, as well as zinc salts can usually control elevated copper levels. Chelating agents bind copper directly to facilitate excretion. Increase of oral intake of zinc impedes absorption of copper but does not help to mobilize copper already in the system.[16,31]

Penicillamine can be administered orally. It chelates not only copper but also other metals. This drug increases copper excretion in the urine and feces. Patients may manifest a transient worsening of their symptoms related to a transient increase in the free copper pool in relationship to ceruloplasmin-bound copper. Starting with a lower dose of the chelating agent may eliminate this problem. Improvement in hepatic function, ascites, and jaundice can be seen as early as 2 to 6 months following initiation of treatment. The dosage of penicillamine begins at 250 mg/d to 500 mg/d, with increases of 250 mg every 4 to 7 days until a maximum dose of 1 g/d to 1.5 g/d is reached. The dose is given 2 to 4 times a day. The drug should be given on an empty stomach at least 1 hour before meals since food decreases its absorption.[29] Adverse effects include sensitivity reactions manifested by fever, cutaneous reactions, neutropenia, thrombocytopenia, lymphadenopathy, and proteinuria. The drug can cause renal toxicity and a lupuslike syndrome with hematuria, proteinuria, arthralgia, appearance of antinuclear antibodies, and bone marrow toxicity.[31] Penicillamine has also been reported to produce or unmask symptoms of myasthenia gravis. Symptoms of myasthenia gravis are usually mild and improve after penicillamine has been discontinued.[35]

Trientine chelates copper, zinc, and iron. It increases urinary excretion of copper. It is more expensive than penicillamine but can be used as an alternative to penicillamine as an initial treatment. It, too, can result in initial worsening of neurologic symptoms in patients with Wilson disease. It can cause nephrotoxicity and bone marrow effects leading to anemia because of copper and iron deficiency. Side effects also include dyspepsia, muscle cramps, and dystonia. The latter may be confused with symptoms of the disease itself.[31]

Treatment of patients with these chelating agents requires monitoring for hepatic function, renal function, copper levels in serum and urine, and anemia and neutropenia. Liver transplantation is not usually considered a treatment for Wilson disease, although it does correct the hepatic genotype and restores copper excretion capacity. In acute liver failure or decompensated cirrhosis secondary to Wilson disease, it may be a treatment consideration in patients who are not responding to medical treatment and those with acute liver failure.[16,31] Symptomatic treatment of neurologic symptoms to be considered includes the use of medications (eg, primidone, propranolol) for tremor or injections of botulinum toxin for dystonia. Deep brain stimulation and thalamotomy may also be an option for management of various movement disorders.[31] For more information on Wilson disease, refer to the article ''Wilson Disease'' by Ronald F. Pfeiffer, MD, FAAN,[36] in the August 2016 Movement Disorders issue of *Continuum*.

VIRAL HEPATITIS

The hepatitis A, B, C, and E viruses are often associated with various neurologic and psychiatric symptoms. Hepatitis A has been associated with Guillain-Barré syndrome. Meningoencephalitis, acute disseminated encephalomyelitis, and acute myelitis have

KEY POINTS

- Fifty percent of patients with hepatitis C have mixed cryoglobulinemia.
- Hepatitis C is a worldwide problem that can cause numerous neurologic problems, including cerebrovascular symptoms, problems with cognitive function, inflammatory processes affecting the spinal cord, and peripheral nerve pathology.

also been reported with hepatitis A infection. Similar neurologic problems rarely occur in patients with hepatitis B infection.[11]

Chronic hepatitis C infection has been associated with a number of neurologic problems. Hepatitis C infection is a global problem, affecting about 185 million people, with an estimated prevalence of 2.8% worldwide.[37] While the virus primarily affects the liver, it is known to involve other organs and can be considered a systemic disease. Chronic hepatitis C infection causes hepatic and systemic inflammation by way of mechanisms that are immunologic as a consequence of B-cell proliferation, circulating inflammatory cytokines/chemokines, and cryoglobulinemia. Chronic infection may possibly increase the risk for type 2 diabetes mellitus, renal disease, cardiovascular disease, and rheumatologic disease. Hepatitis C has been associated with neurologic and psychiatric symptoms in up to half of patients with the infection.[38] Causation has not been conclusively demonstrated, but the adverse effects of hepatitis C therapy are a potential confounder.

Acute and chronic cerebrovascular events occur more often in patients with hepatitis C infection than in the general population. The infection increases atherosclerosis by a number of mechanisms, including increases in cytokines causing oxidative stress, homocysteinemia, insulin resistance, and diabetes mellitus. Fifty percent of patients with hepatitis C have mixed cryoglobulinemia. This may be associated with the deposition of immune complexes in vessel walls leading to occlusion of the vessel. Vasculitic changes in the cerebral arteries can cause ischemic strokes and symptoms of transient cerebral ischemia but rarely hemorrhagic strokes. Small vessel involvement in the cerebral white matter may be associated with acute or subacute encephalopathy, causing impairment of cognition, confusion, dysarthria, and dysphagia.[39]

Encephalomyelitis from cerebral and meningeal inflammation from chronic hepatitis C infection may lead to symptoms of spastic quadriparesis, bladder and bowel dysfunction, and sensory loss. Transverse myelitis and acute disseminated encephalomyelitis have been reported as well.[38,39]

Peripheral neuropathy may occur in patients with mixed cryoglobulinemia.[40] Neuropathy is usually related to ischemic changes in the nerve associated with distal symmetric sensory or sensorimotor polyneuropathy characterized by burning feet, painful paresthesia, and allodynia on examination. Large fiber polyneuropathy is less frequent but has been reported to occur.[41] Mononeuropathy, mononeuritis multiplex, and cranial neuropathy affecting the abducens, facial, and motor trigeminal nerve has also been described.[40,42]

About half of patients with chronic hepatitis C infections develop psychiatric symptoms. Cognitive difficulties known as brain fog and symptoms of depression and anxiety are common. Fatigue is the most frequent symptom, causing both physical and mental exhaustion. This is often associated with difficulty with concentration, poor attention span, feelings of depression, and somatic symptoms such as headache and myalgia. Sleep disturbances such as insomnia are also common. These symptoms seem to be more common in women and older age groups.[38,39]

Hepatitis E infection is not common in Western developed countries, but it has been reported as an emerging disease in the West and in Japan and is more common than previously recognized. It usually causes few symptoms that cannot be distinguished

from other forms of viral hepatitis. Serum transaminases are elevated, and patients usually recover in 4 to 6 weeks; however, hepatitis E can be a cause of acute or chronic liver failure. Chronic infection can occur in patients who are immunosuppressed.[43] The virus now can be found in the blood supplies of Europe and Japan. In the United States, the annual incidence is thought to be only 0.7% at this time.

Hepatitis E is associated with a wide range of extrahepatic manifestations, such as pancreatitis, thrombocytopenia, aplastic anemia, acute thyroiditis, and glomerulonephritis. About 5% of patients may develop neurologic problems,[44] including Guillain-Barré syndrome, brachial plexus neuropathy, encephalitis, ataxic neuropathy, and myopathy.[45–48] Hepatitis E RNA has been detected in the CSF of affected individuals. The recovery from these neurologic conditions ranges from no recovery at all to complete recovery. Treatments for these symptoms include IV immunoglobulin (IVIg), plasma exchange, corticosteroids, and other immunosuppressant drugs along with antiviral therapy.[42]

CONCLUSION

The diagnosis of neurologic symptoms occurring as a result of liver disease is dependent upon numerous factors. It is possible to combine the knowledge gained from an accurate history, neurologic examination, improved laboratory testing, improved imaging, and improved genetic testing to make these diagnoses early. Early diagnosis is key, since many of these conditions may be amenable to treatment.

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KEY POINT

- Hepatitis E is an emerging viral infection that may cause neurologic symptoms in up to 5% of cases.

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Endocrine Emergencies With Neurologic Manifestations

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ABSTRACT

Purpose of Review: This article provides an overview of endocrine emergencies with potentially devastating neurologic manifestations that may be fatal if left untreated. Pituitary apoplexy, adrenal crisis, myxedema coma, thyroid storm, acute hypercalcemia and hypocalcemia, hyperglycemic emergencies (diabetic ketoacidosis and hyperglycemic hyperosmolar state), and acute hypoglycemia are discussed, with an emphasis on identifying the signs and symptoms as well as diagnosing and managing these clinical entities.

Recent Findings: To identify the optimal management of endocrine emergencies, using formal clinical diagnostic criteria and grading scales such as those recently proposed for pituitary apoplexy will be beneficial in future prospective studies. A 2015 prospective study in patients with adrenal insufficiency found a significant number of adrenal crisis–related deaths despite all study patients receiving standard care and being educated on crisis prevention strategies, highlighting that current prevention strategies and medical management remain suboptimal.

Summary: Early diagnosis and prompt treatment of endocrine emergencies are essential but remain challenging because of a lack of objective diagnostic tools. The optimal management is also unclear as prospective and randomized studies are lacking. Additional research is needed for these clinical syndromes that can be fatal despite intensive medical intervention.

Continuum (Minneap Minn) 2017;23(3):778–801.

INTRODUCTION

Endocrine emergencies are a collection of rare and extreme manifestations of common endocrine disorders that are often triggered by an inciting event, such as an acute infection. An endocrine emergency may be the first presentation of the underlying endocrine disorder. The neurologic and systemic complications of endocrine disorders generally worsen with increasing severity of the endocrine dysfunction. However, the rate of change is important, as rapid alterations may result in significant neurologic dysfunction, while severe but chronic endocrine dysfunction may have only minimal symptoms. As many of these endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine disorders.

PITUITARY APOPLEXY

Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.[1] Rarely, pituitary apoplexy can occur in

a normal pituitary gland, such as after a massive postpartum uterine hemorrhage leading to significant hypotension and infarction of the pituitary gland (Sheehan syndrome).[2] While incidentally found subclinical apoplexy is more frequent than acute apoplexy, with up to 25% of all pituitary tumors displaying hemorrhagic or necrotic areas on imaging or autopsy,[1] the focus here is on acute symptomatic pituitary apoplexy.

Epidemiology and Pathophysiology

Pituitary apoplexy occurs infrequently, with community-based studies finding a prevalence of 6.2 cases per 100,000 individuals and an incidence of 0.17 episodes per 100,000 per year.[3,4] Approximately 2% to 12% of patients with all types of pituitary adenomas experience apoplexy, with the diagnosis of pituitary adenoma not previously known in more than 3 out of 4 cases.[1] Pituitary apoplexy is observed in all types of pituitary adenomas and particularly in macroadenomas, with the estimated risk of apoplexy in a conservatively managed nonfunctioning pituitary adenoma between 0.2 and 0.6 events per 100 person-years.[5,6]

Precipitating factors associated with pituitary apoplexy have been identified in up to 40% of all reported cases and include angiographic procedures, surgical procedures, head trauma, pregnancy, and anticoagulant therapy.[1,7] While anticoagulant therapy may incite pituitary apoplexy, a lack of well-designed prospective studies makes it difficult to give recommendations regarding anticoagulant therapy in patients with known pituitary adenomas.[1] Stimulation of the pituitary gland through dynamic testing (eg, insulin, gonadotropin-releasing hormone, growth hormone–releasing hormone, thyrotropin-releasing hormone, and corticotrophin-releasing hormone) and certain hormonal treatments has been implicated in precipitating pituitary apoplexy (**Case 8-1**); however, whether dopamine agonists, which are commonly used in treating prolactinomas, can precipitate pituitary apoplexy remains controversial.[1,8–10]

Clinical Presentation

Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks, or a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.[1,7] Headache is the most prominent and common symptom, occurring in more than 80% of patients, and is classically described as a thunderclap headache that is usually retroorbital but can be bifrontal or diffuse.[1] Visual disturbances are also common and affect more than half of all patients. Mass effect or abrupt pressure increase in the pituitary region caused by the apoplexy can cause visual deficits by superior extension with compression of the optic chiasm/optic nerves or lateral extension into the cavernous sinuses causing ocular motor palsies affecting cranial nerves III, IV, or VI.[1] Meningeal irritation can occur from the extravasation of blood or necrotic tissue into the subarachnoid space, leading to photophobia, nausea, vomiting, meningismus, and, sometimes, fever, as well as variable degrees of altered consciousness.[1] Cerebral ischemia is a rare complication that can be due to cerebral vasospasm or compression of the cerebral arteries, leading to focal neurologic deficits.[11] Endocrine dysfunction is common and can be present before the apoplexy. Corticotropic deficiency occurs in 50%

KEY POINTS

- As endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine emergencies.
- Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.
- Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks to a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.

KEY POINT

- Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage; however, if bacterial meningitis is suspected, CSF cultures should be obtained.

Case 8-1

A 65-year-old man with hypertension and prostate cancer presented to the hospital reporting headache and blurry vision. Three days earlier, he had received his first dose of depot leuprolide for androgen deprivation therapy. A few hours after the initial injection, he started to develop a mild headache and blurred vision. Both the headache and blurred vision worsened over the following days, prompting the patient to seek medical attention. He stated that his headache had now become persistent and unbearable, and he was now unable to move his right eye or raise his right eyelid.

Neurologic examination was notable for a right third cranial nerve palsy. MRI of the brain revealed a large intrasellar mass with hemorrhage. Blood was drawn for endocrine evaluation. Hydrocortisone was empirically administered, and the patient underwent transsphenoidal surgery for diagnosis and resection of the intrasellar mass. Pathology revealed that the tissue was necrotic and hemorrhagic, but viable tissue was positive for follicle-stimulating hormone, consistent with a gonadotroph pituitary adenoma. The patient was in stable condition after surgery and referred to endocrinology for additional evaluation and management.

Comment. This patient presented with new onset of worsening headache and blurry vision, with examination revealing a right oculomotor nerve palsy. While the differential diagnosis can be relatively broad, the use of leuprolide, a gonadotrophin-releasing hormone agonist, immediately before symptoms began suggests an association with the symptoms. In this case, the patient had a previously undiagnosed gonadotroph pituitary adenoma that, when stimulated by leuprolide, led to hemorrhage of the adenoma and the presenting symptoms. Because of the intense headaches and severe neuro-ophthalmologic symptoms, the patient was taken for urgent imaging and neurosurgical decompression. If the symptoms were mild and the patient was stable, a conservative medical approach may have been considered, as pituitary apoplexies can spontaneously resolve; however, the optimal management remains unclear without prospective studies comparing surgical to medical management.

to 80% of cases, with secondary adrenal insufficiency leading to potentially devastating hypotension and hyponatremia.[1] Other pituitary defects (eg, thyrotropic deficiency) are also commonly seen in patients with pituitary apoplexy, but they can usually be addressed after the acute neurologic and corticotropic deficiencies are resolved.[1,7] Diabetes insipidus is rare and may be masked by secondary adrenal insufficiency or hypothyroidism.[1]

Diagnosis and Management

The diagnosis of pituitary apoplexy relies on a combination of clinical assessment, endocrine testing, and radiologic identification. The major differential diagnoses are subarachnoid hemorrhage and bacterial meningitis.[1] Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage, as meningeal irritation caused by rupture of necrotic or hemorrhagic tissue from the apoplexy can cause pleocytosis, increased red blood cell count, and xanthochromia in the CSF;[12,13] however, if bacterial meningitis is suspected, CSF cultures should be obtained. Patients with suspected pituitary apoplexy should have pretreatment endocrine testing, but treatment should not be delayed while waiting for these test results.[7]

Neuroimaging reflects the underlying pathologic process and can show a simple infarction, hemorrhagic infarction, mixed hemorrhagic infarction and clot, or pure clot.[1] Because of its wide availability, CT is often the initial emergency examination for patients with sudden-onset headache. While CT is diagnostic in only 21% to 28% of pituitary apoplexy cases, an intrasellar mass can be visualized in up to 80% of pituitary apoplexy cases.[7] As most cases of pituitary apoplexy have a hemorrhagic component, a patchy or confluent area of hyperdensity can be seen by CT; however, the hyperdensity is not specific for pituitary apoplexy and may be seen with aneurysms, meningiomas, Rathke cleft cysts, germinomas, and lymphomas.[14] Furthermore, if a few days have passed since the initial event, detecting hemorrhagic components of the pituitary apoplexy with CT may be difficult due to a decrease in blood density.[1] Contrast-enhanced CT can show a ring or inhomogeneous enhancement of the pituitary tumor.[1]

MRI is the superior imaging modality for pituitary apoplexy as it can detect fresh blood accurately, correlates with histopathologic analysis, and confirms the diagnosis in over 90% of patients.[7,15] Early changes seen on MRI include increased signal intensity on diffusion-weighted imaging in ischemic tissue.[1] Signal intensities on T1- and T2-weighted images depend on the presence (or absence) of hemorrhage and the stage (time after apoplexy) (**Figure 8-1**).[14]

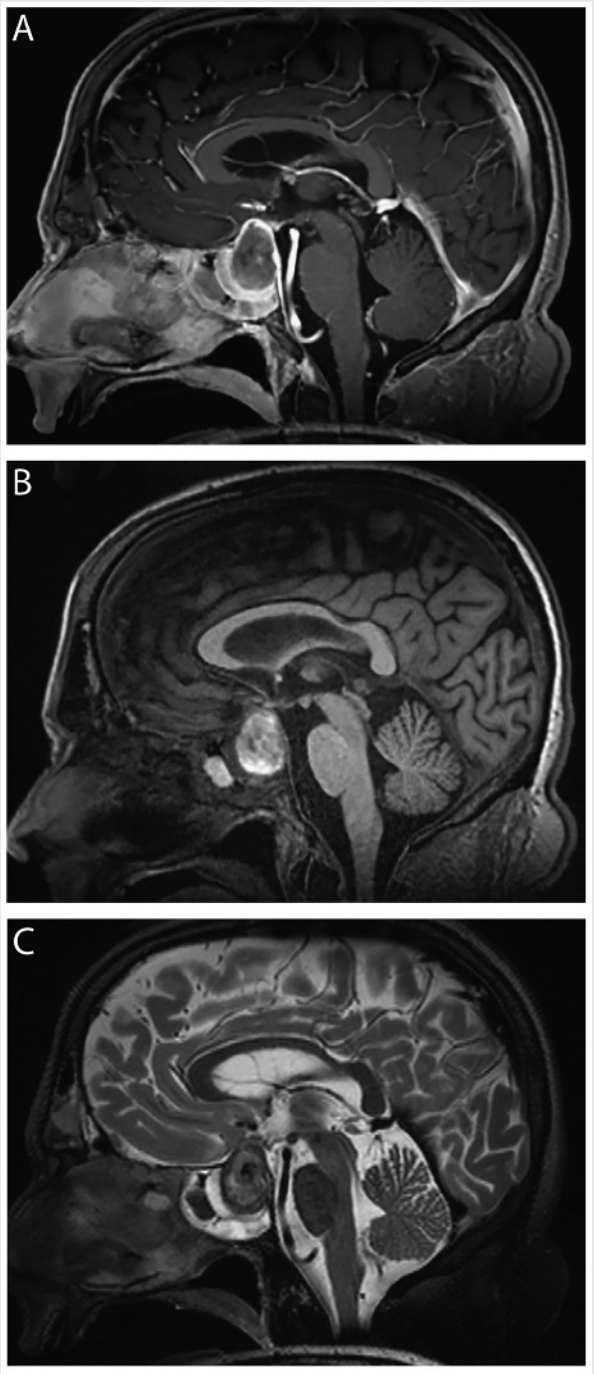

FIGURE 8-1 Sagittal postcontrast T1-weighted (*A*), T1-weighted (*B*), and T2-weighted (*C*) MRIs show hemorrhage within a pituitary adenoma with expansion of the sella.

Once a diagnosis is confirmed, acute pituitary apoplexy can be managed by either surgery or a more conservative medical approach. Surgical management consists of resecting the apoplectic pituitary mass with the goal of resolving the most emergent neurologic and visual symptoms. In the hands of an experienced surgeon, overall complications are rare, but CSF leakage and (sometimes permanent) diabetes

KEY POINTS

- Empiric corticosteroid replacement should be initiated for patients with acute pituitary apoplexy with hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of hypoadrenalism.
- Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy).

insipidus may occur.[1] Because of reports of spontaneous clinical improvement and shrinkage of apoplectic pituitary adenomas, a conservative approach has been suggested in select cases with absent or mild and stable neuro-ophthalmic signs.[1,7] Currently, no randomized prospective trials have been performed comparing the outcomes of surgery to conservative management to help guide treatment of patients with pituitary apoplexy; however, grading systems have recently been developed to better classify and improve the management of patients with pituitary apoplexy (**Figure 8-2** and **Table 8-1**).[7,16] For all patients with pituitary apoplexy who have hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of hypoadrenalism, empiric corticosteroid replacement should be initiated and tapered to a maintenance dose once the patient recovers from the acute period.[7] Additionally, patients will likely need long-term hormonal replacement because of the hypopituitarism caused by the apoplexy.[17]

ADRENAL CRISIS (ADDISONIAN CRISIS)

Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result more commonly from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy) (**Table 8-2**).[18–20] Primary adrenal

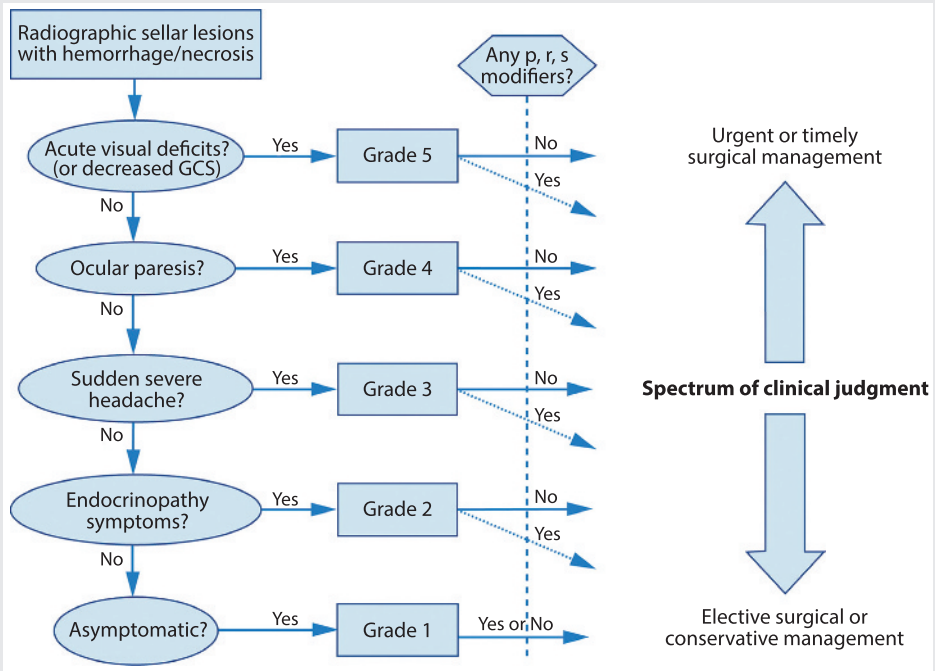

FIGURE 8-2 Flowchart illustrating assessment using the Pituitary Apoplexy Grading System.

GCS = Glasgow Coma Scale; p modifier = prolactinoma; r modifier = hemorrhagic Rathke cleft cyst; s modifier = significant comorbidities.

Modified with permission from Jho DH, et al, World Neurosurg.[16]

TABLE 8-1 Pituitary Apoplexy Score[a]

Variable	Points
Level of consciousness	
Glasgow Coma Scale 15	0
Glasgow Coma Scale 8–14	2
Glasgow Coma Scale <8	4
Visual acuity	
Normal (or no change from pre–pituitary apoplexy visual acuity)	0
Reduced, unilateral	1
Reduced, bilateral	2
Visual field deficits	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present unilateral	1
Present bilateral	2

[a] Reprinted with permission from Rajasekaran S, et al, Clin Endocrinol.[7] © 2010 Blackwell Publishing Ltd. *onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2010.03913.x/full.*

insufficiency is associated with both glucocorticoid and mineralocorticoid deficiency, whereas secondary adrenal insufficiency does not have mineralocorticoid deficiency as the renin-angiotensin-aldosterone system is intact.[18,21] Adrenal insufficiency often presents with systemic symptoms and signs, such as fatigue, anorexia, weight loss, hyperpigmentation of the skin (in primary adrenal insufficiency), gastrointestinal symptoms, orthostatic hypotension, and electrolyte disturbances.[18] Neurologic manifestations are generally nonspecific and neuropsychiatric in nature (eg, depression or delirium), but patients may also present with muscle pain and weakness that may be secondary to electrolyte and metabolic problems.[18,21] While adrenal insufficiency often manifests in an insidious nature, an acute adrenal crisis, or addisonian crisis, is a true medical emergency and can lead to seizures, severe encephalopathy including coma, and death without prompt medical attention.

Epidemiology and Pathophysiology

Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.[19] In a 2015 prospective study of patients with primary and secondary adrenal insufficiency receiving standard care, 8.3 adrenal crises per 100 patient-years and an alarmingly 0.5 adrenal crisis-related deaths per 100 patient-years were reported.[22] A precipitating event triggering the adrenal crisis can be identified for the vast majority of patients (more than 90%), with gastrointestinal illness and fever from an acute infection being the most common.[19,22] Other common precipitating events include surgical stress, emotional stress, and inadequate exogenous corticosteroid treatment, but, rarely, more benign-appearing events, such as flight delays and wasp bites, may trigger an adrenal crisis.[19] The risk of adrenal crisis is likely to be higher in primary adrenal insufficiency compared to secondary adrenal insufficiency and may be the initial clinical presentation in up to 50% of patients with primary adrenal insufficiency.[19] However, all patients with adrenal insufficiency, including drug-induced adrenal insufficiency, are at risk for adrenal crisis.[19]

KEY POINT

- Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.

TABLE 8-2 Etiology of Adrenal Insufficiency[a]

▶ **Primary Disorder: Addison Disease**
Autoimmune (sporadic, autoimmune polyendocrine syndrome type I and type II)
Infections (eg, tuberculosis, fungal, human immunodeficiency virus [HIV])
Metastatic tumors (eg, lung, breast, kidney, and, rarely, lymphoma)
Congenital adrenal hyperplasia
Adrenomyeloneuropathy/adrenoleukodystrophy
Bilateral adrenal hemorrhage
Bilateral adrenalectomy
▶ **Secondary Disorder**
Pituitary tumor or metastases to the pituitary gland
Other tumors (eg, craniopharyngioma, meningioma) in the parasellar region
Pituitary surgery or radiation
Lymphocytic hypophysitis
Head trauma
Pituitary apoplexy/Sheehan syndrome
Pituitary infiltration (eg, sarcoidosis, histiocytosis)
Empty sella syndrome leading to pituitary dysfunction
▶ **Glucocorticoid-induced Adrenal Insufficiency**
Long-term exogenous glucocorticoid use

[a] Modified with permission from Puar TH, et al, Am J Med.[19] © 2016 Elsevier. *sciencedirect.com/science/article/pii/S000293431500827X*.

While chronic and higher doses of glucocorticoid have the highest risk for adrenal insufficiency after glucocorticoid withdrawal, a recent systemic review and meta-analysis found no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded.[23] Therefore, neurologists need to be vigilant when withdrawing glucocorticoids from their patients and test for adrenal insufficiency in any patients who develop unexplained symptoms after glucocorticoid withdrawal. Unfortunately, clinical evidence to support any specific glucocorticoid-tapering regimen to help avoid adrenal insufficiency is lacking. One reasonable option would be to stop without a taper after short-term (1 to 2 weeks) glucocorticoid use of any dosing in an otherwise healthy and stable patient, followed by monitoring for any signs and symptoms of adrenal insufficiency. For patients with longer durations of glucocorticoid therapy, a slow steady taper over several weeks to months, depending on the duration and dose of glucocorticoid therapy, will likely be needed.

Clinical Presentation

In an adrenal crisis, patients often present with gastrointestinal symptoms, nausea, vomiting, muscle cramps, and hypotension, which may be erroneously diagnosed as gastroenteritis or an acute abdomen, potentially leading to a delay in treatment. Neurologic manifestations can include altered mental status (eg, delirium), convulsions, myopathy, and flexion contractures.[21] Without prompt medical attention, patients can quickly

worsen to hypotensive shock and coma that can be fatal.[19,20]

Typical laboratory findings include hyponatremia, hyperkalemia (in primary adrenal insufficiency), increased blood urea nitrogen (BUN) caused by prerenal failure, hypoglycemia (rare in adults and more common in children with primary adrenal insufficiency), and, rarely, hypercalcemia.[19,20,24]

Diagnosis and Management

Treatment should be started immediately in patients with known adrenal insufficiency presenting with symptoms typical of an adrenal crisis.[19,24] For medically unstable patients without a known diagnosis of adrenal insufficiency, treatment should not be delayed while waiting for a diagnosis, but, if possible, blood samples should be drawn just before the start of treatment for evaluation of serum levels of cortisol, adrenocorticotropic hormone (ACTH), aldosterone, dehydroepiandrosterone sulfate, and renin to help confirm the diagnosis.[19,24] Testing for precipitating causes (eg, bacterial or viral infections) should also be initiated.[24]

Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.[19,20,24] Prompt rehydration is needed to correct the hypovolemia and hyponatremia.[19,20,24] Careful monitoring of sodium levels is needed to avoid rapid correction of hyponatremia and development of the osmotic demyelination syndrome.[19] Steroid replacement should be urgently instituted.[19,20,24] Once a patient is clinically stable, the glucocorticoid dose can be quickly tapered over 1 to 3 days to oral maintenance doses, and mineralocorticoid replacement should be restarted when the dose of hydrocortisone falls to less than 50 mg/d.[20,24] Prompt recognition of an adrenal crisis and prevention of future adrenal crises are critical in avoiding potentially fatal outcomes.[19,24,25]

KEY POINT

- Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.

THYROID DISORDERS

Similar to the systemic manifestations, many of the neurologic complications resulting from thyroid disorders (eg, altered mental status in hypothyroidism) can be insidious in nature.[18] However, both myxedema coma from severe untreated hypothyroidism and thyroid storm are acute medical emergencies requiring prompt identification of the thyroid disorder and any underlying inciting factor, as they are often fatal if left untreated.

Hypothyroidism and Myxedema Coma

Hypothyroidism is most commonly seen with autoimmune thyroiditis (Hashimoto disease) but can also be caused by severe dietary iodine deficiency or iatrogenic causes, including postablative thyroiditis in hyperthyroid patients, neck irradiation, and certain medications.[18] The neurologic complications from hypothyroidism may present slowly and subtly at first, with cognitive impairment, neuromuscular deficits, or headache.[18] However, an infection or another inciting factor in a hypothyroid patient can lead to an acute decompensation and a medical emergency known as myxedema coma, which commonly presents with hypothermia and significantly depressed mental status that can be fatal if left untreated.

Epidemiology and pathophysiology. Myxedema coma is a rare clinical entity, with an estimated incidence rate of 0.22 per million per year.[26] Perhaps because of its rarity, one study found that the diagnosis was missed in half of patients with myxedema coma during the initial emergency department stay.[27] Any delay in diagnosing myxedema coma can be fatal and may contribute to the high

KEY POINTS

- Myxedema coma is typically triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism.
- The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma.

mortality rate of 20% to 30%.[28,29] Typically, myxedema coma is triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism (**Table 8-3**).[28] Cold seems to be a strong inciting factor, as up to 90% of cases occur during the winter months.[29] Myxedema coma is more common in older women, with 80% occurring in women older than 60 years; however, rarely, younger patients, including pregnant women, may be affected.[28]

TABLE 8-3 Factors Precipitating Myxedema Coma[a]

▶ **Drugs**
Withdrawal of levothyroxine
Anesthetics
Sedative hypnotics
Narcotics
Amiodarone
Lithium carbonate
▶ **Infections, sepsis**
▶ **Stroke**
▶ **Congestive heart failure**
▶ **Low temperature**
▶ **Trauma**
▶ **Metabolic disturbances**
Acidosis
Hypoglycemia
Hyponatremia
Hypercapnia
▶ **Other**
Gastrointestinal bleeding
Excessive ingestion of raw bok choy

[a] Modified with permission from Klubo-Gwiezdzinska J, Wartofsky L, Med Clin North Am.[28] © 2012 Elsevier. *sciencedirect.com/science/article/pii/S0025712512000168.*

Clinical presentation. The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma (**Case 8-2**).[29] On presentation, patients can have extreme hypothermia (to 26.7°C [80°F]) that may mask an infection.[28] Physical examination often reveals extreme signs of hypothyroidism, including dry, brittle skin and hair; doughlike nonpitting edema; hoarse voice; macroglossia; and delayed reflexes. Hypotension and shock may be seen from decreased cardiac contraction and potentially fatal bradyarrhythmias.[29] Prolonged mechanical ventilation is usually needed for severe hypoventilation.[28] Gastrointestinal bleeding caused by myxedema-associated coagulopathy may also be seen.[29] Neurologic manifestations of myxedema coma include depressed mental status, cerebellar signs, and, in up to 25% of cases, seizures, including reports of status epilepticus.[28,30] Patients may not initially present with frank coma but with milder signs of depressed mental status, only to gradually decline to a coma during the hospitalization. Laboratory testing often shows hyponatremia as well as anemia and acidosis.[28] Lumbar puncture often finds a high opening pressure with an elevated CSF protein level.[28] If an infection is suspected or if no obvious inciting factor that triggered the myxedema coma is found, cultures should be obtained to find a potential source of infection.

Diagnosis and management. Thyroid testing usually finds an abnormally high thyroid-stimulating hormone (TSH) level, but, as up to 10% of the hypothyroidism in myxedema coma can be due to hypothalamic or pituitary dysfunction, the TSH levels may be low or inappropriately normal.[28,31] Free thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) should therefore be measured in all patients with

Case 8-2

A 70-year-old woman with no known medical problems presented to the hospital with significantly depressed mental status. Five months earlier, she had told her daughter that she was starting to feel lethargic. A week before presentation, she mentioned feeling very cold and having difficulty staying warm during the winter weather. On the day of presentation, she was difficult to arouse and was immediately brought by ambulance to the hospital.

On examination, she was hypothermic to 35°C (95°F) and her blood pressure was 90/50 mm Hg with a heart rate of 90/min. She had dry, brittle skin and nonpitting edema in her face and hands. She was somnolent but arousable and diffusely areflexic. Laboratory evaluation revealed mild hyponatremia. Chest x-ray was negative, but urinalysis revealed leukocytes and gram-negative bacteria.

She was started on empiric antibiotics while waiting for urine cultures. Because of a high suspicion of myxedema coma, she was empirically started on IV thyroxine (T4) and stress dose hydrocortisone. The endocrine tests subsequently revealed primary hypothyroidism with a thyroid-stimulating hormone level greater than 100 mU/L (reference range 0.4 mU/L to 5.0 mU/L) and free T4 levels of 2 pmol/L (reference range 9 pmol/L to 23 pmol/L). The patient's condition gradually improved over the next several days. IV T4 therapy was transitioned to oral therapy, and the steroid was slowly tapered before the patient was discharged with close outpatient monitoring by an endocrinologist.

Comment. This patient presented with the cardinal hallmarks of myxedema coma, with hypothermia, depressed mental status, and signs and symptoms of hypothyroidism. The patient had no history of a thyroid disorder, but, as with this case, patients may be relatively asymptomatic or have undiagnosed hypothyroidism until an inciting factor, such as an infection, acutely precipitates the myxedema coma. Immediate recognition and treatment is critical, as myxedema coma has a high mortality rate.

KEY POINT

- The main goal of treatment of myxedema coma should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of any hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.

suspected myxedema coma to confirm hypothyroidism. Treatment should not be delayed while confirming the diagnosis. Because of the rarity of myxedema coma, no randomized clinical trials exist to guide its management; however, the main goal of treatment should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.[28] The optimal thyroid hormone therapy is controversial, with some advocating for the use of IV T4 (eg, 100 mcg to 500 mcg IV T4 followed by a maintenance dose of 50 mcg/d to 100 mcg/d until the patient is able to tolerate an oral regimen) instead of T3 because of reports of increased mortality with T3.[29]

Thyroid Storm (Thyroid Crisis)

Sustained thyrotoxicosis is most commonly due to Graves disease (autoimmune disease with antibody against TSH receptor) but may also be caused by a toxic multinodular goiter or TSH-secreting pituitary adenoma.[18] The neurologic complications of thyrotoxicosis can vary and include neuropsychiatric impairment (eg, anxiety and restlessness), movement disorders (eg, tremor and, rarely, choreoathetosis),[18] and neuromuscular disorders (eg, myopathy, periodic paralysis, and neuropathy) that often present

KEY POINTS

- Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.
- No set serum thyroxine (T4) or triiodothyronine (T3) criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation including thyroid-stimulating hormone, free T3, and free T4 (even with a normal thyroid-stimulating hormone level) should be conducted in all suspected cases.

insidiously; however, a precipitating factor (eg, infection) can trigger a thyroid storm in a susceptible patient who is thyrotoxic, leading to a true medical emergency with exaggerated signs and symptoms of thyrotoxicosis, including severe encephalopathy.[18]

Epidemiology and pathophysiology. The exact incidence of thyroid storm is difficult to accurately assess, but recent reports estimate that 1% to 2% of all hospital admissions for thyrotoxicosis are due to a thyroid storm.[32] Thyroid storm most commonly affects women and those with Graves disease.[32] The exact mechanisms leading to a thyroid storm are not known, but they likely involve an increased response to thyroid hormones, increased availability of free thyroid hormones, and enhanced binding of thyroid hormone to its receptor. Similar to myxedema coma, a precipitating factor, such as an infection or trauma, can trigger the thyroid storm in a patient who is thyrotoxic; however, 25% to 43% of patients presenting with a thyroid storm have no clear inciting factor.[28,32] Factors precipitating throtoxic storm are listed in **Table 8-4**.

TABLE 8-4 Factors Precipitating Thyrotoxic Storm[a]

▶ **Drugs**
Withdrawal of antithyroid drug treatment
Radioactive iodine treatment
Thyroxine/triiodothyronine overdose
Cytotoxic chemotherapy
Aspirin overdose
Iodinated contrast dyes
Organophosphate toxicity
▶ **Sepsis, infection**
▶ **Seizure disorder**
▶ **Pulmonary thrombo-embolism**
▶ **Burn injury**
▶ **Surgery, trauma, vigorous palpation of thyroid**
▶ **Metabolic disturbances**
Diabetic ketoacidosis
Hypoglycemia
▶ **Other**
Parturition
Emotional stress

[a] Modified with permission from Klubo-Gwiezdzinska J, Wartofsky L, Med Clin North Am.[28] © 2012 Elsevier. *sciencedirect.com/science/article/pii/S0025712512000168*.

Clinical presentation. Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.[32] Some of the cardinal manifestations include a high fever out of proportion to any infection; diaphoresis and tachycardia out of proportion to the fever; arrhythmias; and gastrointestinal symptoms, including nausea, vomiting, diarrhea, and possibly jaundice in severe cases.[28] Encephalopathy is commonly seen in the form of agitation, emotional lability, confusion, paranoia, psychosis, and eventually coma.[28] Additionally, cases of patients presenting with seizures or status epilepticus and stroke have been reported.[33] On laboratory evaluation, increased serum calcium levels can be seen due to thyroid-mediated increased bone resorption.[28,32] A moderate leukocytosis can be seen even in the absence of infection.

Diagnosis and management. The diagnosis of thyroid storm remains challenging and is largely based on clinical findings. No set serum T4 or T3 criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation, including TSH, free T3, free T4, and electrolytes will be useful in establishing the thyrotoxicosis and associated electrolyte abnormalities.[32] The goals of treatment of thyroid storm

are to inhibit new thyroid hormone synthesis (eg, with propylthiouracil or methimazole), inhibit thyroid hormone release (eg, with sodium iodine or lithium), block the peripheral effect of thyroid hormones (eg, with beta-blockers), and enhance the clearance of thyroid hormones (eg, with cholestyramine or plasma exchange).[28,32] External cooling and acetaminophen may be needed for hyperthermia.[32] Fluid resuscitation should be initiated for any volume depletion caused by fever, diarrhea, or vomiting.[32] Stress dose steroids can be administered to prevent adrenal insufficiency as well as decrease the peripheral conversion of T4 to T3. Finally, an extensive and exhaustive investigation should be initiated to identify the inciting factor. As infection is a leading trigger of a thyroid storm, empiric antibiotic therapy may also be useful in the management of thyroid storm. Despite early diagnosis and intervention, thyroid storm has a high mortality rate, from 10% to 75% in patients who are hospitalized.[28]

CALCIUM DISORDERS

Calcium homeostasis is normally tightly regulated by parathyroid hormone, calcitonin, and vitamin D.[34] The secretion of parathyroid hormone from the parathyroid gland is activated by low plasma calcium levels and inhibited by high plasma calcium levels. Parathyroid hormone increases calcium levels by activating osteoclasts, prompting the release of calcium from bone, increasing the activation of vitamin D, and stimulating reabsorption of calcium in the kidneys.[34] Vitamin D acts on the intestine to increase calcium absorption. In response to hypercalcemia, calcitonin is secreted by parafollicular C cells of the thyroid gland to inhibit osteoclast-mediated resorption of calcium in the bone.[34] Calcium disorders can develop from any pathologic process that leads to dysfunction in intestinal calcium absorption, bone resorption, or renal calcium reabsorption or calcium excretion.

Hypercalcemia has long been associated with changes in mental status, with hypercalcemic crisis being a true medical emergency that can lead to coma and death.[35,36] Similarly, acute hypocalcemia may present with neurologic manifestations, such as seizures requiring urgent evaluation and treatment.

Hypercalcemia

Hypercalcemia is a relatively common metabolic perturbation, affecting as many as 0.5% of all hospitalized patients, and is generally well tolerated if serum calcium levels are below 3.0 mmol/L (12 mg/dL).[37] However, higher or rapid elevation in serum calcium levels can lead to dysfunction in multiple organs, including the central nervous system.

Epidemiology and pathophysiology. The most common cause of hypercalcemia is underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium (**Table 8-5**).[36] Hypercalcemic crisis typically results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often triggered by an inciting factor such as an illness or thiazide diuretics.[36,38] Overall, hypercalcemic crisis is a rare clinical entity, affecting a reported 1.6% to 6% of patients undergoing parathyroidectomy.[38]

Clinical presentation. Hypercalcemia affects most organs, including the gastrointestinal system, resulting in anorexia, nausea, vomiting, dyspepsia,

KEY POINTS

- The goals of treatment of thyroid storm are to inhibit new thyroid hormone synthesis, inhibit thyroid hormone release, block the peripheral effect of thyroid hormones, and enhance the clearance of thyroid hormones.
- The most common cause of hypercalcemia is an underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium.
- Hypercalcemic crisis usually results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often with a known precipitating factor such as an illness or use of thiazide diuretics.

TABLE 8-5 Etiology of Hypercalcemia[a]

▶ **Parathyroid Disease**
Primary hyperparathyroidism due to benign parathyroid adenoma, parathyroid carcinoma, or parathyroid multiglandular hyperplasia as part of multiple endocrine neoplasia syndromes
Tertiary hyperparathyroidism
▶ **Malignancy**
Parathyroid hormone–related protein (humoral hypercalcemia of malignancy)
Local osteolysis mediated by cytokine release
Lytic bone metastasis
Multiple myeloma
Ectopic production of 1,25-dihydroxyvitamin D by the tumor (eg, lymphoma)
▶ **Endocrinopathies**
Adrenal insufficiency
Multiple endocrine neoplasia type 1, type 2A
Thyrotoxicosis
Pheochromocytoma
VIPoma (pancreatic endocrine tumor that secretes vasoactive intestinal peptide)
▶ **Granulomatous Disease**
Tuberculosis
Sarcoidosis
Endemic mycosis: histoplasmosis, coccidioidomycosis
Leprosy
Crohn disease
Berylliosis
▶ **Medications**
Estrogens
Lithium
Thiazide diuretics
Excess vitamin D or vitamin A ingestion
▶ **Miscellaneous**
Familial hypocalciuric hypercalcemia
Immobilization

[a] Modified with permission from Ahmad S, et al, Am J Med.[36] © 2015 Elsevier. *sciencedirect.com/science/article/pii/S0002934314009152*.

and abdominal pain; pancreatitis that may be severe and necrotizing; and renal dysfunction with dehydration, polydipsia, oliguria, and nephrocalcinosis.[36] Cardiovascular abnormalities are often present (eg, arrhythmias, heart block, and vascular calcification).[36] Neurologic manifestations are mainly neuropsychiatric/cognitive and neuromuscular in nature. Neuropsychiatric dysfunction can range from personality changes, such as irritability and depression, to lack of concentration, memory impairment, and, if the hypercalcemia is severe

enough, lethargy and coma.[34–36] Neuromuscular symptoms include generalized fatigue and muscle weakness affecting primarily the proximal muscles.[34] Other rare reported neurologic manifestations include parkinsonism and posterior reversible encephalopathy syndrome (PRES) as well as clinical symptoms and EEG findings similar to those seen with Creutzfeldt-Jakob disease.[39–41]

Diagnosis and management. While no uniform standard definition for hypercalcemic crisis exists, one reasonable but arbitrary definition is an albumin-corrected serum calcium level greater than 14 mg/dL associated with multiorgan dysfunction.[36] As approximately 40% of total serum calcium is bound to protein, primarily albumin, ionized (free) calcium levels (greater than 5.6 mg/dL) may be a more reliable assessment of calcium status if protein levels fluctuate, such as with sepsis.[37] Parathyroid hormone levels should be measured to determine if primary hyperparathyroidism is the etiology. If the parathyroid hormone level is only mildly elevated or inappropriately normal, then additional underlying processes should be considered (**Table 8-5**). However, in patients with acute and unstable hypercalcemic crisis, the appropriate treatment should not be delayed while trying to diagnose the underlying cause of the hypercalcemic crisis.

The overall goals of therapy are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia (eg, parathyroidectomy in primary hyperparathyroidism).[36] Patients with hypercalcemic crises are hypovolemic.[36,37] Adequate fluid resuscitation will lead to increased filtration of calcium and decreased reabsorption of calcium and promote calciuria in the kidneys. Fluid status should be carefully monitored to avoid fluid overload and congestive heart failure, particularly in patients with cardiac or renal failure.[36] Historically, loop diuretics were administered to further promote calciuresis, but they are no longer recommended because of the risk of aggravating volume contraction, except in patients in whom the fluid resuscitation may have provoked cardiogenic fluid overload.[36,42] Unless a contraindication exists, as soon as severe hypercalcemia is detected, all patients with hypercalcemic crisis should receive bisphosphonate therapy, which directly inhibits osteoclast activity but has a latency until reaching peak effect at 2 to 5 days.[36,37] Calcitonin can be administered to rapidly lower calcium levels, particularly in patients who are acutely ill, but can cause a hypersensitivity reaction and tachyphylaxis, which can be minimized by coadministration of glucocorticoid therapy.[37] Glucocorticoid therapy may be useful in multiple myeloma and lymphoma-related hypercalcemia as well as in hypercalcemia resulting from elevated levels of 1,25-dihydroxyvitamin D as seen in granulomatous diseases.[36] Hypomagnesemia and hypophosphatemia may be present in primary hyperparathyroidism and should be corrected.[34] Once the patient is stable, definitive curative therapy, such as parathyroidectomy for primary hyperparathyroidism, should be expeditiously pursued.[36]

KEY POINT

- The overall goals of therapy of a hypercalcemic crisis are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia.

Acute Hypocalcemia

Hypocalcemia can present with few, if any, symptoms, especially if the fall in calcium level is gradual. However, a significant reduction (to less than 7.5 mg/dL or 1.9 mmol/L) or a rapid rate of decline can lead to a true medical emergency with severe neurologic complications, including encephalopathy and seizures.

KEY POINT

■ Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults.

Epidemiology and pathophysiology. Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults (**Table 8-6**).[34,43,44] The rate of hypoparathyroidism after total thyroidectomies is estimated to be from 0.5% to 6.6%.[43] Since calcium is bound to proteins, serum calcium levels can fall when serum protein is reduced, such as during volume overload, chronic illness, malnutrition, or nephrotic syndrome. Vitamin D is important for intestinal calcium absorption, and severe vitamin D deficiency can also lead to significant hypocalcemia.[34,44] Certain medications can also decrease calcium, such as antiepileptic drugs, chemotherapy drugs, and bisphosphonates.[34,45] Hypomagnesemia can reduce parathyroid secretion or cause resistance to parathyroid hormone.[34]

Clinical presentation. Systemic manifestations of hypocalcemia include myocardial dysfunction, such as prolongation of the QT interval on ECG and cardiomyopathy in long-standing hypocalcemia.[46,47] Acute hypocalcemia can affect both the peripheral nervous

TABLE 8-6 Etiology of Hypocalcemia[a]

▶ **Associated With Low Parathyroid Hormone**
Surgical hypoparathyroidism after thyroid, parathyroid, or radical neck surgery for head/neck cancer
Autoimmune hypoparathyroidism with or without polyendocrine syndrome type I
Parathyroid destruction from radiation or infiltrative diseases (eg, metastasis, sarcoidosis)
Postparathyroidectomy hungry bone syndrome
Familial syndromes (eg, DiGeorge syndrome, Kearns-Sayre syndrome, Kenny-Caffey syndrome)
Activating mutations of the calcium-sensing receptor gene
Hypomagnesemia
Severe hypermagnesemia
▶ **Associated With High Parathyroid Hormone**
Vitamin D deficiency or resistance
Renal disease
Drugs (eg, anticonvulsants, bisphosphonates)
Extravascular deposition (eg, acute pancreatitis)
Parathyroid resistance (eg, missense mutation in parathyroid hormone, pseudohypoparathyroidism, hypomagnesemia)
Osteoblastic metastases of breast and prostate cancer
▶ **Pseudohypocalcemia**
Hypoalbuminemia
Acid-base disturbances
Gadolinium-based contrast agents

[a] Modified with permission from Agrawal L, et al, Handb Clin Neurol.[34] © 2014 Elsevier. *sciencedirect.com/science/article/pii/B9780702040870000498*.

system and the central nervous system. Patients may present with finger paresthesia, perioral numbness, painful finger contractions that may mimic dystonia (carpopedal spasm), or even laryngospasm that can cause respiratory compromise.[34]

Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.[34,45] In two reported cases, seizures were the first presenting symptom of hypocalcemia, appearing months to years after the thyroidectomy that had resulted in iatrogenic parathyroidectomy.[48] In a 2014 study of 70 patients with idiopathic hypoparathyroidism, seizures were common and present in 64.3% of patients, with the majority (86.7%) being generalized tonic-clonic seizures.[49] Seizures due to hypocalcemia can also occur in severe vitamin D deficiency, particularly in children and infants in developing countries due to dietary insufficiencies, while infants in developed countries presenting with hypocalcemic seizures are likely a result of an underlying endocrinologic etiology.[45] On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).[43] Increased intracranial pressure and papilledema may be present with hypocalcemia.[50]

Diagnosis and management. Serum calcium levels are usually lower than 7.0 mg/dL (or ionized calcium level lower than 0.8 mmol/L) in patients with acute symptomatic hypocalcemia.[44] Hypoparathyroidism can be diagnosed in patients who are hypocalcemic when the parathyroid level is normal or inappropriately low once hypomagnesemia has been ruled out.[43] If the parathyroid hormone level is high, then other causes must be evaluated, including measuring vitamin D levels (**Table 8-6**).

Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.[43] Calcium gluconate is preferred over calcium chloride, because it causes less tissue necrosis if extravasated. Vitamin D supplementation is required for patients who are hypocalcemic with significant vitamin D deficiency or hypoparathyroidism. If hypomagnesemia is found, magnesium must be supplemented as hypomagnesemia can lead to parathyroid hormone resistance.[34]

ACUTE GLYCEMIC DISORDERS

With the prevalence of diabetes mellitus increasing worldwide, complications resulting from diabetes mellitus are also increasing, including hyperglycemic crises and acute hypoglycemic episodes. As the brain relies almost entirely on glucose for its energy source, acute alterations in brain glucose levels can have a wide range of potentially devastating neurologic consequences, from profoundly depressed mental status to focal neurologic deficits that are often, but not always, reversible.[51,52] Recognizing these crises is important, as patients may not know they are diabetic and any significant delay in treatment could be fatal.

Hyperglycemic Crises (Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State)

Hyperglycemic crises can be classified as either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state, which are distinct clinical entities that require different clinical management.[53]

KEY POINTS

- Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.
- On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).
- Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.
- As the brain relies almost entirely on glucose for its energy source, insufficient glucose in the brain can have a wide range of potentially devastating neurologic consequences, from altered mental status to focal neurologic deficits that are often, but not always, reversible.

KEY POINTS

- Diabetic ketoacidosis is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.
- Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.
- The most common precipitant of diabetic ketoacidosis and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and altered mental status.

Epidemiology and pathophysiology. DKA is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.[54] The estimated annual incidence in the United States varies with age from 4 to 8 per 1000 patients in all age groups to 13.4 per 1000 patients in those younger than 30 years.[55] Hospital admission for DKA has increased by approximately 75% over the past 2 decades.[56] While DKA used to be seen almost exclusively in type 1 diabetes mellitus, it is now becoming more common in type 2 diabetes mellitus, with one-third of all DKA hospitalizations in the United States occurring in patients with type 2 diabetes mellitus.[55] The overall mortality rate of DKA in adults in the United States is less than 1% and slightly higher than 5% in the elderly and patients with severe comorbid medical conditions; however, DKA remains a significant cause of mortality in children and young adults with type 1 diabetes mellitus.[55]

Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.[54] Hyperglycemic hyperosmolar state is most commonly seen in older patients with type 2 diabetes mellitus but can be seen in younger patients and in patients with type 1 diabetes mellitus.[53,55] The mortality rate in hyperglycemic hyperosmolar state is generally higher than in DKA, with estimates ranging between 5% and 20% in the United States and United Kingdom.[53,54]

In DKA, the absolute or relative insulin deficiency combined with an increase in counterregulatory hormones (eg, glucagon, growth hormone, cortisol, and catecholamines) results in hyperglycemia, ketonemia, and metabolic acidosis.[56] The pathogenesis of hyperglycemic hyperosmolar state is less well understood, but a greater degree of dehydration appears to exist due to osmotic diuresis. Importantly, in hyperglycemic hyperosmolar state, despite a relative insulin deficiency resulting in inadequate glucose utilization, endogenous insulin secretion appears to be greater than in DKA and is adequate to prevent lipolysis and subsequent ketogenesis.[54] Despite the different etiologies, both DKA and hyperglycemic hyperosmolar state frequently have an inciting factor that triggers the crisis. The most common precipitant of DKA and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).[54,55] In the elderly, immobilization or an illness that restricts water intake can contribute to severe dehydration and hyperglycemic hyperosmolar state.[55] In young patients with type 1 diabetes mellitus, psychological and eating disorders are contributing factors in 20% of recurrent DKA.[54] Both DKA and hyperglycemic hyperosmolar state are associated with an inflammatory state with elevation of proinflammatory cytokines, which may explain the relatively high incidence of thrombotic events during a hyperglycemic crisis.[55]

Clinical presentation. A major difference in clinical presentation between DKA and hyperglycemic hyperosmolar state is that the metabolic alterations in DKA usually evolve in less than 24 hours, while a hyperglycemic hyperosmolar state typically evolves over several days to weeks.[54] In both conditions, the hyperglycemic crisis can be the presenting manifestation of the underlying diabetes mellitus. Both DKA and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss,

vomiting, dehydration, weakness, and altered mental status.[54,56] Gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, are frequent in DKA but uncommon in hyperglycemic hyperosmolar state.[54]

On examination, patients may have poor skin turgor, tachycardia, hypotension, and Kussmaul respirations (deep and labored breathing associated with metabolic acidosis in DKA).[54,56] Altered mental status can be severe, including significant lethargy and coma, which are more common in a hyperglycemic hyperosmolar state and correlate with hyperosmolality.[54] Seizures, including epilepsia partialis continua, and focal neurologic signs such as hemichorea and hemiballismus have also been reported in patients with a hyperglycemic hyperosmolar state (**Figure 8-3**).[57,58] Even if an infection was the inciting cause for the hyperglycemic crisis, patients can be normothermic or even hypothermic due to peripheral vasodilation.[54]

Diagnosis and management. The diagnosis of DKA and hyperglycemic hyperosmolar state can be made with the appropriate clinical picture and biochemical tests (**Table 8-7** and **Table 8-8**).[53,55] Patients may have a mildly elevated leukocytosis due to proinflammatory changes associated with DKA and hyperglycemic hyperosmolar state; however, if the leukocytosis is greater than 25,000/mm^3, then investigations into finding the source of an infection should be initiated.[56] Finding and treating any underlying infection is critical as mortality in DKA and hyperglycemic hyperosmolar state is rarely due to metabolic complications but from the underlying inciting illness.[54] Nonspecific elevations in serum amylase and lipase levels can be seen in approximately 15% to 25% of patients with DKA.[59]

KEY POINT

- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state can be associated with altered mental status, including lethargy and coma. These are more common in hyperglycemic hyperosmolar state and correlate with hyperosmolality.

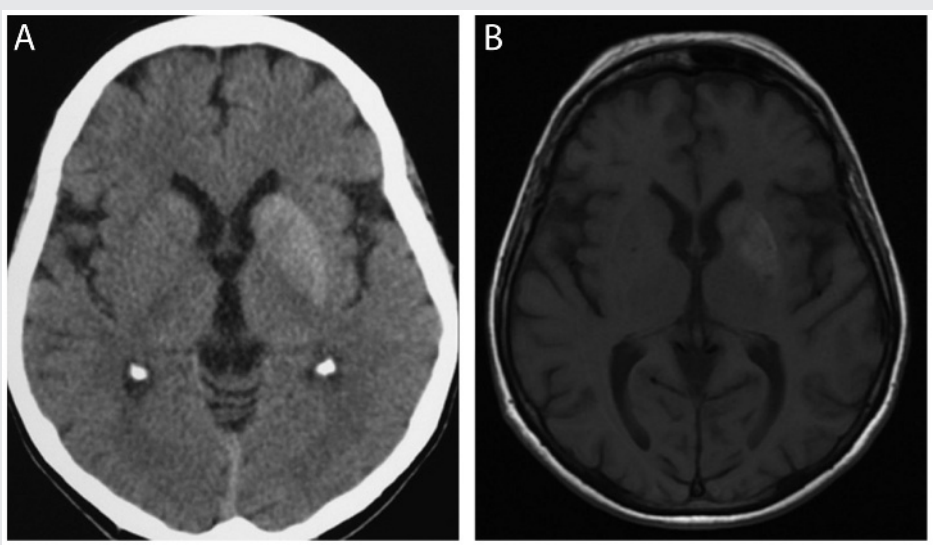

FIGURE 8-3 Brain CT (*A*) and brain MRI (*B*) of a patient with hemichorea-hemiballismus secondary to a hyperglycemic-hyperosmolar state. CT shows hyperdensity in the left caudate and putamen, which was confirmed by subsequent T1-weighted MRI.

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TABLE 8-7 Diagnostic Criteria for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State[a]

Diagnostic Criteria and Classification	Diabetic Ketoacidosis			Hyperglycemic Hyperosmolar State
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–15	<10	>15
Urine ketone	Positive	Positive	Positive	Small
Serum ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Variable

[a] Modified with permission from Nyenwe EA, Kitabchi AE, Diabetes Res Clin Pract.[55] © 2011 Elsevier. *sciencedirect.com/science/article/pii/S0168822711005146.*

KEY POINT

- The goals of therapy in hyperglycemic crises are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.

The goals of therapy in DKA and hyperglycemic hyperosmolar state are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.[53,54,56] Fluid resuscitation should begin with the goal of replacing approximately half of the water deficit in 12 hours.[53,56] Close hemodynamic and laboratory monitoring are critical to ensure that rapid changes and overcorrection leading to hypoglycemia and hypokalemia are avoided. Hydration alone has been shown to be sufficient to reduce blood glucose and osmolality.[53] Adequate fluid replacement is essential before starting insulin, as a risk of potentially devastating cardiovascular collapse exists if insulin is administered before

TABLE 8-8 Water and Electrolyte Deficits in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State[a]

Typical Deficits	Diabetic Ketoacidosis	Hyperglycemic Hyperosmolar State
Total water (L)	6	9
Water (mL/kg of body weight)	100	100–200
Serum sodium (mEq/L)	7–10	5–13
Cl^- (mEq/L)	3–5	5–15
K^+ (mEq/L)	3–5	4–6
PO_4 (mmol/L)	5–7	3–7
Mg^{2+} (mEq/L)	1–2	1–2
Ca^{2+} (mEq/L)	1–2	1–2

[a] Modified with permission from Nyenwe EA, Kitabchi AE, Diabetes Res Clin Pract.[55] © 2011 Elsevier. *sciencedirect.com/science/article/pii/S0168822711005146.*

adequate volume resuscitation. IV insulin therapy should be initiated in all patients with DKA or hyperglycemic hyperosmolar state who are acutely ill and transitioned to subcutaneous insulin when the hyperglycemic crisis is resolved.[53,56] Criteria for resolution of the ketoacidosis in DKA include a blood glucose less than 200 mg/dL and two of the following: a serum bicarbonate level of 15 mEq/L or higher, a venous pH higher than 7.3, and a calculated anion gap of 12 mEq/L or less.[54] A hyperglycemic hyperosmolar state is considered resolved when serum osmolality is normal and mental status returns to baseline.[54] One notable neurologic complication of DKA is cerebral edema, occurring in 0.7% to 1.0% of all DKA episodes in children, especially in those with newly diagnosed diabetes mellitus but also rarely in young adults under 20 years of age.[56] Headache is one of the earliest symptoms of cerebral edema, followed by rapid deterioration including lethargy, seizures, pupillary changes, papilledema, bradycardia, elevation in blood pressure, and respiratory distress.[54,56] Mortality is extremely high once neurologic symptoms manifest. To prevent cerebral edema, excess hydration and rapid reduction of plasma osmolarity and blood glucose levels should be avoided.[54]

Hypoglycemia

Hypoglycemia is probably the most common endocrine emergency and is associated with significant autonomic and neurologic complications in the acute setting, which, if left untreated, could have devastating consequences.[60, 61]

Epidemiology and pathophysiology. The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents; less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symptomatic hypoglycemia.[51,60] Significant hypoglycemia is common in type 1 diabetes mellitus, with a prevalence of 36% reported in one prospective study of 411 patients.[62] Patients with insulin-treated type 2 diabetes mellitus are also at risk for significant hypoglycemia, with one large study by the UK Hypoglycaemia Study Group finding an annual prevalence of 7%.[63]

Clinical presentation. Acute significant hypoglycemia can have widely varying presentations, with the most common being autonomic and neurologic symptoms. Patients having an acute hypoglycemic episode tend to initially have autonomic symptoms of sweating, anxiety, nausea, and palpitations followed by the neurologic symptoms.[64] Initial neurologic symptoms can include drowsiness, fatigue, visual changes, and cognitive changes (eg, erratic and irrational behavior), which, if left untreated, can lead to seizures and coma.[51,64] Rarely, the hypoglycemia can result in focal neurologic deficits that mimic stroke both clinically and on brain MRI.[60,65]

Diagnosis and management. Hypoglycemia may lead to acute neurologic symptoms, particularly when the blood glucose level is below 70 mg/dL (3.9 mmol/L).[66] In symptomatic patients who are awake, oral fast-acting carbohydrates should be the initial treatment. Patients who are comatose should first receive empiric IV thiamine for possible Wernicke-Korsakoff syndrome, followed by IV dextrose-containing solutions, with close monitoring to avoid rebound hyperglycemia.[61] If venous access is not available, subcutaneous or IM glucagon can be given.[61] While the majority of hypoglycemia is from adverse effects of antidiabetic medications, other rare causes (eg, an insulin-secreting tumor) should be investigated as needed. Prevention of any future hypoglycemia in patients with diabetes mellitus requires

KEY POINT

- The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents, but, less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symptomatic hypoglycemia.

a combination of patient education, dietary intervention, exercise management, medication adjustment, glucose monitoring, and clinical surveillance by the medical provider.[66]

CONCLUSION

Endocrine emergencies can present with acute and devastating neurologic manifestations such as seizures and coma, which, if left untreated, are often fatal. Many patients with endocrine emergencies have an undiagnosed underlying endocrine disorder that is acutely worsened by an inciting factor, such as a systemic infection. Therefore, accurately and promptly diagnosing and treating the endocrine disorder and any underlying inciting factor are paramount. As these endocrine emergencies are only infrequently encountered and many do not have a specific objective diagnostic test, a high degree of suspicion is needed to avoid missing the diagnosis. Furthermore, because of the overall rarity of endocrine emergencies, prospective or randomized clinical studies are lacking. Therefore, optimal management is sometimes unclear or controversial. Future studies of endocrine emergencies are clearly needed to help optimize both the diagnosis and the treatment of these disorders.

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Neurologic Complications of Transplantation

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ABSTRACT

Purpose of Review: This article describes the diagnosis and management of neurologic problems during hematopoietic cell and solid organ transplantation using time elapsed since transplantation as a guide to expected complications, including drug toxicities, infections, strokes, autoimmune phenomena, disease recurrence, and secondary neoplasms.

Recent Findings: Growing clinical experience in the neurology of transplantation has led to appreciation of the diverse clinical and radiographic spectrum of calcineurin inhibitor–related posterior reversible encephalopathy syndrome (PRES) and progressive multifocal leukoencephalopathy. Novel autoimmune phenomena illustrate the delicate balance between adequate immunosuppression and necessary host inflammatory defenses that can lead to organ rejection. The spectrum of infectious complications has changed with the evolution of new conditioning regimens.

Summary: Neurologic problems remain an important source of morbidity and mortality, both in the immediate transplantation period and for years after the procedure. As perioperative management has reduced the incidence of acute infections, graft versus host disease, and organ rejection, problems of long-term survivors require neurologic input into multidisciplinary management of chronic neurologic conditions impacting quality of life.

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INTRODUCTION

Since the first solid organ transplantation 60 years ago and the first hematopoietic cell transplantation 50 years ago, thousands of patients worldwide have benefited from these procedures. Neurologic complications remain frequent and devastating, increasing both early mortality and transplanted tissue loss. Neurologists commonly evaluate transplant recipients with altered sensorium, focal weakness, or a possible seizure, yet for these complex patients, consultants also must make more nuanced clinical judgments. Among many transplantation team consultative roles, neurologists must assess cognitive or other neurologic problems and prognosticate about future allograft problems and transplantation fitness based on prior neurologic syndromes; discern subtle infectious, vascular, and treatment-specific clues that have therapeutic implications; and recognize syndromes that impact the timing of transplantation, choice of immunosuppressive therapy, and quality of life in survivors.[1,2] **Figure 9-1** contrasts the consultative dilemmas in both types of procedures, providing an overview of transplantation neurology.

An organized approach to any transplantation problem involves consideration of several important sets of data, including:

- Patient demographics, preexisting comorbidities, and the underlying disease requiring treatment by transplantation

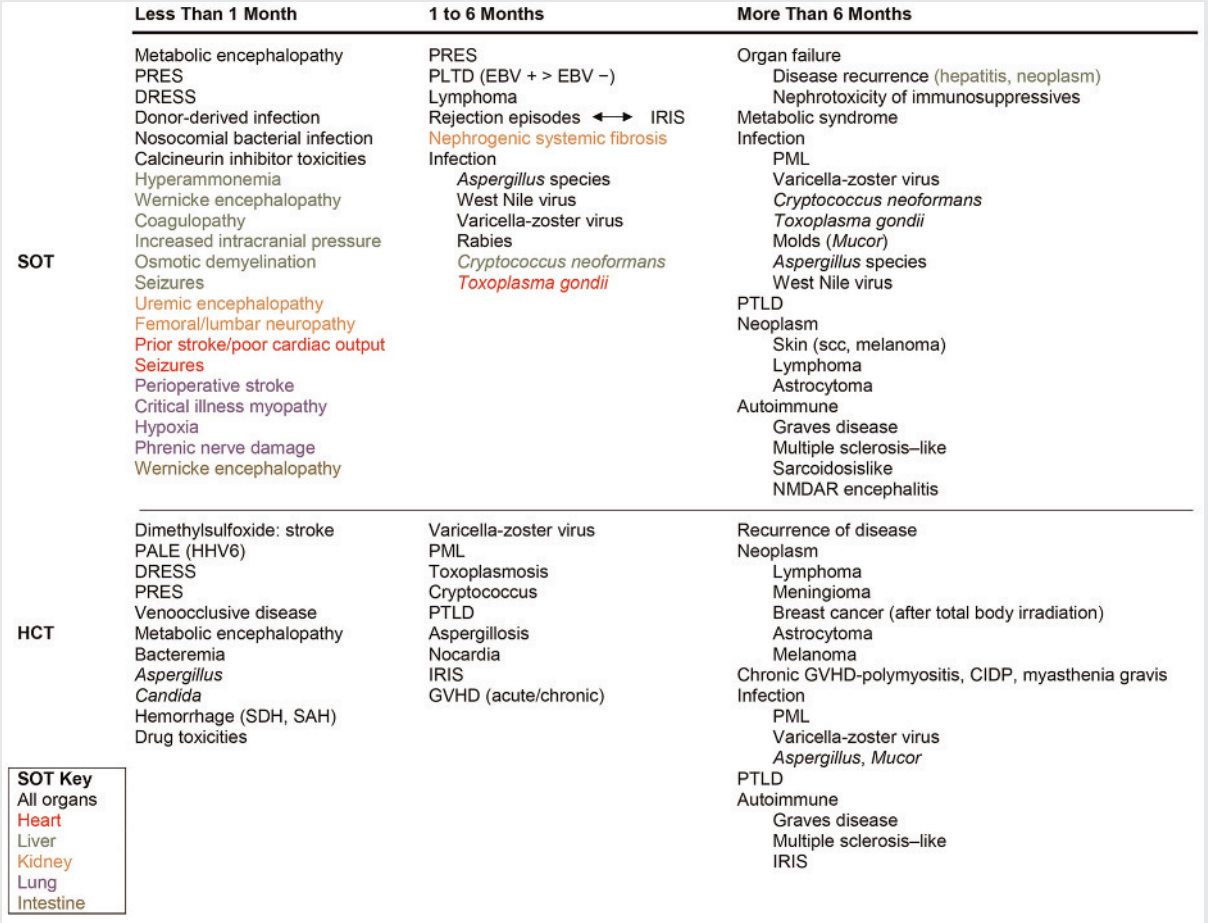

FIGURE 9-1 Comparative urgent transplantation conditions for the neurologist. Many of the most frequent complications occur in all types of solid organ transplantation (black font), while some are unique to specific types of solid organ transplants. The most significant differences between hematopoietic cell transplantation and solid organ transplantation occur in the first few weeks posttransplantation. Time intervals since transplantation are approximate, as considerable overlap exists in timing of complications.

Data from Pruitt AA, et al, Neurohospitalist.[1] *journals.sagepub.com/doi/abs/10.1177/1941874412455338*.

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; DRESS = drug reaction (or rash) with eosinophilia and systemic symptoms; EBV = Epstein-Barr virus; GVHD = graft versus host disease; HCT = hematopoietic cell transplantation; HHV6 = human herpesvirus 6; IRIS = immune reconstitution inflammatory syndrome; NMDAR = *N*-methyl-D-aspartate receptor; PALE = posttransplant acute limbic encephalitis; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; PTLD = posttransplant lymphoproliferative disorder; SAH = subarachnoid hemorrhage; scc = squamous cell carcinoma; SDH = subdural hematoma; SOT = solid organ transplantation.

- Localization of the lesion (central nervous system [CNS] versus peripheral nervous system, focal versus more generalized nervous system dysfunction)
- Donor and recipient antecedent infections and vaccination and prophylactic regimens employed
- Neuroimaging, CSF studies, and, when necessary, brain or meningeal biopsy

This article considers hematopoietic cell transplantation and solid organ transplantation separately, although many of the necessary drugs and their complications are shared by both types

of procedures. From the practical perspective of a consulting neurologist, however, specific metabolic and infectious problems at predictable intervals differ substantially, and the underlying indications for the transplantation procedures (eg, patients' preexisting diseases) require distinct considerations.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation is the preferred treatment for an expanding range of hematologic malignancies and bone marrow failure as well as for congenital metabolic disorders and both peripheral and central autoimmune conditions in a patient population whose median age is 10 years older than it was 2 decades ago.[3,4] The spectrum of neurologic complications varies with the conditioning regimen and the hematopoietic cell transplantation source, but major transplantation complications occur with all transplantation types and represent nearly one-fourth of all requests for inpatient neurology consultations at the author's institution. Hematopoietic cell transplantation procedures involve IV infusion of progenitor cells and are classified by:

- The pretransplantation conditioning regimen (full-intensity or myeloablative conditioning, reduced-intensity conditioning, or minimal-intensity conditioning using antibody-based cell depletion). In reduced-intensity conditioning, the effect of the immune response against the underlying hematologic malignancy, also called graft versus tumor effect, is an important therapeutic adjunct.
- The donor type (allogeneic, with a human leukocyte antigen–compatible donor; autologous, with a patient's own cells).
- The source of stem cells (bone marrow, peripheral blood, or umbilical cord blood).

Engraftment of infused cells occurs at 2 to 4 weeks, but immune reconstitution continues for at least 4 months, with complete recovery in about 1 year. In this article, early complications are defined as those occurring roughly within the first month, complications in the middle period are defined as those occurring during the second through sixth months, and late complications are defined as those occurring at any subsequent point. Graft versus host disease (GVHD) is a complication following allogeneic bone marrow or stem cell transplant. The transplanted cells attack the recipient's own tissues, often involving the skin and gastrointestinal tract but rarely involving the nervous system. Acute GVHD is defined as occurring within 100 days of transplantation.

Complications Occurring in the First Month After Transplantation

Early complications related to stem cell harvesting and conditioning include myocardial infarction and stroke associated with the dimethyl sulfoxide cryopreservative in stem cells.[5] In this period, nosocomial infections and pancytopenia-related problems, such as subarachnoid hemorrhage and subdural hematoma, arise. Seizures of multiple possible etiologies can complicate the perioperative period. Adverse effects of drugs must be distinguished from other causes of encephalopathy. The most important potential drug culprits in this period are the calcineurin inhibitors cyclosporine and tacrolimus.

The following comments about calcineurin inhibitor adverse effects apply both to solid organ transplantation and hematopoietic cell transplantation.

Their protean adverse effects include tremor, insomnia, headache, and mood disturbances, along with more serious problems such as akinetic mutism, optic neuropathy, hearing loss, seizures, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), brachial plexopathy, tumefactive demyelinating lesions, leukoencephalopathy, and brainstem involvement mimicking tumor or infection.[6–8] Thus, the adverse effects of cyclosporine and tacrolimus enter the particular differential diagnosis along with infectious, autoimmune, and neoplastic or paraneoplastic brainstem syndromes, providing an illustration of the broad considerations required for these complex patients, including the following: *Listeria*, enterovirus, herpes simplex virus, demyelination, Behçet disease, anti–delta/notchlike epidermal growth factor repeat containing (*DNER*) antibodies, JC virus (progressive multifocal leukoencephalopathy [PML]), varicella-zoster virus (VZV), osmotic demyelination, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), lymphoma, and GQ1b antibody–associated syndrome (Miller-Fisher variant of Guillain-Barré syndrome).

An important condition caused by calcineurin inhibitors is posterior reversible encephalopathy syndrome (PRES), a form of vasogenic edema first reported 20 years ago. **Figure 9-2**[9] illustrates examples of the diverse radiographic appearances of PRES. Most cases happen within the first 3 months after transplantation, but PRES can occur at any point in the patient's course.[10] The most typical location for PRES is in the posterior cerebral hemispheres. Recently recognized variations include what has been called subacute diencephalic angioencephalopathy, spinal cord PRES, and posterior fossa edema and hydrocephalus.[9,11–13] Since seizures frequently complicate PRES, questions with regard to the appropriate choice and duration of antiepileptic drug (AED) therapy arise in consultations. It is the practice in the author's institution to treat seizures accompanying PRES with a non–enzyme-inducing AED during and for 1 month following an acute episode.[14]

Major complications during the pancytopenic period include coagulation deficits, nosocomial or donor-derived infections, and nosocomial patterns specific to individual institutions, including methicillin-resistant *Staphylococcus aureus* (MRSA), pan-resistant enterococci, gram-negative bacteria, and *Candida* species acquired from IV lines. Reactivation of preexisting neurocysticercosis, Cytomegalovirus (CMV), and herpesviruses occurs both at this stage and months later.

Engraftment of cells is accompanied by rash, fever, and headache 2 to 4 weeks posttransplant as the absolute neutrophil count rises above 500/mm^3. This syndrome resembles and must be distinguished from posttransplant acute limbic encephalitis (PALE) with anterograde amnesia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), CSF pleocytosis, MRI abnormalities (most commonly in the hippocampi), and EEG abnormalities with or without clinical seizures. While other infections, such as herpes simplex virus 1, paraneoplastic disorders, and Wernicke encephalopathy, deserve consideration, the most common cause of this limbic confusional state is human herpesvirus 6 type B.[15,16] The disease is more common in the presence of severe GVHD and when alemtuzumab is part of the anti-GVHD regimen. Treatment includes AEDs and ganciclovir or foscarnet. The syndrome is associated with delayed platelet engraftment, CMV reactivation, and increased early mortality.[17]

KEY POINTS

- Tacrolimus and cyclosporine have multiple adverse effects and must be included in the differential diagnostic possibilities among the wide variety of central and peripheral nervous system complications that may occur following hematopoietic cell transplantation or solid organ transplantation.
- Posterior reversible encephalopathy syndrome, often caused by tacrolimus or cyclosporine, can occur at any point in the patient's course after hematopoietic cell transplantation or solid organ transplantation, is not necessarily related to drug level, and can present variably with altered sensorium, cortical blindness, seizures, spinal cord involvement, or hydrocephalus.
- Posttransplant acute limbic encephalitis is usually caused by human herpesvirus 6 and is associated with seizures, anterograde amnesia, MRI abnormalities in the hippocampi, and severe graft versus host disease, with early posttransplantation mortality.

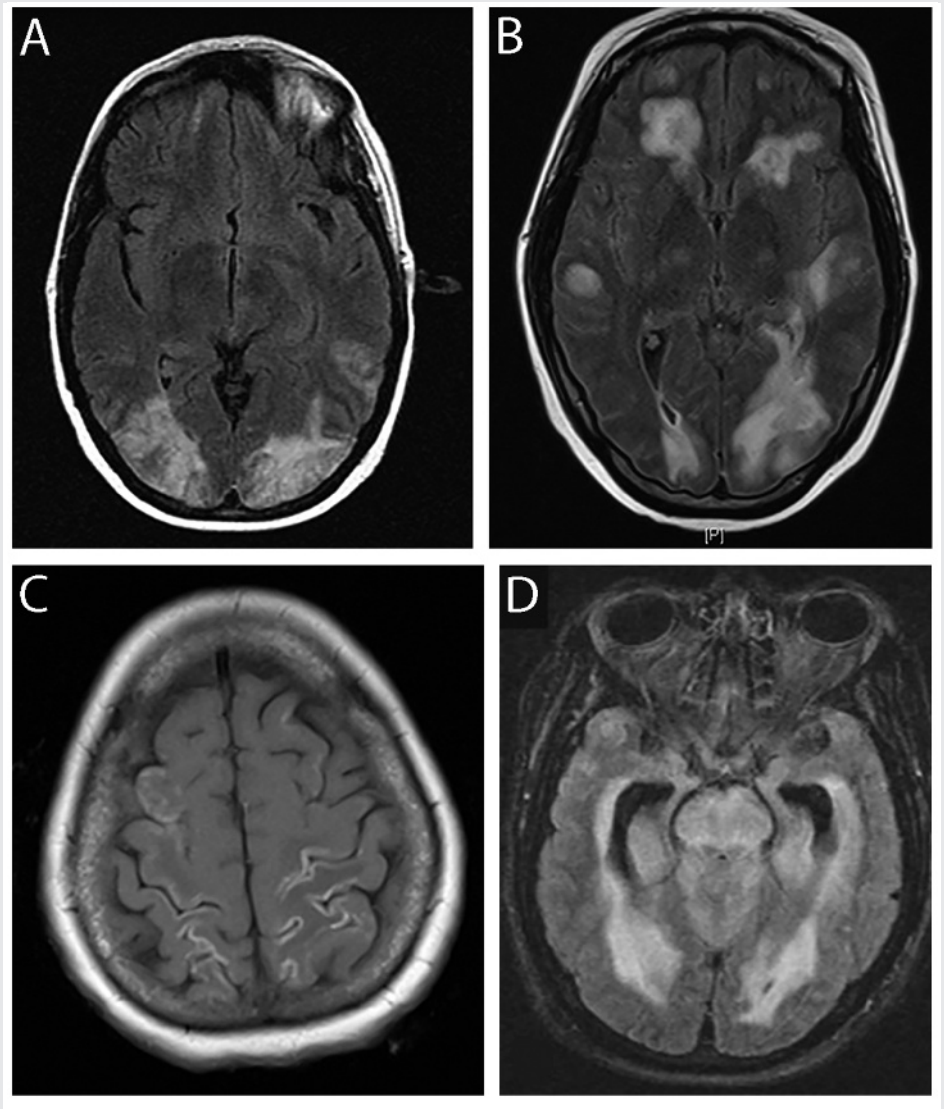

FIGURE 9-2 Posterior reversible encephalopathy syndrome. Posterior reversible encephalopathy syndrome (PRES) can have many MRI variations, as shown in these fluid-attenuated inversion recovery (FLAIR) MRI sequences. *A*, The typical pattern seen in PRES is hyperintensity in the occipital lobes. *B*, More widespread PRES, with involvement of more anterior cerebral areas. *C*, Laminar necrosis after resolution of the acute PRES episode. *D*, An extensive brainstem abnormality producing hydrocephalus caused by PRES and fully reversible.

Panel D reprinted from Kumar A, et al, Neurocrit Care.[9] © 2012, Springer Science + Business Media, LLC. *link.springer.com/article/10.1007/s12028-011-9663-z.*

Second Through Sixth Months Post–Hematopoietic Cell Transplantation

Because of impaired cellular immunity, opportunistic pathogens such as *Aspergillus*, CMV, and JC virus become a risk during the period 2 to 6 months following transplantation. Herpesviruses (eg, Epstein-Barr virus [EBV], VZV) are also important concerns whose risk continues throughout the post-transplantation course. **Table 9-1** lists

TABLE 9-1 **Viral, Fungal, and Protozoal Pathogens in Transplant Recipients**

Organism	Syndromes	Risk Factors	Diagnosis	Initial Treatment
Viruses				
Varicella-zoster virus	Diverse: refer to **Table 9-2**	Graft versus host disease (GVHD), corticosteroid use without antiviral prophylaxis	CSF polymerase chain reaction (PCR), IgG, IgM Serum PCR, IgM	IV acyclovir, foscarnet, ganciclovir
JC virus	Progressive multifocal leukoencephalopathy, cerebellar neuronopathy	Prolonged lymphopenia, steroids	CSF PCR, brain biopsy	Reduce immunosuppression
Human herpesvirus 6 (HHV6)	Limbic encephalitis, myelitis	Cord blood cell source, engraftment, syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	Hippocampal hyperintensity on MRI, CSF HHV6 PCR	Ganciclovir, foscarnet
Epstein-Barr virus	Meningoencephalitis, myelitis, brain tumors (posttransplant lymphoproliferative disorder, primary central nervous system lymphoma)	Solid organ transplantation: donor organ positive	CSF PCR	Rituximab, methotrexate, donor T-cell infusions
Cytomegalovirus (CMV)	Encephalitis, retinitis, myelitis	T-cell depletion, solid organ transplantation: donor organ positive, immune reconstitution inflammatory syndrome	Ependymal enhancement on MRI, CSF PCR	Valganciclovir, foscarnet, cidofovir
Herpes simplex virus 1	Limbic encephalitis, coexisting *N*-methyl-D-aspartate (NMDA) receptor encephalitis	Radiation	CSF PCR	Acyclovir
West Nile virus	Poliomyelitis, encephalitis, stiff person syndrome, movement disorders	Exposure to mosquitoes, rituximab	CSF PCR or CSF IgM/IgG	Supportive
Fungi				
Aspergillus species	Brain abscesses, sinusitis, infarction, meningitis, aneurysms	Hematopoietic cell transplantation: neutropenia, GVHD Solid organ transplantation: hypogammaglobulinemia, CMV, corticosteroids for rejection Both types of transplantation: lung infection	Galactomannan serum and CSF, MRI/MRA, brain biopsy	Voriconazole, amphotericin B

Continued on page 808

TABLE 9-1 **Viral, Fungal, and Protozoal Pathogens in Transplant Recipients** *Continued from page 807*

Organism	Syndromes	Risk Factors	Diagnosis	Initial Treatment
Mucorales	Rhinocerebral disease[a]	Solid organ transplantation: retransplant, iron excess Hematopoietic cell transplantation: GVHD, corticosteroids, CMV Both types of transplantation: diabetes mellitus	Fungal smear, pathology, culture from tissue	Liposomal amphotericin B with or without echinocandin
Cryptococcus species	Meningitis, cryptococcomas	More common in solid organ transplantation, cranial neuropathies, raised intracranial pressure, hydrocephalus	CSF cryptococcal antigen, CSF fungal smear	Liposomal amphotericin B with flucytosine
Candida species	Sepsis, meningitis, abscesses	Neutropenia, IV lines, usually in first 3 months posttransplant	Blood cultures, β-D-glucan	Amphotericin B, voriconazole
Parasites				
Toxoplasma gondii	Meningoencephalitis, brain and spinal cord abscesses	Donor-derived infections Solid organ transplantation: heart Hematopoietic cell transplantation: recipient seropositive, GVHD	Serum PCR, PCR in tissue	Pyrimethamine with sulfadiazine and leucovorin

CSF = cerebrospinal fluid; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging.
[a] Other pathogens causing frontal lobe lesions and sinusitis include *Fusarium* and *Scedosporium*.

KEY POINT

■ Neutropenia for more than 10 days is the biggest risk factor for invasive aspergillosis, which can present as a sentinel headache or sinus infection or as hemorrhage from aneurysms. CSF or serial serum galactomannan testing is useful. CSF may be neutrophilic or acellular.

important CNS pathogens in recipients of both solid organ transplantation and hematopoietic cell transplantation.

This section highlights diagnostic challenges for *Aspergillus* and VZV, two significant pathogens in this population. Clinicians should consult their own infectious disease services for optimal antibiotic coverage based on local epidemiologic and sensitivity trends.[18]

Aspergillus. Patients receiving allogeneic hematopoietic cell transplantation have been neutropenic for prolonged periods as they enter the second month posttransplantation. Prolonged neutropenia with an absolute neutrophil count less than 500/mm^3 is a risk factor for invasive fungal infections. Use of fludarabine and alemtuzumab in nonmyeloablative conditioning are additional risk factors. The usual route of infection is pulmonary or paranasal sinus disease. *Aspergillus* is angiotropic, invading blood vessels and leading to infectious aneurysms, vasculitis, and subarachnoid hemorrhage (**Case 9-1**). CSF can be acellular, but CSF or serum galactomannan testing is useful both for diagnosis and for treatment monitoring. Posterior fossa and corpus callosum lesions are particularly suggestive of aspergillosis. Mucormycosis, often in the setting of diabetic ketoacidosis, can present with similar sinusitis and then posterior fossa stroke presentation. The currently available antifungal agents

Case 9-1

A 50-year-old man with acute myelogenous leukemia presented with sudden altered mental status 3 months after receiving allogeneic hematopoietic cell transplantation from a human leukocyte antigen–matched unrelated donor. His immunosuppressive regimen included tacrolimus, mycophenolate, and prednisone. Several raised, red, nonpruritic nodules had been noted on his left arm 1 month earlier. He had reported painful progressive monocular blurred vision for 3 weeks, and his prednisone dose had been increased with partial response.

MRI showed extensive enhancement in the sphenoid sinus (**Figure 9-3**). Diffusion-weighted sequences showed restricted diffusion in the anterior cerebral artery distribution. Lumbar puncture revealed neutrophilic meningitis with elevated galactomannan levels. His course was complicated by a sudden fatal cerebral hemorrhage and a postmortem study showed focal vascular invasion by *Aspergillus*.

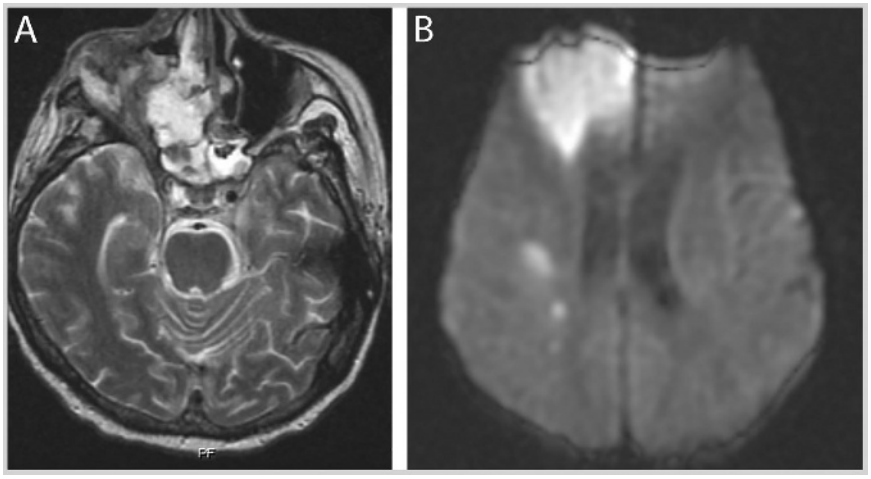

FIGURE 9-3 MRI of the patient in **Case 9-1** showing several features suggestive of invasive fungal infection. *A*, T2-weighted image shows extensive destructive sinus disease. *B*, Diffusion-weighted sequence shows anterior cerebral artery distribution acute infarction as well as smaller subcortical areas of ischemia.

Comment. This case illustrates some of the clues that might lead to an *Aspergillus* diagnosis before catastrophic neurovascular invasion, including skin and pulmonary abnormalities, sinusitis, and ocular involvement that can mimic anterior ischemic optic neuropathy.

differ in their activity against *Candida, Aspergillus,* and other pathogens and have numerous drug-drug interactions. Amphotericin is not metabolized by hepatic enzymes and has few interactions but causes nephrotoxicity exacerbated by coadministration with calcineurin inhibitors. Newer oral triazoles, such as voriconazole, have many drug-drug interactions, mandating clinicians' review of P450-metabolized drugs, such as anticoagulants and AEDs, whenever this class of antifungal is added to the regimen.[19]

Varicella-zoster virus. VZV complicates both hematopoietic cell

KEY POINTS

- Varicella-zoster infections begin to emerge in the second month posttransplant and are common in both hematopoietic cell transplantation and solid organ transplantation recipients, with manifestations ranging from dermatomal rash to cranial neuritis, myelitis, multifocal stroke, acute retinal necrosis, spinal cord infarction, and a temporal arteritis–mimicking syndrome.
- If the symptoms of varicella-zoster virus have been present for less than 1 week, polymerase chain reaction is the best diagnostic test. However, CSF varicella-zoster virus testing should include anti-varicella IgM and IgG in addition to CSF polymerase chain reaction if symptoms have been present longer than 1 week.

transplantation and solid organ transplantation with protean manifestations. Appropriate antiviral prophylaxis has deferred major VZV risk into the middle to late posttransplant periods. Dermatomal or disseminated skin lesions remain the most common manifestations and are associated with a risk of postherpetic neuralgia exceeding that of the immunocompetent population. **Table 9-2** summarizes the diverse syndromes caused by VZV. Diagnosis can be difficult as CSF pleocytosis is absent in one-third of cases, and many lack rash. A patient with neurologic disease potentially due to VZV should have CSF examination for VZV DNA by polymerase chain reaction (PCR) and for anti-VZV IgG and IgM antibodies, which are superior to PCR testing after the first 7 to 10 days of symptoms, as well as for diagnosis of vasculopathy, myelopathy, and brainstem syndromes due to VZV.[20] Patients who are immunocompromised should receive IV acyclovir.

TABLE 9-2 Varicella-Zoster Virus Clinical Syndromes and Diagnostic Tests[a]

▶ **Risk Factors**
Calcineurin inhibitors
Chronic glucocorticoids
Time after transplant: 1 month and thereafter
▶ **Syndromes**
Dermatomal rash
Disseminated rash
Dermatomal pain without rash (sine herpete)[b]
Vasculopathy: multifocal ischemic or hemorrhagic
Segmental motor weakness
Cranial nerves: Ramsay Hunt syndrome (V and VII), Vernet syndrome (IX, X), oculomotor
Eyes: outer retinal necrosis, keratitis
Cerebellar ataxia
Meningitis
Myelitis: acute, chronic
Temporal arteritis
Postherpetic neuralgia
▶ **Diagnosis**
Varicella-zoster virus (VZV) DNA by blood or CSF polymerase chain reaction
OR
Anti-VZV immunoglobulin M serum or CSF
OR
Anti-VZV immunoglobulin G CSF[c]

CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid.
[a] Modified with permission from Pruitt AA, et al, Neurohospitalist.[1] © 2013 The Authors. *journals.sagepub.com/doi/abs/10.1177/1941874412455338.*
[b] No rash present in 37% cases with stroke or encephalitis.
[c] More sensitive than polymerase chain reaction for vasculopathy or meningitis after the first week.

Late Complications of Hematopoietic Cell Transplantation

The majority of complications of hematopoietic cell transplantation occur in patients with allogeneic hematopoietic cell transplantation in the setting of chronic GVHD. Chronic GVHD is the leading cause of morbidity and death after allogeneic hematopoietic cell transplantation. Rarely, chronic GVHD may involve the CNS as a mass lesion or meningoencephalitis. Biopsy may be required for diagnosis.

GVHD affects multiple organs, producing systemic autoimmune disorders resembling Sjögren syndrome or scleroderma. Polymyositis and dermatomyositis are considered distinctive features of chronic GVHD based on the National Institutes of Health 2005 Consensus Criteria, whereas peripheral neuropathies, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or CIDP and myasthenia gravis, are associated with GVHD but require other organ involvement for confirmation.[21] Both B-lymphocyte and T-lymphocyte dysregulation are likely. Treatment of GVHD involving the nervous system includes prednisone, azathioprine, and cyclosporine or tacrolimus as well as IV immunoglobulin (IVIg), sometimes in combination with rituximab. Development of myasthenia gravis or AIDP/CIDP may reflect de-escalation of immunosuppression and improve upon resumption of immunosuppression.

CNS immune-mediated demyelinating syndromes are increasingly recognized. Case reports include optic neuritis and a relapsing-remitting course mimicking multiple sclerosis (MS) and AIDP. Most of these problems occur in the setting of chronic GVHD. For those cases in which association with tacrolimus or a viral etiology could be excluded, patients received IVIg, high-dose steroids, and sometimes rituximab. It is important to recognize the association of demyelinating syndromes with calcineurin inhibitors, as an MS diagnosis might be deemed a contraindication to transplantation listing for some patients or lead to erroneous institution of MS disease-modifying therapy (**Figure 9-4**). Median time from hematopoietic cell transplantation to demyelinating syndromes was 120 days in a series from Memorial Sloan Kettering Cancer Center, but symptoms in both patients who have received solid organ transplantation and those who have received hematopoietic cell transplantation also may occur much later.[22]

Progressive multifocal leukoencephalopathy. Subacute demyelinating disorders due to JC virus, a polyoma DNA virus targeting oligodendrocytes, have become significant problems in patients who have had hematopoietic cell transplantation or solid organ transplantation.[23] Variable MRI patterns and degrees of enhancement are illustrated in **Figure 9-5**. The only established treatment is immunosuppression reduction when possible. Consequences of reduction include exacerbation of GVHD or immune reconstitution and potential rejection of the transplanted organ. PML occurrence differs between patients who have had solid organ transplantation and those who have had hematopoietic cell transplantation, with median time to PML of 27 months after solid organ transplantation versus 11 months after hematopoietic cell transplantation. Median survival is 19.5 months for hematopoietic cell transplantation recipients versus 6.4 months for solid organ transplantation recipients.[24] **Case 9-2** illustrates the difficult compromises involved in balancing adequate immunosuppression and immune competence to fight PML in a solid organ transplant

KEY POINTS

- Chronic graft versus host disease affects multiple organs. The two most distinctive peripheral nervous system manifestations of chronic graft versus host disease are dermatomyositis and polymyositis, although myasthenia gravis, acute inflammatory demyelinating polyradiculoneuropathy, and chronic inflammatory demyelinating polyradiculoneuropathy are also associated with the syndrome.
- A relationship between calcineurin inhibitors and white matter abnormalities on MRI must always be suspected. This consideration will dictate a workup to exclude progressive multifocal leukoencephalopathy and will avoid unnecessary medicines such as multiple sclerosis drugs. Changing the immunosuppressive regimen may improve the clinical and radiographic signs and symptoms.

KEY POINT

■ The clinical and radiographic picture of progressive multifocal encephalopathy can be quite varied. Variable degrees of enhancement can occur, and immune reconstitution after reduction of immunosuppression can lead to neurologic symptom exacerbation as well as intensified graft versus host disease, threatening the viability of transplanted organs.

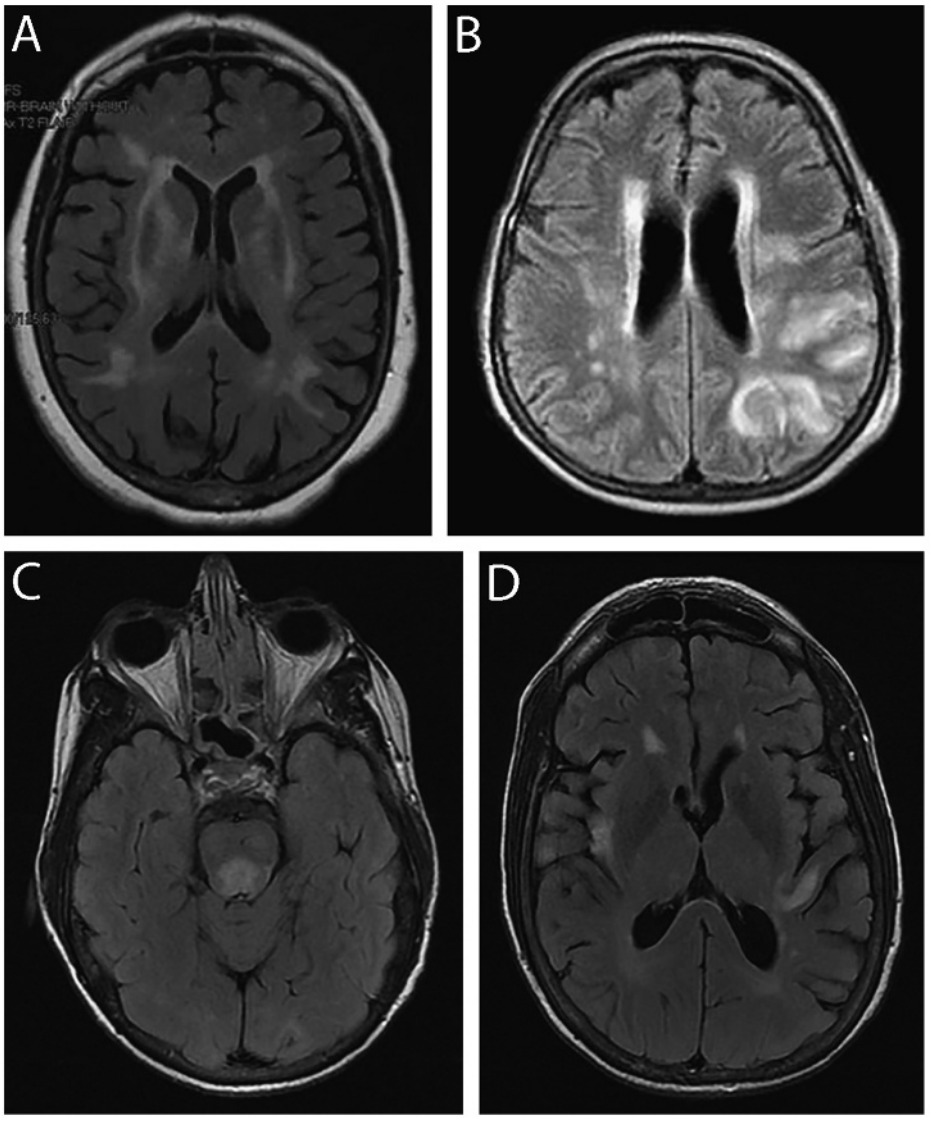

FIGURE 9-4 Reversible white matter abnormalities with calcineurin inhibitors and cyclosporine. Immunosuppressive neurotoxicity should be considered in the differential diagnosis of a progressive neurologic syndrome. All patients described in this figure improved clinically and radiographically with reduction or substitution of immunosuppressive agents. Fluid-attenuated inversion recovery (FLAIR) images (*A, B*) show symmetric leukoencephalopathy in a renal transplant recipient on tacrolimus initially thought to have primary progressive multiple sclerosis (*A*) and more focal white changes in a patient on tacrolimus with refractory seizures (*B*). *Panels C* and *D* show FLAIR abnormalities in a kidney/pancreas recipient who developed internuclear ophthalmoplegia and ataxia 5 years after transplantation. The syndrome resolved with cyclosporine reduction. When the first transplant failed, the patient was cleared for retransplantation based on the neurologic opinion that deficits were not likely to recur if calcineurin inhibitors were avoided.

recipient, although the same issues apply to hematopoietic stem cell transplantation–associated PML.

Long-term hematopoietic cell transplantation complications. Continued infection risk mandates vigilance for herpesviruses, PML, *Nocardia*, and toxoplasmosis, while underlying disease recurrence remains a threat. Of increasing importance with long-term survival is the myriad of consequences of successful therapy.[25] Neurologists become

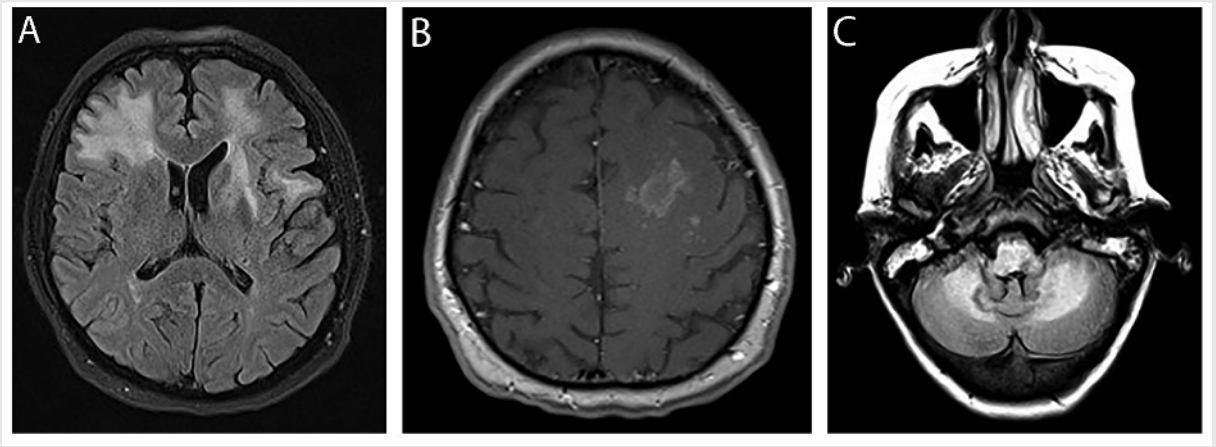

FIGURE 9-5 Progressive multifocal leukoencephalopathy may have variable MRI appearances. *A*, Fluid-attenuated inversion recovery (FLAIR) image shows typical white matter hyperintensities without mass effect. *B*, Gadolinium-enhanced T1-weighted image demonstrates variable enhancement that depends on the degree of host immunosuppression and increases with immune reconstitution. *C*, Diffuse FLAIR hyperintensity is seen in the posterior fossa, another typical location for progressive multifocal leukoencephalopathy.

part of a multidisciplinary surveillance team to maximize the patient's quality of life.[26] Systemic and primary CNS lymphomas and radiation-induced meningiomas continue to evolve years after transplantation. Revaccination is required for vaccine-preventable diseases, including polio, tetanus, measles, influenza, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.[27] Other systemic complications, such as cataracts and osteoporosis, require multidisciplinary team support. Recognition of persistent cognitive changes and suboptimal psychosocial recovery is illustrated by the statistic that only two-thirds of hematopoietic cell transplant recipients are working (either part-time or full-time) 1 year after diagnosis.[28] **Table 9-3**[29] summarizes the clinician's checklist of long-term transplantation complications.

SOLID ORGAN TRANSPLANTATION

Solid organ transplantation is the receipt of an entire organ, such as lung, liver, pancreas, heart, or kidney, from a tissue-matched deceased donor, or receipt of one kidney or partial liver or intestinal tissue from a related or matched unrelated living donor.[30] Few neurologic complications occur exclusively in recipients of specific solid organ transplants. Among solid organ transplant recipients, liver transplant recipients with fulminant failure have the most serious medical problems at transplantation and therefore more early complications (**Figure 9-1**). Pretransplant encephalopathy is present in many patients with end-stage liver disease or end-stage renal disease.

In addition to nosocomial infections, solid organ transplantation recipients are at risk for donor organ–associated infections. Fatal cases of human-to-human rabies transmission via liver, kidney, and arterial allograft have been reported, as have West Nile virus, *Balamuthia mandrillaris* (amebic encephalitis), and lymphocytic choriomeningitis virus.[31] Not surprisingly, infections are unusually severe, with, for example, high incidence of neuroinvasive disease and 30% mortality for West Nile virus.[32] Survival of three previously unvaccinated solid organ transplantation

KEY POINTS

- Management of long-term survivors of transplantation becomes surveillance of a chronic condition, the treatment of which predisposes patients to multiple complications, including metabolic syndrome, cataracts, secondary neoplasm, osteoporosis, the need for revaccination, and ongoing risk of rejection or recurrence of original disease.
- Donor organ–associated infections include West Nile virus, lymphocytic choriomeningitis virus, rabies, *Balamuthia mandrillaris*, and Cytomegalovirus.

Case 9-2

A 58-year-old man received an orthotopic liver transplant for hepatitis C. Nine months after transplantation with stable hepatic function, he developed progressive cognitive changes, leading to an MRI (**Figure 9-6**). CSF was negative for JC virus, but characteristic MRI findings led to a brain biopsy that revealed progressive multifocal encephalopathy (PML). Immunosuppression reduction stabilized the clinical and radiographic changes, but hepatitis C recurred, reducing the host's immune response and potentiating PML. Sofosbuvir improved liver function, but the patient's MRI and clinical parameters worsened, consistent with immune reconstitution inflammatory syndrome. Sofosbuvir was discontinued and the enhancement on MRI reduced, but transaminases became elevated again. Two months later, he was slightly better clinically, a state that remained stable 1 year later.

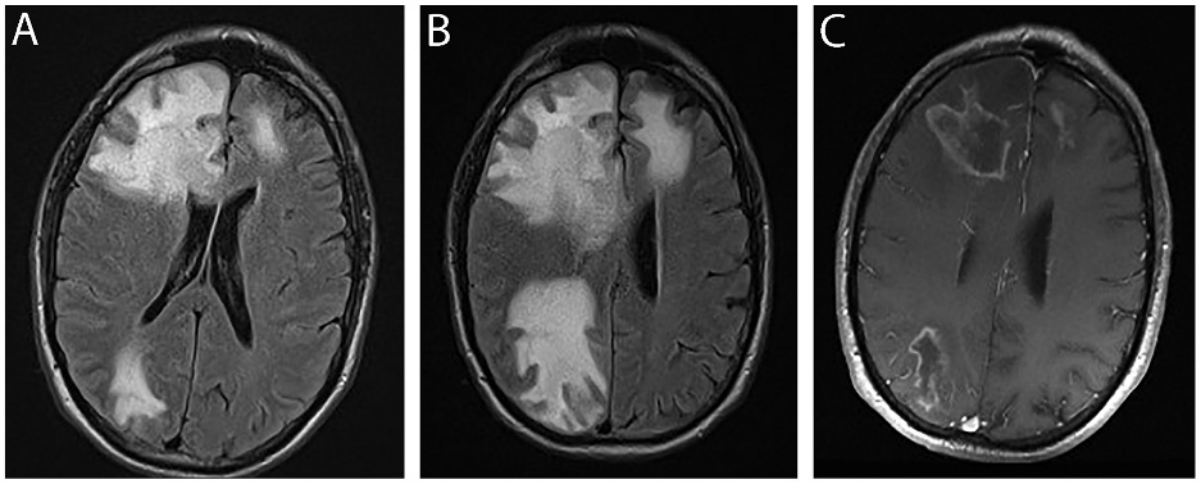

FIGURE 9-6 Imaging of the patient in **Case 9-2**. Initial fluid-attenuated inversion recovery (FLAIR) image shows extensive white matter hyperintensity suspicious for progressive multifocal leukoencephalopathy (*A*). With reduction in immunosuppression and treatment of recurrent hepatitis C, the patient's improved immune response led to worsening FLAIR abnormalities (*B*) and contrast enhancement (*C*) consistent with immune reconstitution inflammatory syndrome.

Comment. This case illustrates the risk of opportunistic infection at any point after transplantation and the dilemma of reducing immune suppression to control PML with the risk of organ rejection in the setting of immune reconstitution. Brain biopsy should be considered if CSF is nondiagnostic when MRI findings are suspicious for PML, as the less likely possibilities of posttransplant lymphoproliferative disorder/lymphoma or calcineurin toxicity must be excluded to design optimal therapy.

recipients from a donor with rabies after postexposure prophylaxis represents an unusual triumph of vigilance and prompt intervention.[33] CMV continues to cause meningeal, retinal, and ependymal complications. CNS fungal infections remain an uncommon, but highly lethal, complication. While cryptococcosis remains the most common fungal infection, endemic fungi such as *Histoplasma* and *Coccidioides* in the appropriate locations may cause fungal meningitis with or without parenchymal abnormalities. As in hematopoietic cell transplantation recipients, frontal lobe lesions should prompt sinus evaluation as a source of fungal infection.[34]

Despite improved antimicrobial prophylaxis, the incidence of cryptococcosis remains unchanged over 2 decades,

TABLE 9-3 Checklist of Potential Problems of Long-term Transplant Survivors[a]

▶ **Consequences of Antiepileptic Drugs, Chemotherapy, and Corticosteroids**
Cognitive impairment
Osteoporosis/avascular necrosis
Impaired fertility
Posterior reversible encephalopathy syndrome (PRES) (at any point after transplant; usually calcineurin inhibitor–related)
Eyes: cataracts, dry eye, glaucoma, optic neuropathy (calcineurin inhibitors)
Hearing loss (calcineurin inhibitors)
Infections: varicella-zoster virus, progressive multifocal leukoencephalopathy, *Pneumocystis jiroveci*, Epstein-Barr virus (posttransplant lymphoproliferative disorder/primary central nervous system lymphoma)
Chemotherapy-associated neuropathy
Metabolic syndrome
Nephrotoxicity (calcineurin inhibitors)
Revaccination requirements
Secondary neoplasms (melanoma, AML, squamous cell carcinoma, posttransplant lymphoproliferative disorder/primary central nervous system lymphoma)
▶ **Consequences of Radiation Therapy (Hematopoietic Cell Transplantation Conditioning Regimen)**
Cognitive impairment
Stroke
Metabolic syndrome
Hypothalamic/pituitary dysfunction
Communicating hydrocephalus
Radiation-induced tumor (astrocytoma, meningioma, sarcoma, breast, thyroid, skin)
Hearing loss
Cavernous angiomas (seizures, hemorrhage, spinal cord injury)
Superficial siderosis (hearing loss, ataxia, myelopathy)
Vascular disease (microangiopathy, pseudoaneurysms, large vessel stenosis)
Melatonin deficiency (sleep disturbances)

[a] Modified with permission from Pruitt AA, Continuum (Minneap Minn).[29] © 2015 American Academy of Neurology. *journals.lww.com/continuum/Fulltext/2015/04000/Medical_Management_of_Patients_With_Brain_Tumors.7.aspx*.

with an overall incidence of 2.8%; the majority of solid organ transplantation patients with cryptococcosis have CNS involvement. The diagnosis is problematic as patients may have little inflammation and initial CSF may be nondiagnostic. Subacute or chronic meningitis can produce progressive hydrocephalus, and multiple lumbar punctures may be required for diagnosis. Fungicidal therapy guidelines dictate lipid formulation of amphotericin B and flucytosine (**Figure 9-7**).

Along with PML and tuberculosis, cryptococcosis highlights the special problem of balancing infection control

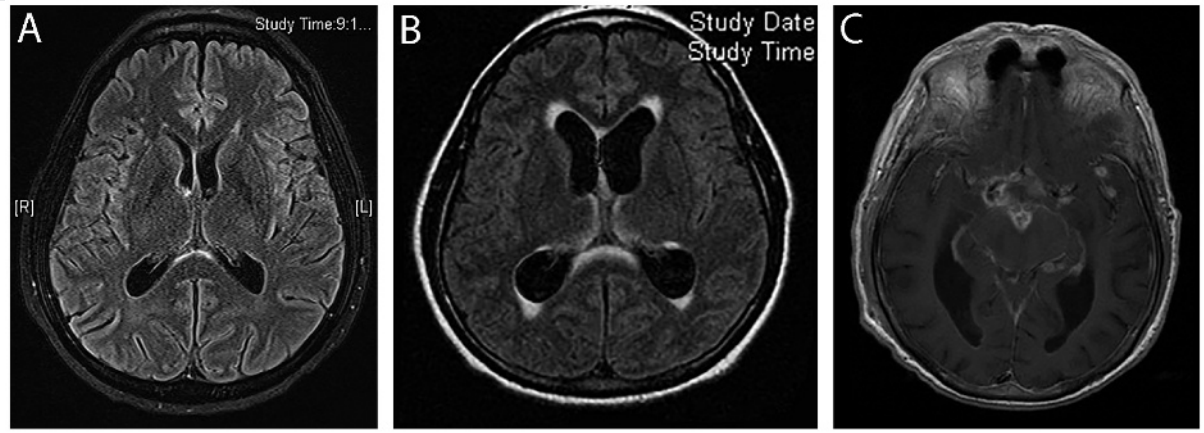

FIGURE 9-7 Cryptococcal meningitis with indolent course in patient with an orthotopic liver transplant and immune reconstitution inflammatory syndrome. A 28-year-old woman had received a liver transplant 2 years prior to presentation with headache and persistent lymphocytic meningitis. She had multiple negative lumbar punctures and a nondiagnostic meningeal biopsy for suspected sarcoidosis. Progressive hydrocephalus developed, shown on fluid-attenuated inversion recovery (FLAIR) images (*A*, *B*). When a cryptococcal diagnosis was confirmed after the fourth lumbar puncture 7 months after initial symptoms, antifungal treatment resulted in transient radiographic and clinical worsening with meningeal enhancement particularly visible around the brainstem, consistent with immune reconstitution (*C*, T1-weighted image with gadolinium).

KEY POINT

- Cryptococcosis can be difficult to diagnose in solid organ transplantation recipients as many patients have little inflammation and nondiagnostic initial CSF. Immune reconstitution inflammatory syndrome can occur when immunosuppression is reduced, with ensuing raised intracranial pressure and meningeal inflammation.

and the inflammatory response in solid organ transplantation recipients. Reduced immunosuppression to fight infection may predispose hosts to immune reconstitution inflammatory syndrome (IRIS) and allograft rejection. CNS IRIS, a diagnosis of exclusion, is suggested by patients' presentation after previously diagnosed infections. IRIS should be suspected when patients exhibit new or worsening clinical or radiographic signs of inflammation with negative cultures.[35] Diagnostic acumen requires broad consideration of infectious possibilities that should always be considered in the differential diagnosis of encephalopathy with negative MRI, as illustrated in the challenges of **Case 9-3**.

Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder denotes a spectrum of disorders ranging from benign polyclonal lymphoid hyperplasia to malignant monoclonal B-cell lymphoma (less often T-cell lymphoma). While primary CNS lymphoma is only 2% of CNS neoplasms in the general population, it is the most common brain tumor in solid organ transplant recipients, although CNS involvement is less common than abdominal or allograft-associated malignancies. Median time from solid organ transplantation to diagnosis was about 4.5 years in recent studies.[37] The risk of systemic lymphoma in the first year after kidney transplant is 20 times higher than in the general population, with higher rates in small intestine recipients (reaching 20% in these patients) and heart-lung transplant recipients. Posttransplant lymphoproliferative disorder leads to allograft loss in one-third of patients. Posttransplant lymphoproliferative disorder results from EBV-induced B-cell proliferation, but CSF and serum may be negative for EBV DNA. EBV may result in a fulminant picture within weeks of transplantation,[38] but over 20% of patients are more than 10 years posttransplant.

Case 9-3

A 68-year-old woman presented 19 months after a single-lung transplant with a 12-day history of severe back and leg pain. She had a rash consistent with varicella-zoster virus (VZV) in a left L2 distribution, which was treated with valacyclovir for 10 days. She received cefepime for pneumonia, but her mental status deteriorated to hypoactive delirium. She was difficult to rouse and had whole-body spasms every 10 minutes that did not correlate with EEG changes. Her tacrolimus level was elevated at 16.6 mcg/L, with dose reduction to a therapeutic level of 5 mcg/L. MRI was unremarkable. Because of inadequate explanation for her mental status changes from these studies, she underwent lumbar puncture, which showed 47 lymphocytes/mm^3, protein 299 mg/dL, and glucose 56 mg/dL. CSF cryptococcal antigen and polymerase chain reaction for VZV; Epstein-Barr virus; Cytomegalovirus; and human herpesvirus 1, 2, and 6 were negative, but VZV IgG was greater than 4000, with IgM elevated at 3.67. She was treated with IV acyclovir with good recovery.

Comment. This case illustrates the multiple etiologic possibilities of a nonspecific encephalopathy. Drug culprits considered appropriately were the elevated tacrolimus level and cefepime, an underrecognized cause of encephalopathy with myoclonic features.[36] However, thorough investigation must include CSF examination in patients who are immunocompromised. Since this patient's symptoms were more than 1 week old at the time of CSF evaluation, the appropriate test for VZV was antibody determination of IgG and IgM levels.

EBV-negative posttransplant lymphoproliferative disorders occur more often later than 1 year after solid organ transplantation. Brain MRI is nonspecific and biopsy is often necessary. Treatment consists of reduction of immunosuppression and administration of methotrexate, rituximab, or, investigationally, donor-derived EBV-specific T-cell infusions.[39,40]

Complications Specific to Type of Solid Organ Transplantation

While general considerations of immunosuppressive drug–related complications and infections apply to all types of solid organ transplant recipients, the neurologic consultant must be aware of important neurologic complications that are organ-specific. These are considered by organ type in the next sections.

Liver. The three most common reasons for orthotopic liver transplantation are alcoholic cirrhosis, primary biliary cirrhosis/sclerosing cholangitis, and hepatitis B or C. Acute liver failure due to acetaminophen overdose accounts for another large group of critically ill potential recipients. Common complications of acute liver failure are hyperammonemic encephalopathy, raised intracranial pressure, and seizures. Following transplantation, stroke, tremor, osmotic demyelination, and PRES are additional concerns. The characteristic MRI signature of hyperammonemic encephalopathy is signal change in the insular and cingulate cortices, with relative sparing of occipital and perirolandic areas.

A special issue requiring neurologic expertise is hepatic myelopathy. Here, the diagnostic role begins pretransplantation, with assessment of evolving neurologic problems that may upgrade patients' standing on transplantation wait lists. After orthotopic liver transplantation, marked improvement in myelopathy can occur.[41]

Similarly, neurologic input for management of cerebral edema and intracranial

KEY POINTS

- Posttransplant lymphoproliferative disorder, the most common brain neoplasm in transplant recipients, is a spectrum of B-cell proliferations ranging from polyclonal hyperplasia to fulminant multifocal parenchymal disease. The fulminant disorder can occur shortly after transplantation, while more indolent neoplasia can develop several years posttransplantation.
- Important neurologic conditions relevant to liver transplantation include both preoperative neurologic problems and those due to the transplantation procedure, including hyperammonemic encephalopathy, raised intracranial pressure, seizures, stroke, osmotic demyelination, and hepatic myelopathy.

KEY POINT

■ Cardiac transplant recipients have the highest risk of posttransplantation stroke and the highest risk for toxoplasmosis.

hypertension is essential. Therapeutic hypothermia has been used for preoperative, intraoperative, and refractory postoperative elevated intracranial pressure. Seizures occur in up to 30% of patients, and long-term EEG monitoring plays an important role in diagnosing altered mental status.

Osmotic demyelination (central pontine myelinolysis) results from large fluid shifts involved principally in the procedure of liver transplantation, with the usual clinical picture being a pontine syndrome. A similar radiographic picture without electrolyte abnormalities should raise suspicion of immunosuppressive toxicity, as reported in a case of tacrolimus-related locked-in syndrome.[7,42] Central pontine myelinolysis can occur without marked fluctuations in sodium levels.[43]

Kidney. The usual indications for renal transplantation include diseases with frequent vascular comorbidity that must be considered in assessing neurologic complications. These conditions include diabetes mellitus, glomerulonephritis, hypertension, and polycystic kidney disease. Specific transplant procedure complications include femoral nerve or lumbar plexus injury. Melanoma and lymphoma incidence are increased posttransplant in these often long-term survivors. Nephrogenic systemic fibrosis due to gadolinium exposure in patients with renal failure has been essentially eliminated by adherence to guidelines restricting gadolinium use to patients with glomerular filtration rate exceeding 30 mL/min or mandating postcontrast dialysis.

Heart. Heart transplant recipients have many pretransplant comorbidities. They have the highest risk of peritransplant ischemic stroke. Toxoplasmosis is a particular infectious risk, usually within 3 months of transplantation, as the parasite can be in myocardium.[44]

Lung. Lung transplant recipients have the highest perioperative mortality rate. High immunosuppression levels are required. Survival rates at 1, 5, and 10 years are 71.4%, 41.2%, and 25.4%, respectively.[45] Two-thirds of deceased patients die of systemic infectious complications. CMV and *Aspergillus* were the most common pathogens, some of which caused neurologic problems.[45] In the Mayo Clinic series, the most frequent in-hospital consultations were perioperative stroke, multifactorial encephalopathy, and critical illness polyneuropathy.[46]

Prognosis for Recipients of Solid Organ Transplantation

Despite great successes, the long-term prognosis remains guarded for recipients of solid organ transplantation because of vascular and infectious problems, the neurotoxicity of immunosuppressives, and disease recurrence, requiring consideration of retransplantation. Recently, kidney transplant recipients who received immunosuppression with belatacept, a non-nephrotoxic fusion protein, had reduced late allograft loss and better renal function.[47]

CONCLUSION

Hematopoietic cell transplantation and solid organ transplantation share many vulnerabilities leading to neurologic complications. Early infectious risks; multifactorial encephalopathy; drug toxicities, including the risk of PRES; and the consequences of long-term immunosuppression contribute to morbidity and mortality. Great strides have been made in the development of less toxic conditioning regimens and better management of infections while preserving grafts and managing GVHD. Neurologists' input is vital to appropriate diagnoses before, immediately after, and for years following transplantation.

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Nutrients and Neurology

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ABSTRACT

Purpose of Review: This article provides an update on the clinical presentation and management of neurologic disease related to key nutrient deficiencies.

Recent Findings: Major advances have been made in understanding the pathway related to vitamin B_{12} absorption and distribution. It is now known that deficiencies of vitamin B_{12} and copper have similar neurologic manifestations. Bariatric surgery is a risk factor for both. Alcoholism is just one of the many causes of thiamine deficiency. Early neurologic complications following bariatric surgery are often due to thiamine deficiency. Encephalopathy in the setting of alcoholism that persists despite thiamine replacement should prompt consideration of niacin deficiency. Pyridoxine deficiency and toxicity both have neurologic sequelae. Vitamin D deficiency and the risk for multiple sclerosis has been an area of ongoing research.

Summary: Optimal functioning of the nervous system is dependent on a constant supply of certain vitamins and nutrients. This article discusses neurologic manifestations related to deficiency of these key nutrients.

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INTRODUCTION

Particularly important for functioning of the nervous system are the B-group vitamins, which include vitamin B_{12} (cobalamin), vitamin B_9 (folic acid), vitamin B_1 (thiamine), vitamin B_3 (niacin), and vitamin B_6 (pyridoxine); vitamin D; vitamin E; and copper. Not infrequently, multiple nutritional deficiencies coexist. Vitamin B_6 and vitamin A toxicities have been implicated in sensory neuronopathy and pseudotumor cerebri, respectively. **Table 10-1**[1] summarizes the salient aspects related to these key nutrients.

Individuals at risk of nutritional deficiency include patients on prolonged or inadequate parenteral nutrition; those who are poor, homeless, or elderly; those who follow food fads or have eating disorders, such as anorexia nervosa or bulimia; those with malnutrition secondary to chronic alcoholism; and patients with pernicious anemia or other disorders that result in malabsorption, such as tropical sprue, celiac disease, cystic fibrosis, intestinal infestations and infections, inflammatory bowel disease, bowel resection or irradiation, and bacterial overgrowth. Malabsorption is also seen in disorders of the liver and pancreas.

For more information on Whipple disease, celiac disease, and inflammatory bowel disease, refer to the article "Gastroenterology and Neurology" by Ronald F. Pfeiffer, MD, FAAN,[2] in this issue of *Continuum*. Cerebrovascular disease, extrapyramidal and spinal cord disorders, and disorders of the peripheral and autonomic nervous system can be associated with gastrointestinal manifestations such as dysphagia, gastroparesis, and constipation. Motility disorders are outside the scope of this article but have been covered elsewhere.[3] Alcohol has been considered a source of "empty calories." The existence of alcohol-related dementia is more controversial than peripheral

neuropathy directly related to alcohol. Alcohol-related muscle damage can be seen in acute and chronic settings. Wernicke encephalopathy and cerebellar degeneration are the best characterized neurologic complications of alcoholism. Marchiafava-Bignami disease is an unusual disorder related to alcoholism that preferentially involves the corpus callosum.

Of particular concern in the developed world is the epidemic of obesity. The rising rates of bariatric surgery have been accompanied by neurologic complications related primarily to nutrient deficiencies, commonly vitamin B_{12}, thiamine, and copper. Early neurologic complications following bariatric surgery may be related to thiamine deficiency, while delayed complications are often due to copper or vitamin B_{12} deficiency. Mechanical or inflammatory mechanisms are also responsible for early neurologic manifestations following bariatric surgery. The early postoperative period is associated with compressive or stretch peripheral nerve injury, rhabdomyolysis, Wernicke encephalopathy, and inflammatory polyradiculoneuropathies. Late complications include peripheral neuropathy, myelopathy, and, less commonly, optic neuropathy or myopathy. Neurologic complications are more commonly seen after procedures associated with significant malabsorption, such as Roux-en-Y gastric bypass or biliopancreatic diversion with duodenal switch, as compared to predominantly restrictive procedures, such as adjustable gastric band placement or sleeve gastrectomy. Several recent reviews have addressed the topic of neurologic complications related to bariatric surgery.[4–6] The interested reader is also directed to a position article cosponsored by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery that addresses key issues pertaining to nutritional, metabolic, and nonsurgical support of the patient who has had bariatric surgery.[7]

While "overnutrition" is a problem in the developed world, undernutrition is an epidemic in the developing world. Protein and calorie deficiency in infants and children in underdeveloped countries results in kwashiorkor and marasmus, respectively.[8] Marasmus is due to caloric insufficiency and results in growth failure and emaciation in early infancy. It is caused by early weaning coupled with inadequate and unbalanced feeding. Kwashiorkor presents between 2 and 3 years of age. Its underlying cause is protein deficiency. Kwashiorkor arises when a child is weaned on a low-protein diet after prolonged breastfeeding. Clinically, it presents with growth failure and edema due to hypoalbuminemia. Generalized muscle wasting and weakness with hypotonia and hyporeflexia are seen. Hair loss and skin depigmentation may occur. The nervous system is susceptible to adverse effects of malnutrition during early stages of development. Malnourished children are indifferent and irritable. Cognitive deficits may be permanent and are associated with learning disability and behavioral problems.

While fortification of salt with iodine is a global success story, iron deficiency remains a concern in many parts of the world. The epidemic of myeloneuropathy seen in Cuba in the late 20th century was primarily due to nutritional factors. Tropical ataxic myeloneuropathy is generally due to toxic-nutritional factors. Cyanide toxicity due to cassava is the likely reason for the spastic paraparesis seen in the disorder called konzo; a high concentration of fluorine in drinking water results in the compressive

KEY POINTS

- Early neurologic complications following bariatric surgery may be related to thiamine deficiency, while delayed complications are often due to copper or vitamin B_{12} deficiency.
- Marasmus is due to caloric insufficiency and results in growth failure and emaciation in early infancy.
- Kwashiorkor presents between 2 and 3 years of age. Its underlying cause is protein deficiency.

TABLE 10-1 Summary of Sources, Causes of Deficiency, Neurologic Significance, Laboratory Tests, and Treatment for Deficiency States Related to Cobalamin, Folate, Copper, Vitamin E, Thiamine, Niacin, and Pyridoxine[a]

Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated With Deficiency
Cobalamin/ vitamin B_{12}	Meat, fish, egg, dairy products, fortified cereals, legumes	Pernicious anemia, advanced age (due to atrophic gastritis and food-cobalamin malabsorption), gastric surgery, acid reduction therapy, gastrointestinal disease, parasitic infestation by fish tapeworm, hereditary enzyme defects, nitrous oxide toxicity, rarely strict vegetarianism, often unknown	Myelopathy or myeloneuropathy, peripheral neuropathy, neuropsychiatric manifestations, optic neuropathy, autonomic dysfunction
Folate/vitamin B_9	In most foods (green vegetables, peas, beans, broccoli, yeast, fruits, nuts, dairy products, eggs, meat, liver, poultry, seafood); grains and cereals are fortified with folic acid	Alcoholism, gastrointestinal disease, folate antagonists (eg, methotrexate, trimethoprim), errors of folate metabolism The reduced folates in food are labile and readily lost under certain cooking conditions such as boiling	Neurologic manifestations are rare and indistinguishable from those due to vitamin B_{12} deficiency
Thiamine/thiamin/ vitamin B_1	Enriched, fortified, or whole-grain products, legumes, nuts, organ meats Dairy products, green vegetables, seafood, and fruits are poor sources	Recurrent vomiting, gastric surgery, alcoholism, extreme dieting, critical illness, increased demand with marginal nutritional status	Beriberi (dry, wet, infantile), Wernicke encephalopathy, Korsakoff syndrome
Niacin/vitamin B_3	Meat, fish, poultry, eggs, dairy products, enriched bread, fortified/whole-grain cereals, pulses	Corn as primary carbohydrate source, alcoholism, malabsorption, carcinoid and Hartnup syndrome, vitamin B_6 deficiency, excess dietary neutral amino acids, frequent dialysis	Encephalopathy (peripheral neuropathy)

Laboratory Tests	Treatment	Additional Comments
Serum cobalamin, serum methylmalonic acid, plasma total homocysteine, hematologic tests (anemia, macrocytosis, neutrophil hypersegmentation), serum gastrin, intrinsic factor and parietal cell antibodies (Schilling test no longer available)	IM vitamin B_{12} 1000 mcg daily for the first week, followed by weekly for the first month, then monthly thereafter Cyanocobalamin is the form commonly used in United States; hydroxocobalamin is the form preferred in parts of Europe as it requires less frequent injections; may be more allergenic	Even in the presence of severe malabsorption, many years may pass before vitamin B_{12} deficiency develops
Serum folate, red blood cell folate (more reliable indicator of tissue stores than serum folate), plasma total homocysteine	Oral folate 1 mg 3 times a day followed by a maintenance dose of 1 mg/d; for patients who are acutely ill, 1–5 mg/d (parenteral); supplementation with 0.4 mg/d in women in childbearing years as prophylaxis against neural tube defects	Clinically significant depletion of body folate stores may be seen in weeks to months Higher requirements in pregnancy, lactation, methotrexate toxicity Folate in foods has a bioavailability of less than 50%; folic acid supplements are in the monoglutamate form and have a bioavailability approaching 100% Folate deficiency generally coexists with other nutrient deficiencies
Urinary thiamine, serum thiamine, erythrocyte transketolase activation assay, red blood cell thiamin diphosphate	100–300 mg/d thiamine (IV, IM, oral); higher doses may be required in Wernicke encephalopathy; infantile beriberi: 5–20 mg parenteral thiamine	Patients who are at risk should receive parenteral thiamine before administration of glucose or parenteral nutrition
Urinary excretion of methylated niacin metabolites	25–100 mg nicotinic acid given 3 times a day (IM, oral)	A short half-life of nicotinic acid necessitates 3-times-a-day dosing

Continued on page 826

TABLE 10-1 **Summary of Sources, Causes of Deficiency, Neurologic Significance, Laboratory Tests, and Treatment for Deficiency States Related to Cobalamin, Folate, Copper, Vitamin E, Thiamine, Niacin, and Pyridoxine**[a] *Continued from page 825*

Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated With Deficiency
Pyridoxine/ vitamin B_6	Meat, fish, eggs, soybeans, nuts, chickpeas, dairy products, starchy vegetables, noncitrus fruits, whole-grain cereals	Vitamin B_6 antagonists (isoniazid, hydralazine, penicillamine), alcoholism, gastrointestinal disease	Infantile seizures, peripheral neuropathy (pure sensory neuropathy with toxicity)
Vitamin A	Liver, β-carotene (carrots, papaya, oranges, green leafy vegetables)	Diet containing predominantly rice and wheat, alcoholism, malabsorption	Night blindness, impaired taste, keratinization (cornea, conjunctiva, respiratory, gastrointestinal, urinary tract)
Vitamin D	Sunlight, eggs, dairy products, liver	Inadequate exposure to sunlight, malabsorption, gastric bypass	Proximal myopathy, tetany
Vitamin E (α-tocopherol)	Vegetable oils (sunflower and olive), leafy vegetables, fruits, meats, nuts, cereal	Chronic cholestasis (particularly in children), pancreatic insufficiency, gastrointestinal disease, total parenteral nutrition, ataxia with vitamin E deficiency, homozygous hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease	Spinocerebellar syndrome with dorsal column involvement and peripheral neuropathy, ophthalmoplegia, pigmentary retinopathy
Copper	Organ meats, seafood, nuts, mushrooms, cocoa, chocolate, beans, legumes, whole-grain products	Gastric surgery, zinc toxicity, gastrointestinal disease, total parenteral nutrition and enteral feeding, rarely acquired dietary deficiency, often unknown	Myelopathy or myeloneuropathy

IM = intramuscular; IV = intravenous.
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Laboratory Tests	Treatment	Additional Comments
Plasma pyridoxal phosphate	50–100 mg/d pyridoxine (oral); pyridoxine supplementation in patients on isoniazid	Excess consumption of vitamin B_6 can cause a sensory neuronopathy
Vitamin A levels	Severe deficiency may require 100,000 IU/d orally or IM for 3 days, followed by 50,000 IU/d for 2 weeks; followed by 10,000–20,000 IU/d for 2 months	Pseudotumor cerebri due to vitamin A toxicity
Serum 25-hydroxy vitamin D, calcium, phosphorus, alkaline phosphatase, parathyroid hormone levels	400 IU/d prevents deficiency, 50,000 IU per week may be required to treat clinical deficiency	Vitamin D functions more like a hormone than a vitamin Multiple sclerosis risk linked to vitamin D deficiency
Serum vitamin E, ratio of serum vitamin E to sum of serum cholesterol and triglycerides, adipose tissue vitamin E level	Vitamin E ranging from 200 mg/d to 200 mg/kg/d (oral, IM); supplementation of bile salts in some patients	Vitamin E deficiency is virtually never the consequence of a dietary inadequacy Neurologic findings are rare in vitamin E–deficient adults with chronic cholestasis Vitamin E bioavailability is dependent on food fat Years of malabsorption are required before stores are depleted
Serum and urinary copper, serum ceruloplasmin, serum and urinary zinc, hematologic parameters (anemia, neutropenia, vacuolated myeloid precursors, ringed sideroblasts, iron-containing plasma cells)	Oral elemental copper: 8 mg/d for the first week, 6 mg/d for the second week, 4 mg/d for the third week, and 2 mg/d thereafter Parenteral therapy: 2 mg elemental copper IV, given daily for 5 days and periodically thereafter Commonly used copper salts include copper gluconate, copper sulfate, and copper chloride	Hyperzincemia of indeterminate cause may be present even in the absence of excess zinc ingestion Speculative whether copper deficiency may be responsible for subacute myelo-optic neuropathy (secondary to clioquinol)

KEY POINT

■ Food-bound cobalamin malabsorption refers to reduced liberation of cobalamin from food proteins and results from achlorhydria, gastritis, gastrectomy, and the use of proton pump inhibitors or antacids. It is the most common cause of vitamin B_{12} deficiency and may affect up to 20% of older adults.

myeloradiculopathy seen in fluorosis; and the neurotoxin responsible for the chickling peas (*Lathyrus sativus*)–related spastic paraparesis of lathyrism is β-*N*-oxalyl-amino-L-alanine (L-BOAA). The subacute myelo-optic neuropathy seen in Japan in the past century was likely due to clioquinol toxicity. It has been suggested that clioquinol-induced copper deficiency may have been the basis of clioquinol toxicity.[9,10] Whether a flour made from seeds of the false sago palm (*Cycas circinalis* or *Cycas micronesica*) may have been the cause of the amyotrophic lateral sclerosis and parkinsonism dementia complex of Guam is unclear.[11]

Vitamin B_2 (riboflavin), vitamin B_5 (pantothenic acid), and vitamin B_7 (biotin) are excluded from this article but summarized briefly here. Mutations in *SLC52A2* encoding the riboflavin transporter RFVT2 are known to cause some childhood-onset motor neuron diseases (referred to as Brown-Vialetto-van Laere syndrome).[12] The modern-day neurologic significance of pantothenic acid relates to pantothenate kinase–associated neurodegeneration, an extrapyramidal disorder associated with brain iron accumulation that results from mutations in the *PANK2* gene.[13] The clinical significance of biotin deficiency is primarily in the context of the neonatal-onset disease due to biotinidase deficiency and the infantile-onset disease due to holocarboxylase deficiency.[14] Seizures, ataxia, hypotonia, and encephalopathy may be associated with alopecia and an eczematous rash in biotin deficiency.

VITAMIN B_{12}

Vitamin B_{12} refers to a specific group of cobalt-containing corrinoids, also referred to as cobalamins. Food cobalamin is hydroxocobalamin. Adenosylcobalamin and methylcobalamin are the active coenzyme forms. Cyanocobalamin is a stable synthetic pharmaceutical that has to be converted to adenosylcobalamin or methylcobalamin to become metabolically active. Even though vitamin B_{12} refers specifically to cyanocobalamin, the terms cobalamin and vitamin B_{12} are generally used interchangeably. Foods of animal origin are the major dietary sources. In some countries, cobalamin-fortified cereals are particularly efficient sources. Biochemical and genetic approaches have identified novel proteins in the cobalamin transport pathway that are responsible for its uptake and transport (**Figure 10-1**).[15–17] Methylcobalamin is a cofactor for methionine synthase in a methyl-transfer reaction that converts homocysteine to methionine. Methionine is adenosylated to *S*-adenosylmethionine, a methyl group donor required for neuronal methylation reactions. Decreased *S*-adenosylmethionine production leads to reduced myelin basic protein methylation. Adenosylcobalamin is a cofactor for mitochondrial L-methylmalonyl coenzyme A (CoA) mutase, which catalyzes the conversion of L-methylmalonyl CoA to succinyl CoA. Accumulation of methylmalonate and propionate provides abnormal substrates for fatty acid synthesis.

Causes of Deficiency

An acidic environment in the stomach is required for the release of cobalamin from food protein. Food-bound cobalamin malabsorption refers to reduced liberation of cobalamin from food proteins and results from achlorhydria, gastritis, gastrectomy, and the use of proton pump inhibitors or antacids. It is the most common cause of vitamin B_{12} deficiency and may affect up to 20% of older adults.[18–20] Food-bound cobalamin malabsorption does not affect free cobalamin, including recycled biliary cobalamin. Food-bound

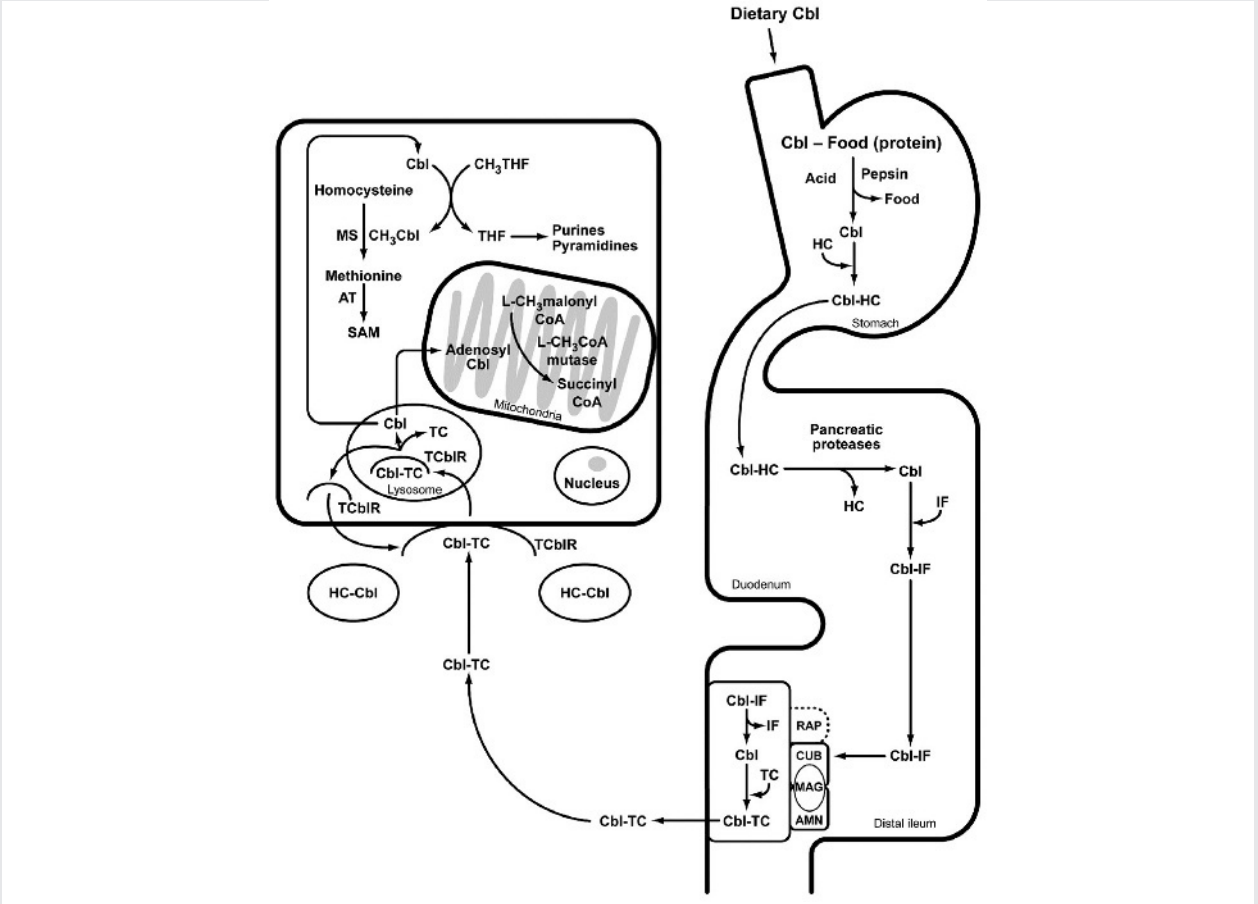

FIGURE 10-1 Cobalamin absorption and metabolism. In the stomach, cobalamin (Cbl) bound to food is dissociated from proteins in the presence of acid and pepsin. The released Cbl binds to haptocorrin (HC). HC is secreted by many cell types, including glandular cells (salivary glands, gastric mucosa, and others). In the small intestine, pancreatic proteases partially degrade the Cbl-HC complex at neutral pH and release Cbl, which then binds with intrinsic factor (IF). IF is a Cbl-binding glycoprotein secreted by parietal cells in the fundus of the stomach. The Cbl-IF complex binds to a specific receptor in the ileal mucosa called cubilin (CUB) and is then internalized. The internalization of CUB with Cbl-IF is facilitated by amnionless (AMN), an endocytic receptor protein that directs sublocalization and endocytosis of CUB with its Cbl-IF complex. The megalin receptor (MAG) may play a role in the stability of the CUB-AMN complex. Like MAG, the receptor-associated protein (RAP) can interact with CUB, but the precise role of these proteins in CUB-mediated Cbl-IF absorption has not been determined. The Cbl-IF complex enters the ileal cell, where IF is destroyed. In addition to the IF-mediated absorption of ingested Cbl, there is a nonspecific absorption of free or crystalline Cbl that occurs by passive diffusion at all mucosal sites. This is a relatively inefficient process by which 1% to 2% of the ingested amount is absorbed. This passive diffusion pathway supports the use of oral formulations instead of IM injection for treatment of vitamin B_{12} deficiency.

Transcobalamin (TC) is a nonglycosylated plasma protein that carries 10% to 30% of the total Cbl. The rest is bound to HC. Cbl bound to HC is called holohaptocorrin. It is metabolically inert and reflects tissue levels of vitamin B_{12}. TC-bound Cbl (holotranscobalamin) represents the active form of Cbl, is available for cellular uptake, and reflects rapidly turning over vitamin B_{12}. Serum Cbl determination measures both serum holohaptocorrin and serum holotranscobalamin, and therefore may mask true deficiency or falsely imply a deficient state (Table 10-3).

TC binds to and transports the newly absorbed Cbl in the distal ileum to cells throughout the body, where it is internalized by transcobalamin receptor (TCblR)-mediated endocytosis. Following internalization, the Cbl-TC complex is degraded by the lysosome and the receptor is recycled to the plasma membrane. Intracellular lysosomal degradation releases Cbl (hydroxocobalamin) for conversion to methylcobalamin in the cytosol or adenosylcobalamin in the mitochondria (refer to the article text for discussion of the role of these cofactors).

AMN = amnionless; AT = adenosyltransferase; C = one carbon unit; Cbl = cobalamin; CH_3 = methyl; CoA = coenzyme A; CUB = cubilin; DHF = dihydrofolate; DHFR = : dihydrofolate reductase; FTHF = formyl tetrahydrofolate; FTHFS = formyl tetrahydrofolate synthase; HC = haptocorrin; IF = intrinsic factor; MAG = megalin; MS = methionine synthetase; MTHFR = methylene tetrahydrofolate reductase; RAP = receptor-associated protein; SAM = *S*-adenosylmethionine; TC = transcobalamin; TCblR = transcobalamin receptor; THF = tetrahydrofolate.

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KEY POINTS

- Many patients with clinically expressed or disabling cobalamin deficiency have intrinsic factor–related malabsorption such as that seen in pernicious anemia.
- Vitamin B_{12} deficiency is not universal in vegetarians but does develop more rapidly with malabsorption in vegetarians.

cobalamin malabsorption is insidious in onset and often not associated with overt clinically significant deficiency. It may, however, be associated with subtle, subclinical, or biochemical cobalamin deficiency, a controversial concept in itself.[21]

Many patients with clinically expressed or disabling cobalamin deficiency have intrinsic factor–related malabsorption such as that seen in pernicious anemia.[22,23] Pernicious anemia is an autoimmune gastritis resulting from destruction of gastric parietal cells. This results in a lack of intrinsic factor and impaired binding of ingested cobalamin. The immune response is directed against the gastric H^+/K^+-adenosine triphosphatase (ATPase), which accounts for associated achlorhydria.[16] Malabsorption of vitamin B_{12} in autoimmune gastritis may be preceded by malabsorption of iron and related deficiency. Other causes of vitamin B_{12} deficiency, some of which may coexist, are noted in **Table 10-2**. Not infrequently, the cause of cobalamin deficiency is unknown.[15,18]

Most of the cobalamin secreted in the bile is reabsorbed along with cobalamin derived from sloughed intestinal cells. Hence, vitamin B_{12} deficiency

TABLE 10-2 Clinical Conditions Associated With Vitamin B_{12} Deficiency

Elderly	Age-related atrophic gastritis-associated hypochlorhydria and resulting food-cobalamin malbsorption
Autoimmune	Pernicious anemia
Gastric surgery	Gastrectomy, bariatric surgery
Gastrointestinal disorders	Celiac disease, inflammatory bowel disease, tropical sprue, intestinal lymphoma, intestinal tuberculosis, Whipple disease, ileal resection, intestinal radiation, graft versus host disease, blind loop syndrome, bacterial overgrowth, diverticulosis, strictures and fistulae, enteroanastomosis, duodenal gastrinoma
Pancreatic disease	Zollinger-Ellison syndrome and other pancreatic disorders
Dietary factors	Vegans and vegetarians, poor nutrition (alcoholism), infants born to cobalamin-deficient mothers
Increased requirements	Growth in children or adolescents, pregnancy, hemolysis
Drugs[a]	Anatacids, proton pump inhibitors, H2 blockers, metformin, sunitinib, slow potassium preparations, cholestyramine, colchicine, oral contraceptives/ hormone replacement therapy, para-aminosalicylic acid, neomycin, isoniazid, cyclosporine, sodium nitroprusside, some antiepileptic drugs, some cytotoxic drugs

Continued on page 831

TABLE 10-2 **Clinical Conditions Associated With Vitamin B_{12} Deficiency**
Continued from page 830

Genetic factors	Mutations in genes responsible for cobalamin uptake and transport (intrinsic factor deficiency or functional abnormality, abnormalities in cobalamin-intrinsic factor uptake as in Imerslund-Gräsbeck syndrome, which may be accompanied by proteinuria, transcobalamin deficiency)
	Disorders involving synthesis of cobalamin cofactors (cobalamin A to cobalamin G) that affect intracellular processing and utilization of cobalamin[b]
Toxicity	Nitrous oxide (inhalational abuse, postoperative, commonly dental procedures)
Infections	*Helicobacter pylori, Diphyllobothrium latum,* giardiasis, human immunodeficiency virus (HIV)[c]
Unknown/idiopathic	Not uncommon

[a] Other than the vitamin B_{12} deficiency seen with antacids and proton pump inhibitors, the clinical significance of low vitamin B_{12} levels seen with other listed medications is unclear.
[b] These disorders are rare and generally present in childhood with multisystem clinical abnormalities, including developmental, hematologic, and neurologic findings with methylmalonic aciduria or homocystinuria and, in some cases, neuroimaging evidence of severe white matter abnormalities.
[c] Neurologic manifestations of infection with human immunodeficiency virus (HIV) and low vitamin B_{12} levels may be related to derangements in transmethylation pathways rather than vitamin B_{12} deficiency.

KEY POINT

- Clues to possible vitamin B_{12} deficiency in a patient with polyneuropathy include a relatively sudden onset of symmetric symptoms, findings suggestive of an associated myelopathy, the onset of symptoms in the hands, concomitant involvement of upper and lower limbs, and the presence of a risk factor for vitamin B_{12} deficiency or laboratory markers of vitamin B_{12} deficiency.

is not universal in vegetarians but does develop more rapidly with malabsorption in vegetarians. Given large hepatic stores and minute daily losses, a reduction in vitamin B_{12} intake or absorption may take 5 to 10 years to manifest itself clinically.

Clinical Significance

Neurologic manifestations may be the earliest and often the only manifestation of vitamin B_{12} deficiency. The severity of the hematologic and neurologic manifestations may be inversely related in a particular patient. The commonly recognized neurologic manifestations may include a myelopathy with or without an associated neuropathy, optic neuropathy (impaired vision, optic atrophy, centrocecal scotomas), and paresthesia without abnormal signs.[15,19,23,24] The best characterized neurologic manifestation of vitamin B_{12} deficiency is a myelopathy that has commonly been referred to as *subacute combined degeneration* (**Case 10-1**). Clues to possible vitamin B_{12} deficiency in a patient with polyneuropathy include a relatively sudden onset of symmetric symptoms, findings suggestive of an associated myelopathy, the onset of symptoms in the hands, concomitant involvement of upper and lower limbs, and the presence of a risk factor for vitamin B_{12} deficiency or laboratory markers of vitamin B_{12} deficiency.[25] Neuropsychiatric manifestations of vitamin B_{12} deficiency include decreased memory, personality change, psychosis, emotional lability, and, rarely, delirium or coma. MRI abnormalities in vitamin B_{12} deficiency include signal change in the posterior and lateral columns and, less commonly, subcortical white matter (**Figure 10-2**[26]).

KEY POINT

- The bulk of evidence suggests that vitamin B_{12} supplementation does not result in improved cognition or slowed cognitive decline despite normalization of vitamin B_{12} levels.

Case 10-1

A 38-year-old woman presented with a 1-year history of progressive imbalance and distal upper and lower limb paresthesia. Her past history was remarkable for gastric bypass surgery (for obesity) done 9 years earlier. She had been on vitamin B_{12} replacement for the first 4 years following surgery.

On examination, she had a spastic gait with an upper motor pattern of lower limb weakness. Perception of vibration was reduced to the anterior superior iliac spine, and position perception was impaired at the toes and malleoli. Her deep tendon reflexes were brisk, except the ankle reflexes, which were decreased. She had a graded decreased perception of pinprick and touch distal to the wrists and ankles. Her plantar responses were extensor. Imaging of the cervical spine showed increased signal involving the dorsal columns. Her vitamin B_{12} level was 189 ng/L (normal: 180 ng/L to 914 ng/L).

Comment. This patient's clinical presentation is suggestive of a myeloneuropathy. Evidence of involvement of the pyramidal tracts, the dorsal columns, and peripheral nerves was seen. The simultaneous onset of hand and foot paresthesia should suggest the possibility of a myeloneuropathy. Vitamin B_{12} replacement is routine after bariatric surgery. In the absence of vitamin B_{12} administration, it takes about 4 to 5 years for the body's vitamin B_{12} stores to be depleted. Even though this patient had normal vitamin B_{12} levels, it should be noted that her vitamin B_{12} level is on the lower side of the normal range, and she could have metabolically significant vitamin B_{12} deficiency that should be assessed by determination of methylmalonic acid levels. Vitamin B_{12} deficiency can coexist with other nutrient deficiencies, in particular copper deficiency. Copper deficiency and vitamin B_{12} deficiency can cause identical neurologic presentations and imaging findings of increased dorsal column signal. While theoretically, folate deficiency could cause a similar clinical presentation, isolated folate deficiency is rare. Other nutrient deficiencies, such as iron or vitamin E deficiency, should also be looked for. Iron deficiency does not cause a myelopathy or neuropathy. Vitamin E deficiency can cause a myeloneuropathy but more often has a spinocerebellar presentation.

Epidemiologic data on vitamin B_{12} deficiency and cognitive impairment are rather complex, often contradictory, somewhat contentious, and likely reflect the heterogeneous nature of the study design and populations studied. The bulk of evidence suggests that vitamin B_{12} supplementation does not result in improved cognition or slowed cognitive decline despite normalization of vitamin B_{12} levels. Additionally, the vitamin B_{12} deficiency–related hyperhomocysteinemia likely does not increase the risk of vascular disease, although this too has been controversial. The presence of a low vitamin B_{12} level in association with neurologic manifestations does not imply cause and effect or indicate the presence of metabolically significant vitamin B_{12} deficiency. The incidence of cryptogenic polyneuropathy, cognitive impairment, and vitamin B_{12} deficiency increase with age, and the latter may be a chance occurrence rather than causative.

Hematologic manifestations of vitamin B_{12} deficiency result from dyssynchrony between cytoplasmic and nuclear maturation.[27] Hematologic manifestations include macrocytosis, immature nuclei, and hypersegmented

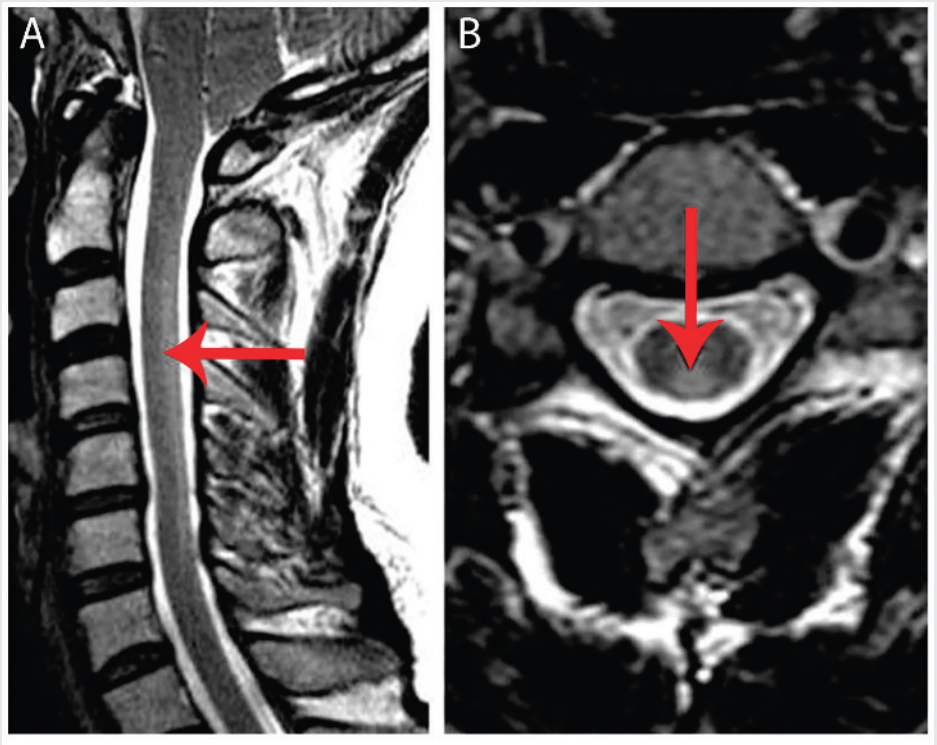

FIGURE 10-2 Spinal cord MRI in vitamin B_{12} or copper deficiency myelopathy. Sagittal (*A*) and axial (*B*) T2-weighted images showing increased signal in the paramedian aspect of the dorsal cervical cord (*arrows*).

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KEY POINT

- Although a widely used screening test, serum vitamin B_{12} measurement has technical and interpretive problems and lacks specificity and sensitivity for the diagnosis of vitamin B_{12} deficiency.

granulocytes. Anemia, leukopenia, thrombocytopenia, or pancytopenia may be seen. The ineffective erythropoiesis may result in intramedullary hemolysis and lactate dehydrogenase release. Severe pernicious anemia may mimic a myelodysplastic syndrome.

Investigations

No gold standard exists for the diagnosis of vitamin B_{12} deficiency. Serum vitamin B_{12} determination has been the mainstay for evaluating vitamin B_{12} status.[19] The older microbiologic and radioisotopic assays have been replaced by immunologically based chemiluminescence assays (competitive-binding luminescence assay). Although a widely used screening test, serum vitamin B_{12} measurement has technical and interpretive problems and lacks specificity and sensitivity for the diagnosis of vitamin B_{12} deficiency.[6,17,19,28] A proportion of patients with vitamin B_{12} deficiency may have vitamin B_{12} levels that are on the lower side of the normal range, and a proportion of patients with low vitamin B_{12} levels are not truly vitamin B_{12} deficient (ie, are falsely low). Levels of serum methylmalonic acid and plasma total homocysteine are useful as ancillary diagnostic tests. The American Academy of Neurology recommends measurements of vitamin B_{12}, methylmalonic acid, and homocysteine in patients with symmetric polyneuropathy.[29] The ancillary tests also have significant limitations. The specificity of methylmalonic acid is superior to that of homocysteine.

Although homocysteine is a very sensitive indicator of vitamin B_{12} deficiency, its major limitation is its poor specificity. **Table 10-3**[30] indicates causes other than vitamin B_{12} deficiency that can result in abnormal levels of vitamin B_{12}, methylmalonic acid, and homocysteine.[3,15] In recent years, normal or falsely high values of vitamin B_{12} have been reported in many patients with pernicious anemia.[31,32] Failure of the competitive-binding luminescence

TABLE 10-3 Common Causes, Other Than Cobalamin Deficiency, for Abnormal Cobalamin, Methylmalonic Acid, and Homocysteine Levels[a]

▶ **Cobalamin**
Decrease (falsely low)
Haptocorrin deficiency (genetic)
Folate deficiency
Pregnancy (third trimester)
Human immunodeficiency virus (HIV)
Hematologic disease: sickle cell disease, myeloma
Drugs: anticonvulsants, oral contraceptives, radionuclide isotopes
Idiopathic
Increase (falsely normal)
Hematologic disease[b,c]
Renal failure[b]
Liver disease[b]: cirrhosis, hepatitis, hepatocellular cancer, liver metastasis
Acute phase reactant in the setting of malignancy (liver, colon, breast)
Measurement of inert vitamin B_{12} analogues: intestinal bacterial overgrowth, high-dose vitamin C, nitrous oxide
Inherited disorders of cobalamin metabolism associated with decreased transcobalamin or low-affinity transcobalamin polymorphisms
Assay methodologic errors
Increased ingestion or therapeutic administration
▶ **Methylmalonic Acid**
Decrease
Antibiotic-related reductions in flora
Increase
Bacterial contamination of gut
Renal insufficiency, dehydration
Methylmalonyl coenzyme A mutase deficiency or other methylmalonic acid–related enzyme defects
Infancy, pregnancy, aging

Continued on page 835

TABLE 10-3 **Common Causes, Other Than Cobalamin Deficiency, for Abnormal Cobalamin, Methylmalonic Acid, and Homocysteine Levels**[a] *Continued from page 834*

▶ **Homocysteine**
Decrease
Drugs: estrogens, tamoxifen, statins
Increase
Folate or vitamin B_6 deficiency
Renal insufficiency, dehydration
Hypothyroidism, renal transplant, leukemia, psoriasis
Aging, excess caffeine or alcohol, increased muscle mass (males)
Drugs: isoniazid, colestipol, niacin, levodopa, diuretics
Enzyme defects: cystathionine β-synthase deficiency, methylene tetrahydrofolate reductase deficiency
Inappropriate sample processing

[a] Modified from Carmel R, et al, Hematology Am Soc Hematol Educ Program.[30] © 2003 the American Society of Hematology. *asheducationbook.hematologylibrary.org/content/2003/1/62.full*.
[b] Alteration of cobalamin levels in these conditions is due to increased tissue release, decreased tissue uptake of cobalamin, or altered levels of cobalamin binding proteins (increased haptocorrin or decreased transcobalamin concentration).
[c] Polycythemia vera, chronic myelogenous leukemia, chronic myelofibrosis, hypereosinophilic syndrome.

assay to inactivate serum intrinsic factor antibodies may be responsible for false detection of normal vitamin B_{12} levels in patients with pernicious anemia. Assay failure rates as high as 35% have been reported.[32]

High levels of serum vitamin B_{12} in the absence of exogenous administration may reflect concomitant systemic disease in some individuals. High serum levels of vitamin B_{12} can be seen in many systemic diseases (**Table 10-3**) and may be associated with increased mortality.[28]

Only 10% to 30% of the total measured vitamin B_{12} is on the cellular delivery protein transcobalamin (**Figure 10-2**). Vitamin B_{12} bound to transcobalamin (holotranscobalamin) is the fraction of total vitamin B_{12} available for tissue uptake. Holotranscobalamin concentration and transcobalamin saturation (holotranscobalamin to total transcobalamin) have been proposed by some as potentially useful alternative indicators of vitamin B_{12} status.[16,33] Serum holotranscobalamin measurement may also circumvent the problem of interference from intrinsic factor autoantibodies that characterizes the competitive-binding luminescence assay. A major limitation had been availability of sensitive and reproducible methods of detecting holotranscobalamin levels, but this is changing.

To determine the cause of vitamin B_{12} deficiency, tests directed at determining the cause of malabsorption are undertaken. Concerns regarding cost, accuracy, and radiation exposure have led to discontinuation of the Schilling test in clinical practice. Further, the Schilling test does not detect food-bound cobalamin malabsorption. An elevated serum gastrin and

KEY POINT

■ Vitamin B_{12} bound to transcobalamin (holotranscobalamin) is the fraction of total vitamin B_{12} available for tissue uptake. Holotranscobalamin concentration and transcobalamin saturation (holotranscobalamin to total transcobalamin) has been proposed by some as potentially useful alternative indicators of vitamin B_{12} status.

KEY POINTS

- A common approach in the diagnosis of pernicious anemia as a cause of vitamin B_{12} deficiency is to combine the specific but insensitive intrinsic factor antibody test with the sensitive but nonspecific serum gastrin or pepsinogen I level.
- Patients with pernicious anemia have a higher frequency of thyroid disease, diabetes mellitus, carcinoid, and iron deficiency and should be screened for these conditions.

decreased pepsinogen I are commonly seen with pernicious anemia, but the specificity of these tests is limited. Anti–intrinsic factor antibodies are specific (over 95%) but lack sensitivity and are found in approximately 50% to 70% of patients with pernicious anemia.[19] The presence of antiparietal cell antibodies is more than 90% sensitive but has limited specificity. They may be seen in 10% of people older than 70 years of age and are also present in other autoimmune endocrinopathies. A common approach in the diagnosis of pernicious anemia as a cause of vitamin B_{12} deficiency is to combine the specific but insensitive intrinsic factor antibody test with the sensitive but nonspecific serum gastrin or pepsinogen I level.[19]

Management

The goals of treatment are to reverse the signs and symptoms of deficiency, replete body stores, ascertain the cause of deficiency, address comorbidities such as coexisting nutrient deficiencies, and monitor response to therapy. With normal cobalamin absorption, daily oral administration of 3 mcg to 5 mcg vitamin B_{12} may suffice. In patients with food-bound cobalamin malabsorption, absorption of crystalline vitamin B_{12} is adequate and daily oral administration of 50 mcg to 100 mcg vitamin B_{12} is probably adequate. More recent studies have shown blunted metabolic responses in elderly persons with subclinical deficiency until daily oral doses reached 500 mcg or more.[34] The more common situation is one of impaired absorption in which parenteral therapy (IM or subcutaneous) is desirable. A short course of daily or weekly therapy is often followed by weekly and then monthly maintenance therapy (**Table 10-1**). A common regimen is a 1000 mcg IM injection of vitamin B_{12} daily for 5 to 7 days, followed by weekly injections until clear improvement is shown and then monthly 500 mcg to 1000 mcg IM injections.[23] Cobalamin and holotranscobalamin levels inevitably rise after injection. Hence methylmalonic acid and homocysteine are more reliable ways to monitor therapy response. If the oral dose is large enough (1000 mcg/d to 2000 mcg/d), even patients with an absorption defect, including pernicious anemia, may respond to oral vitamin B_{12}.[35,36] The response to oral therapy is less predictable, and oral therapy has not been well studied in the presence of neurologic disease.[36] Patients with pernicious anemia also have a higher frequency of thyroid disease, diabetes mellitus, carcinoid, and iron deficiency and should be screened for these conditions.

Hydroxocobalamin is commonly used in parts of Europe. It is more allergenic but has superior retention and may permit injections every 2 to 3 months. Vitamin B_{12} is also available in sublingual preparations, oral sprays, nasal gels and sprays, and transdermal patches. Data on the absorption and efficacy of these alternative preparations are lacking. Oral preparations of intrinsic factor are available but not reliable.

FOLIC ACID

Folate is the naturally occurring form of vitamin B_9, and folic acid is the synthetic form, although the term folate is commonly used to include both folate and folic acid. Folic acid is used in fortified foods and supplements and has a higher bioavailability than food folates. Humans cannot synthesize folate de novo. Folate is found naturally in a wide variety of foods but is destroyed by cooking. Food folates contain glutamate residues, making

them polyglutamates. The biologically active forms are dihydrofolate and tetrahydrofolate. Dietary folates are hydrolyzed upon ingestion into monoglutamates in the brush border cells of the duodenum and jejunum. Folate is absorbed by a saturable mechanism that occurs in the proximal small intestines and an unsaturable mechanism that predominates in the ileum. In the enterocyte, folate is converted into methyltetrahydrofolate and a carrier-mediated mechanism exports it into the bloodstream. Cellular folate uptake occurs via a carrier-mediated process and passive diffusion. Once internalized, folate undergoes polyglutamation that permits its attachment to enzymes. Folic acid enters the folate cycle after a two-step reduction via dihydrofolate reductase into tetrahydrofolate. Methyltetrahydrofolate is the predominant folate and is required for the cobalamin-dependent remethylation of homocysteine to methionine (**Figure 10-1**). Folate is thus involved in *S*-adenosylmethionine-mediated DNA methylation, which is one of the epigenetic mechanisms that may underlie brain development.[37] During methionine synthesis, methyltetrahydrofolate donates the methyl group and is converted into tetrahydrofolate. Tetrahydrofolate is a precursor for purine and pyrimidine synthesis. Methionine facilitates the formation of formyltetrahydrofolate. Formyltetrahydrofolate is involved in purine synthesis. Methylation of deoxyuridylate to thymidylate is mediated by methylenetetrahydrofolate. Impairment of this reaction results in accumulation of uracil. Uracil replaces the decreased thymine in nucleoprotein synthesis, and this results in megaloblastic anemia. Impaired DNA synthesis likely interferes with oligodendrocyte growth and myelin production.

Causes of Deficiency

Acquired folate deficiency rarely exists in the pure state. Hence, attribution of neurologic manifestations exclusively to folate deficiency requires exclusion of other nutrient deficiencies. Populations at increased risk of folate deficiency include alcoholics, premature infants, and adolescents. Increased folate requirements are seen in pregnancy, lactation, and chronic hemolysis. Folate deficiency may be seen with small bowel disorders associated with malabsorption. Small intestinal bacterial overgrowth, however, may be associated with increased folate levels due to bacterial synthesis. Folate absorption may be decreased with gastric surgery, atrophic gastritis, acid-suppressive therapy, and acid neutralization by treatment of pancreatic insufficiency. Alcohol, aminopterin, some antiseizure agents (phenobarbital, phenytoin), antimalarial agents (quinine, chloroquine, primaquine, artemether, lumefantrine, sulfadoxine-pyrimethamine), contraceptive drugs, and some antibiotics (tetracycline, ampicillin and other penicillins, chloramphenicol, nitrofurantoin, erythromycin) interfere with the absorption and proper distribution of folic acid.[38] Folate analogues bind to dihydrofolate reductase and result in folic acid deficiency. Agents with high folate analogue activity include methotrexate, pemetrexed, raltitrexed, proguanil, pyrimethamine, aminopterin, triamterene, and trimethoprim.

Congenital errors of folate metabolism can be related either to defective transport or to defective intracellular utilization. These disorders are often associated with central neurologic dysfunction. Several inherited disorders of folate metabolism and transport have been described: methylenetetrahydrofolate reductase (MTHFR) deficiency, methionine synthase deficiency,

KEY POINTS

- Acquired folate deficiency rarely exists in the pure state.
- Small intestinal bacterial overgrowth may be associated with increased folate levels due to bacterial synthesis.

KEY POINTS

- Serum folate falls within 3 weeks after decrease in folate intake or absorption, red blood cell folate declines weeks later, and clinically significant depletion of folate stores may be seen within months.
- For unclear reasons, neurologic manifestations involving the spinal cord or peripheral nerves, such as those seen in vitamin B_{12} deficiency, are relatively rare in folate deficiency.
- Plasma homocysteine levels are commonly elevated in patients with clinically significant folate deficiency.
- Serum folate fluctuates daily and does not correlate with tissue stores. Red blood cell folate is more reliable than plasma folate because its levels are less affected by short-term fluctuations in intake.

cerebral folate deficiency, hereditary folate malabsorption, glutamate formiminotransferase cyclodeaminase deficiency, and dihydrofolate reductase deficiency.[39] Cerebral folate deficiency is caused by a defect in the transport activity of folate receptor-α (FRα or FOLR1) due to circulating antibodies to the receptor. A more common condition is C-to-T substitution at codon 677 in the gene coding for N5, N10-MTHFR. Homozygotes for this mutation have mildly increased homocysteine levels and possibly increased vascular risk. The clinical significance of literature on the association of folate gene polymorphisms with various cancers, neural tube defect risk, and depression awaits further studies.[40] The effect of polymorphisms may potentially be counterbalanced by higher folate intake, as is seen with mandatory fortification.[39]

Serum folate falls within 3 weeks after decrease in folate intake or absorption, red blood cell folate declines weeks later, and clinically significant depletion of folate stores may be seen within months. Clinical features of folate deficiency occur more rapidly with low stores or coexisting alcoholism. The ratio of body stores to daily requirement is 100:1. Daily folate losses may approximate 1% to 2% of body stores.

Clinical Significance

Because of its importance in the production of methionine, *S*-adenosylmethionine, and tetrahydrofolate, folate deficiency could theoretically cause the same deficits as those seen with vitamin B_{12} deficiency. For unclear reasons, neurologic manifestations involving the spinal cord or peripheral nerves, such as those seen in vitamin B_{12} deficiency, are relatively rare in folate deficiency.[41] Although controversial, in some studies, folate deficiency has been associated with cognitive impairment and affective disorders, in particular depression.[41] Some evidence suggests that chronic folate deficiency and elevated homocysteine may increase the risk of vascular disease and venous thrombosis.[41] Vitamin supplementation with reduction in homocysteine has not, however, been shown to conclusively affect vascular outcomes.

Folate deficiency causes increased frequency of neural tube defects in babies born to folate-deficient mothers.[41,42] Autoantibodies to FRα have been detected in up to three-fourths of mothers who have given birth to a child with a neural tube defect.[43] Emerging evidence from epidemiologic studies suggests that maternal folate status may also influence the risk of autism spectrum disorders.[44]

Investigations

Plasma homocysteine levels are commonly elevated in patients with clinically significant folate deficiency. Generally, serum folate of 2.5 mcg/L has been considered the cutoff for folate deficiency. It has been suggested that serum folate levels between 2.5 mcg/L and 5 mcg/L may be indicative of a mildly compromised folate status. Serum folate fluctuates daily and does not correlate with tissue stores. Red blood cell folate is more reliable than serum folate because its levels are less affected by short-term fluctuations in intake. Reticulocytes have a higher folate content than mature red blood cells. Their presence can affect red blood cell folate levels as can blood transfusions.

Management

Women of childbearing age with epilepsy should take a daily oral folate supplement of 0.4 mg for prophylaxis against neural tube defects. In the presence of documented folate

deficiency, an oral dose of 1 mg 3 times a day may be followed by a maintenance dose of 1 mg/d (**Table 10-1**). Patients who are acutely ill may need parenteral administration in a dose of 1 mg to 5 mg. Daily doses as high as 20 mg may be needed in patients with severe malabsorption. Even in high doses, toxicity due to folic acid is rare. Reduced folates, such as folinic acid, are required only with drug-induced impaired folate metabolism, such as with methotrexate, or by an inborn error of metabolism. The biologically active folinic acid and 5-methylenetetrahydrofolate are efficiently transported to the brain, but no general consensus exists regarding their dosing schedules. High folate levels or folic acid supplements may be detrimental in the presence of vitamin B_{12} deficiency.[41] In countries that have mandatory fortification of food with folic acid, some concern has been expressed about the potential for adverse effects in older adults with a low cobalamin status. Coexisting vitamin B_{12} deficiency should therefore be excluded before instituting folate therapy. Plasma homocysteine is used for monitoring response to therapy; it decreases soon after instituting folate therapy but does not respond to inappropriate vitamin B_{12} therapy.

THIAMINE

The terms vitamin B_1 and thiamine are used interchangeably. The highest concentrations of thiamine are found in yeast and in the pericarp of grain. At low concentrations, thiamine is absorbed in the jejunum and ileum by an active, carrier-mediated, rate-limited process. At higher concentrations, absorption takes place by passive diffusion. Following gastrointestinal uptake, thiamine is transported to the liver by portal blood. Both passive and active mechanisms transport thiamine across the blood-brain barrier. Following cellular uptake, thiamine is phosphorylated into thiamine diphosphate, the metabolically active form. Thiamine diphosphate is a cofactor for the pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase, and transketolase. Pyruvate dehydrogenase and α-ketoglutarate dehydrogenase are involved in the tricarboxylic acid cycle in oxidative decarboxylation of α-ketoacids (pyruvate and α-ketoglutarate to acetyl CoA and succinate, respectively). Transketolase transfers activated aldehydes in the hexose monophosphate shunt (pentose-phosphate pathway) in the generation of nicotinamide adenine dinucleotide phosphate for reductive biosynthesis. Thiamine diphosphate may be further phosphorylated to thiamine triphosphate. Thiamine has a role in energy production by adenosine triphosphate synthesis, myelin sheath maintenance, and neurotransmitter production. Thiamine-deficient membranes are unable to maintain osmotic gradients.

Causes of Deficiency

The thiamine requirement is related to the total caloric intake and proportion of calories provided as carbohydrates. Additionally, the thiamine requirement increases during periods of high metabolic demand. With a marginal nutritional status, increased metabolic demand can precipitate symptoms of thiamine deficiency. **Table 10-4**[45] lists the clinical settings that can be associated with thiamine deficiency. Alcoholism is just one of many causes of thiamine deficiency, and thiamine deficiency is increasingly being recognized in individuals who are not alcoholics. Often multiple contributing factors coexist. Because of a short half-life and absence of significant storage amounts, a continuous dietary supply of

KEY POINT

- Alcoholism is just one of many causes of thiamine deficiency, and thiamine deficiency is increasingly being recognized in individuals who are not alcoholics.

TABLE 10-4 Conditions Reported as Being Associated With Thiamine Deficiency[a]

▶ **Increased Requirements**
Children, pregnancy, lactation, vigorous exercise
Critically ill
Hyperthyroidism
Malignancy, chemotherapy (eg, erbulozole, ifosfamide), bone marrow transplantation
Systemic infection, prolonged febrile illness
▶ **Marginal Nutritional Status (Decreased Intake or Decreased Absorption or Increased Losses)**
Acquired immunodeficiency syndrome (AIDS)
Alcoholism
Anorexia nervosa, extreme dieting, starvation, hunger strike, food refusal, dietary neglect in the elderly
Commercial dietary formula, slimming diets, food fads
Decreased absorption due to excess antacid use
Diet: polished rice, foods containing thiaminase or antithiamine compounds including herbal supplements, infants breast-fed by thiamine-deficient mothers
Gastrointestinal surgery (including bariatric surgery)
Inactivation of thiamine in food by excessive cooking or thiaminase-containing foods
Inadequate supplementation in parenteral or enteral nutrition
Magnesium deficiency
Persistent vomiting (pancreatitis, migraine attacks, hyperemesis gravidarum) or diarrhea
Renal failure, hemodialysis, peritoneal dialysis
Severe gastrointestinal or liver or pancreatic disease
Tolazamide, high-dose nitroglycerin infusion (effect of the diluents ethyl alcohol and propylene glycol on thiamine metabolism), possibly diuretics
▶ **High Glucose Intake**
IV glucose administration, nasogastric feeding, total parenteral nutrition, IV hyperalimentation
Refeeding after prolonged starvation
▶ **Others**
Genetic conditions associated with altered thiamine requirement or transport

IV = intravenous.
Data from Sechi G, et al, Nutr Rev[24] and Kumar N, Neurol Clin.[45] *academic.oup.com/nutritionreviews/article-abstract/74/5/281/1751881/Advances-in-clinical-determinants-and-neurological?redirectedFrom=fulltext* and *neurologic.theclinics.com/article/S0733-8619(09)00062-0/pdf*.

thiamine is necessary. Given the daily thiamine requirement of approximately 1 mg to 2 mg and body stores of approximately 30 mg to 50 mg, it takes approximately 4 to 6 weeks for body stores to be depleted.[46] A severely thiamine-deficient diet may result in clinically significant depletion of body stores in as little as 2 to 3 weeks. Early neurologic manifestations following bariatric surgery are therefore commonly due to thiamine deficiency.

Clinical Significance

Thiamine deficiency affects the central nervous system, peripheral nervous system, and cardiovascular system.[3,45,47,48] The best characterized disorders related to thiamine deficiency are beriberi, Wernicke encephalopathy, and Korsakoff syndrome (also referred to as Korsakoff psychosis).

The three forms of beriberi are dry beriberi, wet beriberi, and infantile beriberi. Dry beriberi refers to a sensorimotor, distal, axonal peripheral neuropathy. Autonomic neuropathy may be present. A rapid progression mimics Guillain-Barré syndrome.[49] Pedal edema may be seen due to coexisting wet beriberi, a high cardiac output heart failure state. This distinction is of limited significance since the wet form may be converted to the dry form after diuresis. Shoshin beriberi refers to a fulminant form that presents with tachycardia and circulatory collapse. Infantile beriberi bears little resemblance to the adult form. It is seen in infants breast-fed by mothers with thiamine deficiency or in infants with thiamine-deficient diets. Infantile beriberi is seen between 2 and 12 months of age and may present with the cardiac, aphonic, or pseudomeningitic forms. Clinical features include cardiomyopathy, vomiting, diarrhea, failure to thrive, irritability, nystagmus, ophthalmoplegia, dysphonia, and respiratory symptoms.[50] The term gastrointestinal beriberi has been used to describe a primary gastrointestinal thiamine deficiency syndrome characterized by abdominal pain, vomiting, and lactic acidosis.[51]

Because of the close relationship between Wernicke encephalopathy and Korsakoff syndrome, the term Wernicke-Korsakoff syndrome is commonly used. Wernicke encephalopathy often results from severe short-term thiamine deficiency, while peripheral neuropathy is more often a consequence of prolonged mild to moderate thiamine deficiency. Wernicke encephalopathy related to alcoholism is more common in men, while Wernicke encephalopathy related to bariatric surgery is more commonly reported in women. Wernicke-Korsakoff syndrome outside the context of alcoholism is more often seen in women and has been associated with younger age, shorter duration of precipitating illness, and better survival as compared to alcohol-related Wernicke-Korsakoff syndrome.[52] The clinical features of Wernicke encephalopathy include a subacute onset of the classic triad of ocular abnormalities (notably ophthalmoplegia), gait ataxia, and mental status changes (**Case 10-2**).[1,53,54] The onset may be gradual, and the classic triad is frequently absent. In fact, patients with Wernicke encephalopathy may have none of the manifestations related to the classic triad, although one or more components of the triad do generally appear later in the course. Ocular abnormalities include nystagmus (horizontal more common than vertical), ophthalmoparesis (commonly involving the lateral recti), and conjugate gaze palsies (usually horizontal). Complete ophthalmoplegia is rare. The gait and trunk ataxia is due to cerebellar and vestibular dysfunction and may be

KEY POINTS

- Wernicke encephalopathy often results from severe short-term thiamine deficiency, while peripheral neuropathy is more often a consequence of prolonged mild to moderate thiamine deficiency.
- Patients with Wernicke encephalopathy may have none of the manifestations related to the classic triad, although one or more components of the triad do generally appear later in the course.

KEY POINTS

- It is important to recognize that a patient who does not recover fully and spontaneously from intoxication may have Wernicke encephalopathy.
- Korsakoff syndrome is an amnestic-confabulatory syndrome characterized by severe anterograde and retrograde amnesia that follows Wernicke encephalopathy; Korsakoff syndrome emerges as ocular manifestations and encephalopathy subside. Rarely, Korsakoff syndrome may be present without Wernicke encephalopathy.

Case 10-2

A 41-year-old man with recurrent vomiting in the setting of gallstone pancreatitis presented with the subacute onset of diplopia and ataxia. His examination revealed restricted extraocular motility and gait and appendicular ataxia. He had no cognitive deficits. His brain MRI was unremarkable. Laboratory investigations were notable for an elevated blood urea nitrogen suggestive of prerenal azotemia. A clinical suspicion of thiamine deficiency prompted a serum thiamine determination, which was normal. Given the high index of suspicion, parenteral thiamine was administered and resulted in clinical improvement.

Comment. A normal serum thiamine level does not rule out thiamine deficiency, and when the index of suspicion is high, results of thiamine level testing should not be waited for before administering thiamine. Although the classic neurologic manifestation of thiamine deficiency is Wernicke encephalopathy, patients may not have any mental status abnormalities, as in this case. The classic triad of Wernicke encephalopathy is ocular dysmotility, gait ataxia, and mental status changes. One or more components of the triad generally appear during the disease course. While MRI is the imaging modality of choice, it may not necessarily be abnormal. While thiamine deficiency has often been described in the setting of alcohol use, it can occur in any patient who is critically ill. The body has limited thiamine stores; in the absence of adequate intake and with increased demand, the disease can become manifest. Thiamine deficiency should be suspected in the early postbariatric surgery setting in particular, when recurrent vomiting can precipitate thiamine deficiency with associated neurologic complications.

compounded by a coexisting peripheral neuropathy. Mental status changes include the inability to concentrate, apathy, delirium, and frank psychosis. If untreated, this can progress to coma and death. Rarely, coma may be the sole manifestation of Wernicke encephalopathy. It is important to recognize that a patient who does not recover fully and spontaneously from intoxication may have Wernicke encephalopathy.[55] Clinical features may also result from involvement of the hypothalamic and brainstem autonomic pathways. Other unusual reported manifestations include seizures, myoclonus, or hearing loss.

About 80% of patients with Wernicke encephalopathy who survive develop Korsakoff syndrome. Korsakoff syndrome is an amnestic-confabulatory syndrome characterized by severe anterograde and retrograde amnesia that follows Wernicke encephalopathy; Korsakoff syndrome emerges as ocular manifestations and encephalopathy subside. Rarely, Korsakoff syndrome may be present without Wernicke encephalopathy or may be present at the time of diagnosis of Wernicke encephalopathy.[56] In Korsakoff syndrome, memory is disproportionately impaired relative to other aspects of cognitive function. This is possibly due to involvement of the anterior and medial thalamic nuclei. Alertness, attention, social behavior, and other aspects of cognitive functioning are generally preserved.

The symptoms of subclinical thiamine deficiency are often vague and nonspecific and include fatigue, irritability,

headaches, and lethargy. Two recently recognized conditions include thiamine-responsive pyruvate dehydrogenase deficiency and thiamine-responsive megaloblastic anemia.

Alcoholic neuropathy is distinct from thiamine deficiency–related neuropathy.[57] Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential involvement of small fiber function. In contrast, thiamine deficiency–related neuropathy is often a more rapidly progressive sensorimotor neuropathy, with large fiber–predominant sensory loss.

Investigations

Wernicke encephalopathy is largely a clinical diagnosis. Urinary thiamine excretion and serum thiamine levels do not accurately reflect tissue concentrations and are therefore not reliable indicators of thiamine status. A normal serum thiamine level does not exclude Wernicke encephalopathy. The preferred tests are the erythrocyte transketolase activation assay and measurement of erythrocyte thiamine diphosphate in whole blood. These laboratory abnormalities resolve quickly. A blood sample is best drawn before initiation of treatment. Thiamine deficiency may result in lactate accumulation. An anion-gap metabolic acidosis with a primary respiratory alkalosis may also be present.

CT is of limited utility. Typical MRI findings include increased T2 or fluid-attenuated inversion recovery (FLAIR) signal in the paraventricular regions (thalamus, hypothalamus, mammillary body, periaqueductal midbrain, tectum, pons, fourth ventricle floor, medulla, midline cerebellum, and, rarely, splenium of the corpus callosum or basal ganglia structures), as shown in **Figure 10-3**.[47,58–60] Involvement of cortical regions on MRI has been reported and may indicate irreversible lesions. Contrast enhancement and diffusion-weighted abnormalities may be present in the early stages. Hemorrhagic lesions are rare. Signal alterations involving the red nucleus, dentate, or substantia nigra have been rarely reported. Increased signal may involve the hypoglossal, medial vestibular, facial, and dentate nuclei.[58] Shrunken mammillary bodies may persist as sequelae. Findings in the chronic stages also include dilated aqueduct and third ventricles. Atrophy of the midbrain tegmentum, paramedian thalamic nuclei, and frontal lobes may be seen.

Management

IV glucose infusion in patients with thiamine deficiency may consume the available thiamine and precipitate acute Wernicke encephalopathy. Patients who are at risk should therefore receive parenteral thiamine before administration of glucose or parenteral nutrition. The parenteral route for thiamine administration is also employed when doubts exist about gastrointestinal absorption. Thiamine for parenteral use should be diluted in 100 mL normal saline or 5% glucose and infused over 30 minutes. A commonly used thiamine replacement regimen is 200 mg IV every 8 hours (**Table 10-1**).[48] Higher doses of thiamine may be required in Wernicke encephalopathy, particularly when it occurs in the setting of alcoholism.[61] It has been suggested by some experts that patients with Wernicke encephalopathy should receive 500 mg thiamine 3 times a day for 2 to 3 days. Subsequently, the dose may be reduced to 250 mg thiamine given IV or IM daily for 3 to 5 days. Similar doses may be given prophylactically in conditions of alcohol withdrawal or severe malnutrition. Long-term oral maintenance with 50 mg to 100 mg

KEY POINTS

- Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential involvement of small fiber function. In contrast, thiamine deficiency–related neuropathy is often a more rapidly progressive sensorimotor neuropathy, with large fiber–predominant sensory loss.
- Wernicke encephalopathy is largely a clinical diagnosis.
- A normal serum thiamine level does not exclude Wernicke encephalopathy.
- IV glucose infusion in patients with thiamine deficiency may consume the available thiamine and precipitate acute Wernicke encephalopathy. Patients who are at risk should therefore receive parenteral thiamine before administration of glucose or parenteral nutrition.
- A commonly used thiamine replacement regimen is 200 mg IV every 8 hours. Higher doses of thiamine may be required in Wernicke encephalopathy, particularly when it occurs in the setting of alcoholism.

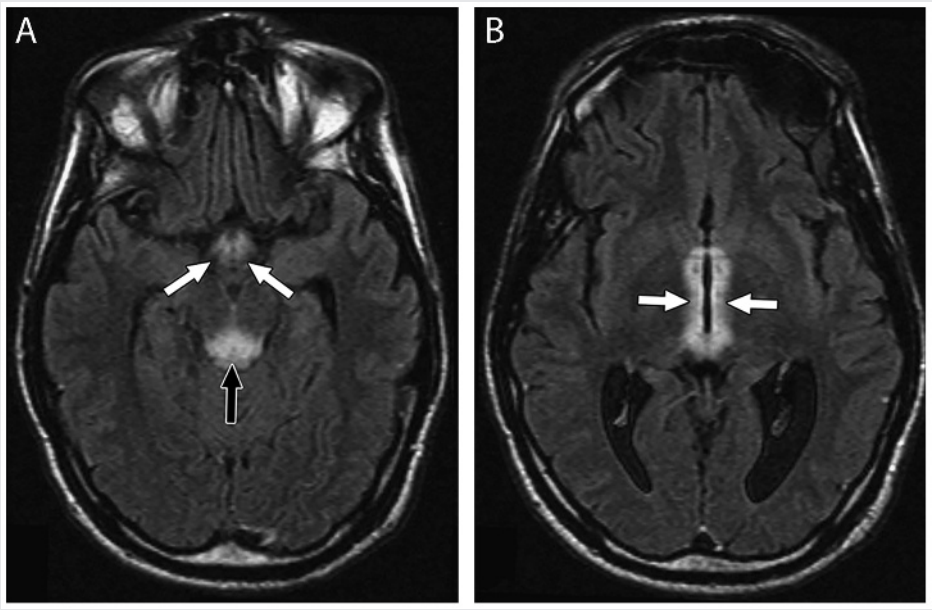

FIGURE 10-3 Neuroimaging in Wernicke encephalopathy. Fluid-attenuated inversion recovery (FLAIR) images in a patient with Wernicke encephalopathy showing increased signal involving the mammillary bodies (*A*, *white arrows*), periaqueductal area (*A*, *black arrow*), and periventricular region of the third ventricle (*B*, *white arrows*).

Reprinted with permission from Zuccoli G, Pipitone N, AJR Am J Roentgenol.[58] © 2009 American Roentgen Ray Society. *ajronline.org/doi/abs/10.2214/AJR.07.3959*.

thiamine daily is commonly employed. Coexisting conditions associated with increased metabolic demand that may have precipitated Wernicke encephalopathy (such as an infection) need independent attention. In wet beriberi, rapid improvement of heart failure is seen. Improvement in motor and sensory symptoms takes months.

Response in Wernicke encephalopathy is variable. Ocular signs improve promptly, but a fine horizontal nystagmus may persist. Improvement in gait ataxia and memory is often delayed. Mental status changes improve over weeks. Recovery of consciousness may be seen even in patients in deep coma. Korsakoff syndrome does not respond to thiamine therapy but may improve spontaneously over time. Even with thiamine treatment, the mortality may be high. Sudden death can occur due to hemorrhagic brainstem lesions.

NIACIN

Nicotinic acid and its amide (nicotinamide) are the common forms of niacin, which is also known as vitamin B_3. Meat, whole-grain cereals and pulses (beans, lentils, chickpeas), dairy products, and eggs are rich sources of niacin. Niacin and its amide are absorbed through the intestinal mucosa by active uptake and simple diffusion. Niacin is taken up by tissues and converted in the body to nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, two coenzymes that have a role in carbohydrate metabolism. In humans, niacin is an end product of

tryptophan metabolism. The major metabolite of niacin is nicotinuric acid, and the major metabolite of nicotinamide is N^1-methylnicotinamide and its oxidized products, 2- and 4-pyridones. Excess niacin is excreted in the urine. The body lacks significant tryptophan reserves.

Causes of Deficiency

Niacin deficiency (pellagra) is seen in populations that are dependent on corn as the primary carbohydrate source.[62] Corn lacks niacin and tryptophan. Nonendemic pellagra may be seen in the setting of alcoholism and malabsorption. Chronic infections can increase the demand for niacin. Pellagra may also be seen in the carcinoid syndrome because tryptophan is converted to serotonin instead of niacin. Transformation of tryptophan to nicotinic acid requires vitamins and minerals, such as vitamin B_2, vitamin B_6, iron, and copper. Since tryptophan is necessary for niacin synthesis, vitamin B_6 deficiency can result in secondary niacin deficiency. Excess neutral amino acids in the diet, such as leucine, can compete with tryptophan for uptake and predispose to niacin deficiency. Hartnup syndrome is an autosomal recessive disorder characterized by impaired synthesis of niacin from tryptophan. Bacterial colonization of the gut can lead to conversion of dietary tryptophan to indoles. Deficiency has also been described with frequent dialysis.

Clinical Significance

Pellagra affects the gastrointestinal tract, skin, and nervous system.[62] The dermatologic and gastrointestinal manifestations are frequently absent, particularly so in nonendemic pellagra. Skin changes include a reddish-brown hyperkeratotic and photosensitive rash that has a predilection for the face, chest, and dorsum of the hands and feet. Gastrointestinal manifestations include anorexia, abdominal pain, diarrhea, and stomatitis.

The neurologic syndrome due to niacin deficiency has not been well characterized. Reported cases are confounded by the presence of coexisting nutrient deficiencies as is common in alcoholics. Manifestations include irritability, anxiety, depression, and lack of concentration. Severe deficiency may be accompanied by a confusional state that may progress to coma and be accompanied by spasticity, ataxia, and myoclonus. Unexplained progressive encephalopathy in alcoholics that is not responsive to thiamine or escalating doses of benzodiazepines should raise the possibility of pellagra. Alcoholics with encephalopathy who receive thiamine and pyridoxine without niacin may develop an encephalopathy due to niacin deficiency. The peripheral neuropathy seen in pellagra resembles the peripheral neuropathy seen with thiamine deficiency.

Investigations

No sensitive and specific blood measures of niacin status exist. Researchers have suggested that measures of erythrocyte nicotinamide adenine dinucleotide and plasma metabolites of niacin may be indirect markers. Urinary excretion of the methylated metabolites of niacin may be a more reliable measure of niacin status.

Management

Oral nicotinic acid in a dose of 50 mg 3 times a day or parenteral doses of 25 mg to 100 mg 3 times a day are used for treatment of patients who are symptomatic (**Table 10-1**).[62] Nicotinamide does not have the vasodilatory and cholesterol-lowering activities of nicotinic acid but has comparable therapeutic efficacy in pellagra.

KEY POINT

- Unexplained progressive encephalopathy in alcoholics that is not responsive to thiamine or escalating doses of benzodiazepines should raise the possibility of pellagra.

KEY POINT

■ The two most prevalent forms of pyridoxine-dependent epilepsy include the autosomal recessive disorders associated with antiquitin deficiency and pyridoxal 5'-phosphate oxidase deficiency.

Prompt response of dermatologic and gastrointestinal manifestations to treatment supports the diagnosis. Response of the neuropsychiatric manifestations to treatment is more variable.

PYRIDOXINE

The term pyridoxine is used synonymously with vitamin B_6. Vitamin B_6 is present mainly as pyridoxine and pyridoxine phosphate in plant-derived foods and as pyridoxal phosphate and pyridoxamine phosphate in animal-derived foods. Humans and other mammals cannot synthesize vitamin B_6 and thus must obtain this micronutrient from exogenous sources via intestinal absorption. Food processing reduces the bioavailability of vitamin B_6. Vitamin B_6 is also produced by normal microflora of the large intestine.

Pyridoxine functions as a prosthetic group for many cellular enzymatic activities. It is involved in the pathways of gluconeogenesis and glycolysis and in neurotransmitter and heme biosynthesis. Pyridoxine serves as a cofactor for enzymes involved in the metabolism of amino acids, lipids, nucleic acid, and one-carbon units. Niacin, carnitine, and folate require pyridoxine for their metabolism. Examples of conversions dependent on pyridoxine include histidine to histamine, tryptophan to serotonin, tryptophan to niacin, glutamate to γ-aminobutyric acid (GABA), and dihydroxyphenylalanine to dopamine.[63] Pyridoxine is responsible for the degradation of homocysteine via the transsulfuration pathway in one-carbon metabolism. Lysyl oxidase is also a pyridoxine-dependent enzyme.

Pyridoxine uptake by intestinal epithelial cells occurs by a carrier-mediated, pH-dependent mechanism that has saturable and nonsaturable components. Vitamin B_6 (mostly in the form of pyridoxal) is readily absorbed in the proximal small intestine. It enters the portal circulation and is transported bound to albumin in plasma and hemoglobin in red blood cells. Absorbed dietary pyridoxine, pyridoxal, and pyridoxamine are phosphorylated by kinases for metabolic trapping. Tissue uptake of vitamin B_6 from the circulation requires dephosphorylation. The interconversion and metabolism of vitamin B_6 is dependent on riboflavin, niacin, and zinc. Pyridoxal phosphate and pyridoxal are the main circulating forms of vitamin B_6. Pyridoxine is excreted in the urine.

Causes of Deficiency

Most diets are adequate in vitamin B_6. Pyridoxine deficiency most commonly occurs with malnourishment, malabsorption, and alcoholism.[45,63] Individuals at risk of developing vitamin B_6 deficiency include pregnant and lactating women and the elderly. Inflammatory states and tissue injury have been associated with pyridoxine deficiency. Additional risk factors for pyridoxine deficiency include chronic diseases, such as renal or hepatic disease, human immunodeficiency virus (HIV), sickle cell disease, hereditary sideroblastic anemia, rheumatoid arthritis, hyperoxaluria, and tissue injury. Valproate, carbamazepine, and phenytoin increase the catabolism of pyridoxine. Vitamin B_6 deficiency has also been implicated with other medications, such as hydrocortisone, cyclosporin, cycloserine, isoniazid, hydralazine, and penicillamine.

The two most prevalent forms of pyridoxine-dependent epilepsy include the autosomal recessive disorders associated with antiquitin deficiency and pyridoxal 5′-phosphate oxidase (PNPO) deficiency.[14,64] The former disorder results from mutations in

the *ALDH7A1* gene, which encodes α-aminoadipic semialdehyde dehydrogenase (antiquitin). This results in a deficiency of antiquitin in the cerebral lysine degradation pathway. Patients with antiquitin deficiency have elevated α-aminoadipic semialdehyde and are responsive to pyridoxine. PNPO is essential for the synthesis of pyridoxal phosphate. Patients with PNPO deficiency lack a specific biomarker and need pyridoxal phosphate. Recent evidence suggests that some patients with PNPO deficiency may respond to pyridoxine also, and pyridoxine responsiveness with normal biomarkers for antiquitin deficiency should prompt *PNPO* mutation analysis.[65] Vitamin B_6–responsive epilepsy has also been reported due to inherited glycosylphosphatidylinositol deficiency.[66]

Clinical Significance

Infantile seizures due to dietary vitamin B_6 deficiency are rare and may be seen in breast-fed infants of malnourished mothers from poor socioeconomic backgrounds in underdeveloped countries. Both pyridoxine-dependent epilepsy due to antiquitin deficiency and pyridoxine-dependent epilepsy due to PNPO deficiency present with neonatal multifocal myoclonic-tonic seizures that may be accompanied by epileptic encephalopathy and a high mortality. In the long term, some learning disability with speech and language involvement may persist.

Adults are much more tolerant of vitamin B_6 deficiency. Even with low levels, symptoms are rare. Peripheral neuropathy may be seen with vitamin B_6 deficiency. Chronic vitamin B_6 deficiency may cause a microcytic hypochromic anemia. One form of sideroblastic anemia can be treated with vitamin B_6. Patients who are chronically vitamin B_6 deficient may develop hyperoxaluria and nephrolithiasis. Glossitis, stomatitis, cheilosis, and dermatitis may be seen.

Excess consumption of vitamin B_6 has been associated with a predominantly sensory ganglionopathy. It is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and a positive Romberg sign. The presence of a Lhermitte sign in some patients suggests involvement of the spinal cord as well. The risk of developing neurotoxicity increases at doses significantly greater than 100 mg/d to 200 mg/d. Additional manifestations of pyridoxine toxicity may include nausea, vomiting, diarrhea, tachypnea, and rash.

Investigations

Vitamin B_6 status can be assessed by measuring its levels in the blood or urine. The most commonly used measure is plasma pyridoxal phosphate. A plasma pyridoxal phosphate concentration of over 30 nmol/L has been considered to indicate adequate status. Levels of 4-pyridoxic acid can be measured in the urine. Because of the 120-day lifespan of erythrocytes, the erythrocyte aspartate aminotransferase and erythrocyte aspartate aminotransferase activation coefficient are useful for long-term pyridoxine status. Functional indicators of vitamin B_6 status are based on pyridoxal phosphate–dependent reactions. The methionine load test is used as a functional indicator of vitamin B_6 status. Vitamin B_6 deficiency results in a higher postmethionine load homocysteine concentration due to impairment of the transsulfuration pathway. Vitamin B_6 is required for conversion of homocysteine to cysteine and subsequently to glutathione. Vitamin B_6 deficiency, however, has little

KEY POINT

- Excess consumption of vitamin B_6 has been associated with a predominantly sensory ganglionopathy. It is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and a positive Romberg sign.

effect on fasting plasma homocysteine concentration. The tryptophan load test relies on the fact that vitamin B_6 is required for the conversion of tryptophan to niacin and involves measuring urinary excretion of tryptophan metabolites.

Management

Isonicotinic acid hydrazide–induced neuropathy is reversible by drug discontinuation or vitamin B_6 supplementation. Vitamin B_6 may be supplemented in a dose of 50 mg/d to 100 mg/d to prevent development of the neuropathy (**Table 10-1**). Pyridoxine is a specific antidote to acute isoniazid overdose. The neuronopathy due to vitamin B_6 toxicity may reverse once the supplementation is withdrawn. Patients with pyridoxine-dependent epilepsy develop symptoms despite a normal dietary supplementation of pyridoxine. High doses of parenteral vitamin B_6 or pyridoxal phosphate are required and may cause a blood pressure drop. Even after years of successful therapy, seizures reappear within days of vitamin B_6 withdrawal.

VITAMIN A

Retinol refers to vitamin A. The term *retinoids* refers to vitamin A derivatives, such as retinal (vitamin A aldehyde), retinoic acid (vitamin A acid), and the carotenoids. Vitamin A is derived from numerous animal sources, with liver of shark, halibut, and polar bear being the highest sources. β-Carotene is an important but insufficient source of vitamin A. It is present in many plant sources. The other major carotenoids (lycopene, lutein, zeaxanthin) have important biological properties, but more evidence is needed before recommending their use in various chronic disease states. In the intestinal mucosa, retinol is esterified to retinyl palmitate, which is incorporated into chylomicrons and transported into the circulation. Vitamin A is stored in the liver as retinyl palmitate. Chronic daily vitamin A consumption of over 25,000 IU may result in toxicity. Vitamin A is essential for visual function, normal organogenesis and tissue differentiation, epithelial cell integrity, and immune competence.[67] Retinol binds with the protein opsin to form rhodopsin, which is responsible for vision at dim illumination.

Causes of Deficiency

Nutritional deficiency of vitamin A is seen when the diet consists predominantly of rice and wheat (grains lacking β-carotene). Dietary deficiency may be seen in alcoholics, the elderly, and the poor. Vitamin A deficiency is also seen in conditions associated with fat malabsorption.

Clinical Significance

Vitamin A deficiency causes night blindness and corneal or conjunctival dryness and keratinization. White foamy spots on the conjunctiva due to sloughed cells (Bitot spots) may be seen. Other manifestations include impaired taste and keratinization of the skin and respiratory, gastrointestinal, and urinary tracts. Excess ingestion of carotenes may cause yellow skin pigmentation.

Excess vitamin A ingestion causes dry skin, pruritus, cheilitis, brittle nails, alopecia, petechiae, bone pain, painful joints, hyperostosis, anorexia, fatigue, nausea, diarrhea, and hepatotoxicity. Neurologic manifestations of vitamin A toxicity include headache, insomnia, irritability, and pseudotumor cerebri.[68] Osteoporosis and hip fractures may also result from vitamin A excess.

Investigations

Normal vitamin A levels range from 30 mcg/dL to 65 mcg/dL. Levels less

than 10 mcg/dL are clearly low, and levels over 100 mcg/dL are suggestive of toxicity.

Management

Prophylactically treating high-risk infants and children with large oral doses of vitamin A prevents development of clinically significant deficiency. In the setting of malabsorption-related vitamin A deficiency, oral vitamin A supplementation is undertaken to normalize plasma levels (**Table 10-1**).

VITAMIN D

Vitamin D is a fat-soluble vitamin that exists in two forms: vitamin D_2 (ergocalciferol, produced by plants) and vitamin D_3 (cholecalciferol, produced in skin when 7-dehydrocholesterol is exposed to ultraviolet light). Sun-stimulated cutaneous vitamin D synthesis provides the majority of the daily vitamin D requirement. Small bowel enterocyte receptors enhance calcium absorption, and bone receptors stimulate mineralization of newly formed bone. In the presence of bile salts, ingested vitamin D is packaged into micelles and absorbed passively in the small bowel. It is then bound to lipoproteins and transported to the liver in chylomicrons via the lymphatic system. In the liver it is hydroxylated to 25-hydroxyvitamin D (calcidiol). Further hydroxylation to 1,25-dihydroxyvitamin D (calcitriol), the active form, occurs in the kidney. With replete stores, 25-hydroxyvitamin D is hydroxylated to 24,25-dihydroxyvitamin D, which is then excreted in the bile and urine. Vitamin D acts intracellularly at high-affinity nuclear receptors, which, when stimulated, alter gene transcription.

Causes of Deficiency

Inadequate sun exposure may cause vitamin D deficiency, particularly in individuals who are chronically ill, institutionalized, or housebound. Inadequate sunlight exposure may result from fewer daylight hours in temperate latitudes and covering of skin by clothing and sunscreens. Additional causes of vitamin D deficiency include dietary insufficiency, gastrointestinal surgeries, and various diseases associated with malabsorption, including liver and pancreatic disease. Older antiepileptic drugs, such as phenytoin and phenobarbital, inhibit vitamin D hydroxylation in the liver, and their long-term use can compromise bone health.[69]

Clinical Significance

Vitamin D deficiency causes defective mineralization of newly formed bone, which manifests as rickets in children and osteomalacia in adults. Vitamin D deficiency results in hypocalcemia with secondary hyperparathyroidism and is a risk factor for osteoporosis.

Vitamin D deficiency can cause a proximal myopathy with preferential involvement of the pelvic girdle muscles. Myalgia may be present. Vitamin D deficiency has been associated with nonspecific musculoskeletal pain and heightened central sensitivity in patients with chronic pain.[70] Muscle involvement in vitamin D deficiency is likely due to impaired calcium influx into the sarcoplasmic reticulum and impaired production of the muscle proteins actin and troponin C. Additionally, severe hypocalcemia may cause tetany and may be associated with hypomagnesemia.

Vitamin D deficiency is being increasingly recognized as an independent risk factor for multiple sclerosis (MS).[71,72] Epidemiologic studies suggest causality between latitude, sunlight exposure, vitamin D status, and MS risk. The association relates not just to risk of developing MS, but also

KEY POINTS

- Older antiepileptic drugs, such as phenytoin and phenobarbital, inhibit vitamin D hydroxylation in the liver, and their long-term use can compromise bone health.
- Vitamin D deficiency can cause a proximal myopathy with preferential involvement of the pelvic girdle muscles. Myalgia may be present.
- Vitamin D deficiency is being increasingly recognized as an independent risk factor for multiple sclerosis.

KEY POINTS

- Vitamin D status is assessed by 25-hydroxyvitamin D levels.
- Mutations in *TTPA*, the gene that encodes α-tocopherol transfer protein, results in ataxia with vitamin E deficiency. Additional disorders associated with vitamin E deficiency include hypobetalipoproteinemia, abetalipoproteinemia, and chylomicron retention disease.

to risk of relapse, MRI evidence of disease activity, severity of disease course, and disease-related disability. Vitamin D deficiency has been also identified as a risk factor for recurrence following an initial episode of transverse myelitis.[73] Low vitamin D levels are associated with neuromyelitis optica (NMO) spectrum disorder, and an inverse correlation has been shown with Expanded Disability Status Scale (EDSS) scores in patients with NMO spectrum disorder.[74]

The association between vitamin D deficiency and cognitive impairment is controversial, and causality has not been conclusively demonstrated.[75] Several areas of uncertainty exist, as well as concern that an apparent association may be an artifact of reverse causation.

Investigations

Vitamin D status is assessed by 25-hydroxyvitamin D levels.[76] Other laboratory abnormalities may include hypocalcemia, hypophosphatemia, raised parathyroid hormone, raised alkaline phosphatase of bone origin, reduced urinary calcium excretion, and raised urinary hydroxyproline.

Management

Vitamin D can be given as vitamin D_2 or vitamin D_3. To prevent deficiency in individuals with minimal sun exposure, 400/d IU vitamin D given orally is adequate. With clinical deficiency, 50,000 IU oral vitamin D_2 or D_3 weekly may be required for 6 to 8 weeks (**Table 10-1**). This may be followed by 800 IU/d. Larger oral doses or parenteral administration may be required in the presence of severe malabsorption. Adequate calcium repletion can prevent parathyroid stimulation and potential complications related to parathyroid hormone–induced hypercalcemia. An inappropriately high phosphate level may be a clue to secondary hyperthyroidism. Doses of 50,000 IU 3 times a week require laboratory monitoring. Serum and urine calcium and serum 25-hydroxyvitamin D should be monitored, and when urinary calcium excretion exceeds 100 mg/d, the vitamin D dose should be reduced. In the presence of liver disease, 25-hydroxyvitamin D can be used for treatment.

VITAMIN E

α-Tocopherol is the active form of vitamin E. Important dietary sources include vegetable oils and leafy vegetables. Vitamin E's absorption from the gastrointestinal tract is a non-energy–requiring diffusion-mediated process that requires bile acids, fatty acids, and monoglycerides for micelle formation. **Figure 10-4** shows the pathways involved in vitamin E metabolism. Analysis of vitamin E content in adipose tissue provides a useful estimate of long-term vitamin E intake. Most ingested vitamin E is eliminated by the fecal route. Vitamin E is a lipid-soluble antioxidant and free radical scavenger. It appears to protect cellular membranes and is essential for physiologic processes such as permeability of lipid bilayers, cell adhesion, and gene expression.

Causes of Deficiency

Vitamin E deficiency can be seen with chronic cholestasis, pancreatic insufficiency, and other causes of malabsorption. Vitamin E supplementation in total parenteral nutrition may be inadequate to maintain stores. Vitamin E deficiency is rarely due to dietary insufficiency.

Mutations in *TTPA*, the gene that encodes α-tocopherol transfer protein (α-TTP), result in ataxia with vitamin E deficiency. Additional disorders associated with vitamin E deficiency include

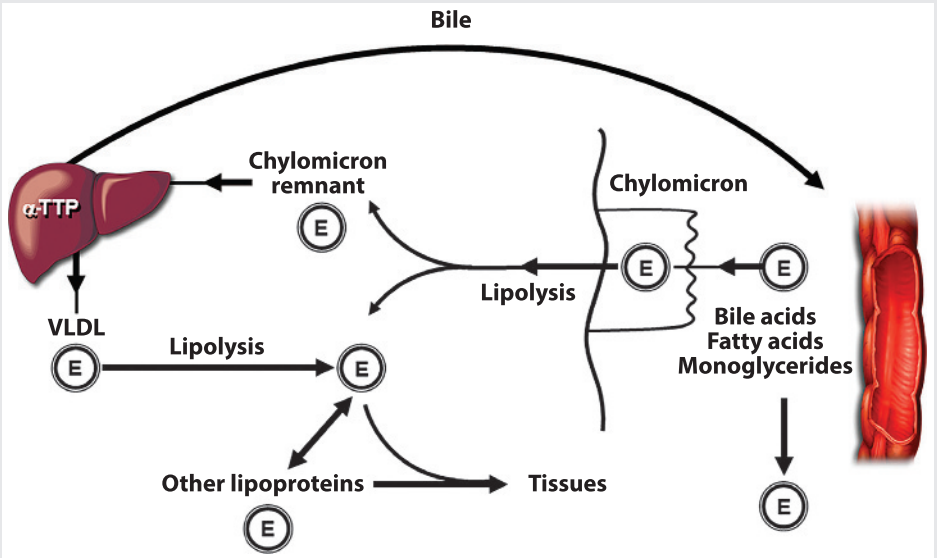

FIGURE 10-4 Normal vitamin E metabolism. Following uptake by enterocytes, all forms of dietary vitamin E are incorporated into chylomicrons. The chylomicrons are secreted into the circulation, where lipolysis by lipoprotein lipase takes place. During lipolysis, various forms of vitamin E are transferred to high-density lipoproteins or other circulating lipoproteins and subsequently to tissues. The chylomicron remnants are taken up by the liver. In the liver, the α-tocopherol transfer protein (α-TTP) incorporates α-tocopherol into very-low-density lipoproteins (VLDLs), which are secreted into plasma. Lipolysis of VLDL results in enrichment of circulating lipoproteins with α-tocopherol, which is delivered to peripheral tissue. The majority of vitamin E in the human body is localized in the adipose tissue.

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KEY POINT

■ The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement. The phenotype is similar to that of Friedreich ataxia.

hypobetalipoproteinemia, abetalipoproteinemia, and chylomicron retention disease. Salient features of these disorders are noted in **Table 10-5**.

Clinical Significance

Development of neurologic symptoms in adults with acquired fat malabsorption takes decades. Many years of malabsorption are required to deplete vitamin E stores. The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement.[77,78] The phenotype is similar to that of Friedreich ataxia. Ophthalmoplegia, ptosis, and pigmentary retinopathy may occur. A myopathy with inflammatory infiltrates and rimmed vacuoles has been described.[79] The neuropathy associated with vitamin E deficiency involves centrally directed fibers of large myelinated neurons. Swollen dystrophic axons (spheroids) have been seen in the gracile and cuneate nuclei of the brainstem. Lipofuscin may accumulate in the dorsal sensory neurons and peripheral Schwann cell cytoplasm. A 2012 Cochrane Review found no convincing evidence that vitamin E is of benefit in the treatment of Alzheimer disease or mild cognitive impairment.[80]

Investigations

Serum vitamin E levels are dependent on the concentrations of serum lipids,

TABLE 10-5 Summary of Disorders of Vitamin E Metabolism[a]

	Ataxia With Vitamin E Deficiency	Homozygous Hypobetalipoproteinemia
Source of defect	Mutations in *TTPA* gene on chromosome 8q13 (autosomal recessive)	Defect in *APOB* gene (autosomal dominant)
Consequence of defect	Impaired incorporation of vitamin E into hepatic lipoproteins for tissue delivery	Apolipoprotein B–containing lipoproteins secreted into the circulation turn over rapidly
Fat malabsorption	Absent	Present
Age of onset	Generally, first decade; adult onset described	Early childhood
Other clinical features (in addition to spinocerebellar/ dorsal column/peripheral nerve/muscle involvement)	Retinitis pigmentosa, skeletal deformities, cardiomyopathy	Retinitis pigmentosa, acanthocytosis, retarded growth, steatorrhea
Laboratory findings	Very low serum vitamin E (as low as 1/100 of normal)	Low serum vitamin E and other fat-soluble vitamins, low to nondetectable circulating lipoproteins (apolipoprotein B, chylomicrons, very-low-density lipoproteins, or low-density lipoproteins), serum cholesterol and triglycerides are markedly reduced (the ratio of free to esterified cholesterol in plasma is normal in hypolipoproteinemia and elevated in abetalipoproteinemia)
Treatment	800–1200 mg/d vitamin E (prompt normalization of plasma α-tocopherol concentration)	100–200 mg/kg/d vitamin E

[a] Modified with permission from Kumar N, Continuum (Minneap Minn).[11] © 2008 American Academy of Neurology. *journals.lww.com/continuum/Fulltext/2008/06000/METABOLIC_AND_TOXIC_MYELOPATHIES.7.aspx*.

KEY POINT

- Hyperlipidemia increases the plasma carriers for vitamin E. Hyperlipidemia can, therefore, independently increase serum vitamin E without reflecting similar alterations in tissue levels of the vitamin.

cholesterol, and very-low-density lipoprotein. Hyperlipidemia increases the plasma carriers for vitamin E. Hyperlipidemia can, therefore, independently increase serum vitamin E without reflecting similar alterations in tissue levels of the vitamin.[77] Effective serum vitamin E concentrations are calculated by dividing the serum vitamin E by the total of serum cholesterol and triglycerides. Serum vitamin E concentrations may be in the normal range in patients with vitamin E deficiency because of cholestatic liver disease, which is also associated with high lipid levels. In patients with neurologic manifestations due to vitamin E deficiency, the serum vitamin E levels are frequently severely reduced. Additional markers of fat malabsorption, such as increased stool fat, may be present. Vitamin E determination can be done in adipose tissue. Urinary excretion of the vitamin E metabolite α-carboxyethyl-hydroxychromanol may be a potential biomarker for inadequate vitamin E status but has not been adequately studied.[77] Spinal MRI in patients with vitamin E deficiency–related myeloneuropathy may show increased signal in the dorsal columns of the cervical cord.

Abetalipoproteinemia (Bassen-Kornzweig Syndrome)	Chylomicron Retention Disease
Genetic defect in microsomal triglyceride transfer protein (autosomal recessive)	Chylomicron synthesis and secretion
Normal lipidation of apolipoprotein B is prevented, and secretion of apolipoprotein B–containing lipoproteins is virtually nonexistent	Impaired assembly and secretion of chylomicrons with chylomicron retention in intestinal mucosa
Present	Present
Early childhood	Early childhood
Retinitis pigmentosa, acanthocytosis, retarded growth, steatorrhea	Impacts growth and has gastrointestinal manifestations, but acanthocytes are essentially absent, neuromuscular manifestations are less severe, and ocular manifestations are subclinical
Low serum vitamin E and other fat-soluble vitamins, low to nondetectable circulating lipoproteins (apolipoprotein B, chylomicrons, very-low-density lipoproteins, or low-density lipoproteins), serum cholesterol and triglycerides are markedly reduced (the ratio of free to esterified cholesterol in plasma is normal in hypolipoproteinemia and elevated in abetalipoproteinemia)	Hypocholesterolemia, normal fasting triglycerides, reduced plasma low-density lipoprotein, apolipoprotein B, absence of chylomicrons after a fat test meal
100–200 mg/kg/d vitamin E	100–200 mg/kg/d vitamin E

Management

In ataxia with vitamin E deficiency, supplementation with 600 IU vitamin E 2 times a day is accompanied by beneficial effects on neurologic function (**Table 10-5**). In the presence of fat malabsorption, IM administration or use of a water-miscible product or doses as high as 10 mg/kg to 100 mg/kg α-tocopherol may be required. Supplements with bile salts may be of value in some patients.

COPPER

Copper is widely distributed in foods. Copper is a component of enzymes that have a role in the structure and function of the nervous system (**Table 10-6**).[81] It is absorbed from the proximal intestines and stomach (**Figure 10-5**[82]). The stomach's acidic environment facilitates solubilization of copper by dissociating it from copper-containing macromolecules. Absorption occurs by a saturable active transport process at lower levels of dietary copper and by passive diffusion at high levels of dietary copper. The Menkes P-type ATPase (*ATP7A*) transfers copper to the secretory pathway for efflux from enterocytes and other cells. Absorbed

KEY POINTS

- The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.
- Excessive zinc ingestion is a well-recognized cause of copper deficiency.

TABLE 10-6 Copper-dependent Enzymes and Their Function

Enzyme(s)	Function
Cytochrome *c* oxidase	Electron transport and oxidative phosphorylation
Copper/zinc superoxide dismutase	Antioxidant defense
Tyrosinase	Melanin synthesis
Dopamine β-hydroxylase	Catecholamine biosynthesis
Lysyl oxidase	Cross-linking of collagen and elastin
Peptidylglycine α-amidating monooxygenase	Neuropeptide and peptide hormone processing
Ceruloplasmin, hephaestin, zyklopen	Iron homeostasis
Monoamine oxidase	Serotonin synthesis

copper binds to plasma albumin and amino acids in the portal blood and is taken to the liver where it is incorporated into ceruloplasmin and then released into the plasma. The primary pathway that regulates copper homeostasis and prevents deficiency or toxicity is excretion of copper into the gastrointestinal tract. The Wilson P-type ATPase (*ATP7B*) transfers copper to the secretory pathway for ceruloplasmin biosynthesis and for endosome formation before biliary secretion.

Causes of Deficiency

Copper deficiency since infancy results in Menkes disease. The low daily requirement of copper coupled with its ubiquitous distribution makes acquired copper deficiency rare. The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.[10,83,84] Current bariatric surgery guidelines underscore the importance of monitoring copper status following bariatric surgery.[7] Typically, neurologic manifestations are delayed by years following gastric surgery. An increased awareness of the association between copper deficiency and bariatric surgery is particularly important given the increase in the number of bariatric surgeries performed in the United States over the past decade.

Excessive zinc ingestion is a well-recognized cause of copper deficiency.[82,83,85–89] In addition to the common use of zinc in the prevention or treatment of common colds and sinusitis, zinc therapy has been used for conditions such as acrodermatitis enteropathica, decubitus ulcers, sickle cell disease, celiac disease, memory impairment, diarrhea, and acne. Unusual sources of excess zinc have included consumption of excessive amounts of denture cream for long periods and, less commonly, swallowing zinc-containing coins.[86,87,89,90] Zinc-free denture creams are now available. Individual susceptibility may play a role in hyperzincemia-induced hypocupremia and related neurologic manifestations.[87] Overloading with parenteral zinc during chronic hemodialysis has also been associated with copper deficiency myelopathy. Zinc causes upregulation of metallothionein production in the enterocytes (**Figure 10-5**). Metallothionein is an intracellular ligand, and copper has a higher affinity for metallothionein

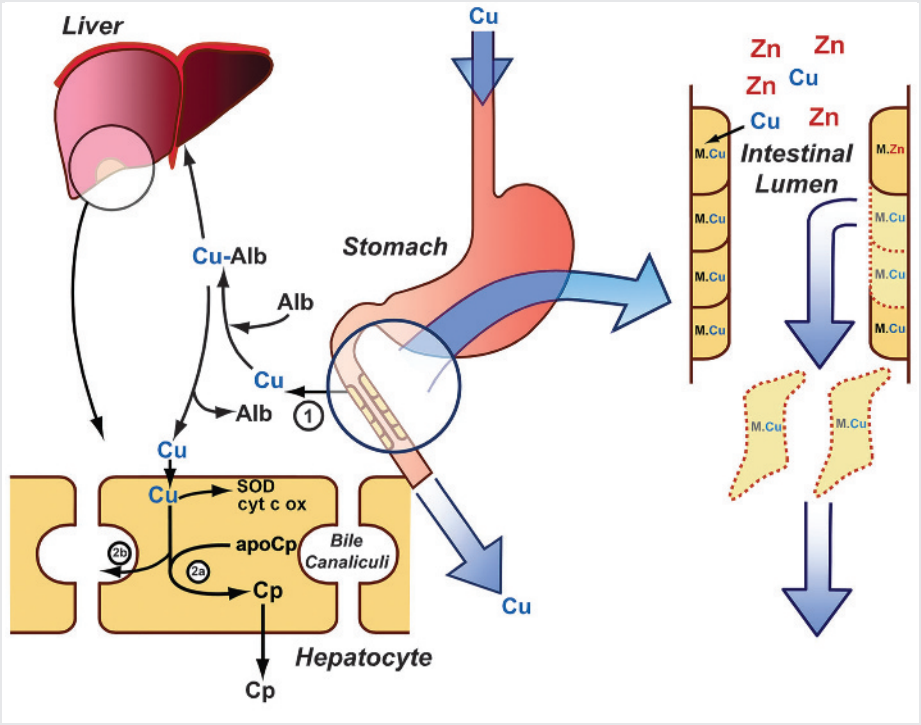

FIGURE 10-5 Copper kinetics and mechanism of zinc-induced copper deficiency. Excretion of copper into the gastrointestinal tract is the major pathway that regulates copper homeostasis and prevents deficiency or toxicity. Excessive zinc ingestion is a well-recognized cause of copper deficiency. The zinc-induced inhibition of copper absorption could be the result of competition for a common transporter or a consequence of induction of metallothionein in enterocytes. Metallothionein has a higher binding affinity for copper than for zinc. Copper is retained within the enterocytes and lost as the intestinal cells are sloughed off. Failure to mobilize absorbed copper from intestinal cells forms the basis of Menkes disease (1). In Wilson disease, there is decreased incorporation of copper into ceruloplasmin (2a) and impaired biliary excretion of copper (2b).

Alb = albumin; apoCp = apceruloplasmin; Cp = ceruloplasmin; Cu = copper; cyt c ox = cytochrome c oxidase; M = metallothionein; SOD = superoxide dismutase; Zn = zinc.

than zinc. Copper displaces zinc from metallothionein and binds preferentially to the metallothionein; it remains in the enterocytes and is lost in the stools as the intestinal cells are sloughed off.

Copper deficiency may occur in premature infants and in low-birthweight or malnourished infants. Copper bioavailability may be affected by antacids or proton pump inhibitor use and the amount of molybdenum or iron in the diet. Copper deficiency has been reported in various enteropathies associated with malabsorption and, rarely, in nephrotic syndrome and glomerulonephritis. Copper deficiency and related manifestations in celiac disease may occur in the absence of gastrointestinal symptoms. Copper deficiency may be a complication of prolonged total parenteral nutrition and enteral feeding. Overtreatment of Wilson disease with zinc has been reported to cause copper deficiency–related hematologic and neurologic manifestations.[91] At times, despite extensive investigations, the cause of copper deficiency may not be evident. Our knowledge about copper transport may help clarify the

KEY POINTS

- Other nutrient deficiencies, notably vitamin B_{12} deficiency, can coexist with copper deficiency.
- The most common manifestation of acquired copper deficiency is that of a myelopathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.
- A rise in ceruloplasmin is accompanied by an increase in serum copper in conditions such as pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, myocardial infarctions, uremia, and various inflammatory and infectious diseases.

etiology in some cases of idiopathic hypocupremia.[92]

The coexistence of multiple causes of copper deficiency increases the chances of development of a clinically significant deficiency state. Other nutrient deficiencies, notably vitamin B_{12} deficiency, can coexist with copper deficiency.

Clinical Significance

The hematologic hallmark of copper deficiency is anemia and neutropenia.[93] The anemia may be microcytic, macrocytic, or normocytic. Thrombocytopenia and resulting pancytopenia is relatively rare. A left-shift in granulocytic and erythroid maturation with cytoplasmic vacuolization in erythroid and myeloid precursors are common bone marrow findings. Ringed sideroblasts or hemosiderin-containing plasma cells may be present. Patients may be given hematologic diagnoses, such as sideroblastic anemia, myelodysplastic syndrome, or aplastic anemia.

The most common manifestation of acquired copper deficiency is that of a myelopathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.[10,83] Continued neurologic deterioration in patients with a history of vitamin B_{12} deficiency–related myelopathy who have a normal vitamin B_{12} level when on vitamin B_{12} replacement should lead to evaluation for copper deficiency. Copper and vitamin B_{12} deficiency may coexist. Peripheral nerve or optic nerve involvement is variably present. Also reported is progressive asymmetric weakness or electrodiagnostic evidence of denervation suggestive of lower motor neuron disease.[86,94] The neurologic syndrome due to acquired copper deficiency may be present without the hematologic manifestations. Copper deficiency–associated myelopathy has been described in various animal species and has been called swayback or enzootic ataxia.

Investigations

Laboratory markers of copper deficiency include decrease in serum copper or ceruloplasmin and in 24-hour urinary copper excretion.[95] These parameters are insensitive to marginal copper status and are suboptimal for assessing body copper stores. Changes in serum copper generally parallel the ceruloplasmin concentration. Ceruloplasmin is an acute-phase reactant, and the rise in ceruloplasmin is accompanied by an increase in serum copper in conditions such as pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, myocardial infarction, uremia, and various inflammatory and infectious diseases. Copper deficiency could be masked in these conditions. Serum zinc and 24-hour urinary zinc excretion levels should be obtained, and an elevation in these should prompt a search for an exogenous source of zinc.

It has been suggested that copper-containing enzymes, such as erythrocyte superoxide dismutase and platelet or leukocyte cytochrome c oxidase, may be a better indicator of metabolically active copper stores.[81] These have not been well studied clinically as markers for copper deficiency. A low serum copper or ceruloplasmin can be seen in Wilson disease or in carriers of the Wilson disease gene. An elevation in urinary copper excretion suggests Wilson disease or the heterozygote state as a cause for low serum copper levels. Serum ceruloplasmin is absent in aceruloplasminemia and is low in carriers with a mutation in the ceruloplasmin gene. It is important to note that the laboratory determination of a low serum copper does not imply copper deficiency.[95]

The most common abnormality on spine MRI is increased T2 signal involving the dorsal columns (**Figure 10-2**).[10,26,83] Additionally, signal change involving the lateral columns may be present. The cervical cord is most commonly involved. A 2010 report noted symmetric hyperintensities involving the pyramidal tract in the medulla, pons, and midbrain.[96] Nonspecific areas of increased T2 signal involving the subcortical white matter have been reported but are of uncertain significance.

Management

In patients in whom excess zinc ingestion is the likely cause of copper deficiency, stopping zinc supplementation may suffice, and no additional copper supplementation may be required. Copper supplementation is generally started in the presence of neurologic disease in addition to stopping zinc supplementation (**Table 10-1**).[10,83] Parenteral therapy may be required in the presence of severe malabsorption, severe depletion, rapid neurologic deterioration, or significant hematologic derangement or with failure of oral therapy (**Table 10-1**). Some have used parenteral administration followed by oral administration.[97] Even with a suspected absorption defect, oral copper supplementation is the desired route of supplementation. Because of the need for long-term replacement, parenteral therapy is not a first-line approach and is generally not required. Periodic assessment of serum copper helps determine adequacy of replacement. Copper deficiency in gastrointestinal disease may be accompanied by deficiency of vitamin B_{12}, vitamin D, vitamin E, and iron. Iron therapy in a patient with copper deficiency may be further responsible for decreasing copper absorption. Response of the hematologic parameters is prompt and often complete. Recovery of neurologic signs and symptoms is variable.

CONCLUSION

The central and peripheral nervous systems are both vulnerable to nutritional deficiencies. Multiple nutrient deficiencies often coexist. The eminently treatable nature of the disorders discussed in this article makes it an important topic. Prognosis depends on early recognition and prompt and adequate institution of therapy.

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Environmental Neurologic Injuries

Rodolfo Savica, MD, PhD

ABSTRACT

Purpose of Review: This article discusses neurologic complications resulting from environmental injuries and the treatment modalities for these conditions.

Recent Findings: Recent advances include improved management of altitude sickness. Relatively uncommon conditions, such as keraunoparalysis (lightning-induced paralysis) and high-pressure neurologic syndrome, are areas of ongoing study.

Summary: Environmental injuries may be associated with serious neurologic sequelae. This article reviews thermal and electrical injuries as well as injuries related to aviation, altitude, and diving. Recognition of signs and symptoms of such complex injuries and exposures will permit accurate diagnoses and improved outcomes.

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INTRODUCTION

During our lifetime, we may be exposed to a number of environmental agents that may be detrimental to the function of the nervous system. Neurologic injury can be caused by lightning strikes, electrical current, or thermal injury or can occur in the context of diving or high altitude.

THERMAL INJURIES

The human body is able to keep a constant temperature between 37.0°C (98.6°F) and 37.2°C (99°F) despite continuous changes. The anterior and posterior areas of the hypothalamus serve as heat receptors, and the preoptic area of the anterior hypothalamus has a role in regulating temperature.

Heatstroke and Heat Exhaustion

Heatstroke occurs when body temperature exceeds 40.6°C (105°F), at which point a number of systemic symptoms can develop. Heat shock protein 72, free radicals, nitric oxide, monoamines, dopamine, and interleukins are increased as a result of the high temperature. **Table 11-1** lists symptoms associated with increased body temperature.[1] Severe heatstroke may also produce encephalopathy, severe confusion, and seizures. MRI findings may include increased signal in diffusion sequences as a result of possible myelinolysis-related cellular damage. Notably, malignant hyperthermia, serotonin syndrome, and neuroleptic malignant syndrome may have clinical features similar to those of heatstroke. About 20% of cases of heatstroke and high-temperature syndrome may have long-term consequences, such as ataxia, encephalopathy, and parkinsonism.[2]

It is important to differentiate between heatstroke and heat exhaustion. In heat exhaustion, temperatures are typically between 37°C (98.6°F) and 40°C (104°F); it is usually caused by dehydration and electrolyte loss and occurs more often in older adults. The neurologic syndrome is milder than in heatstroke but can be associated with mental status abnormalities (**Case 11-1**). It is crucial to treat the underlying condition and reduce the core temperature.

TABLE 11-1 Neurologic Manifestations of Heatstroke

- Confusion
- Vertigo
- Abnormal oral movements
- Hemiparesis
- Pancerebellar syndrome
- Seizures
- Encephalopathy

External (water immersion) and internal (iced peritoneal or gastric lavage) cooling can be considered; these methods have a temperature reduction rate of 0.2°C/min (0.36°F/min). Antipyretics do not decrease the core temperature and thus should be used with caution. Dehydration and electrolyte imbalance should be corrected according to current guidelines, avoiding rapid correction of sodium.[1,3]

In addition, a number of medications can interfere with thermoregulation, inhibiting the ability to release heat through appropriate perspiration. All the agents that lead to hypohidrosis can increase the susceptibility to hyperthermia: anticholinergic agents, opioids, barbiturates, α2 receptor antagonists, and botulin toxin.[4] Topiramate is a common agent that has been described as a possible cause of hypohidrosis and thus of transient hyperthermia; the symptoms of topiramate-induced hypohidrosis and hyperthermia can range from heatstroke to coma; however, when identified early, the symptoms are usually reversible, leading to a full recovery.[5,6]

Hypothermia

The neurologic consequences of hypothermia are less well known; however, when core temperature drops to between 33°C (91.4°F) and 35°C (95°F), patients may have confusion, incoordination, and slow reaction

KEY POINTS

- Approximately 20% of cases of high-temperature syndromes may have long-term consequences.
- Heat exhaustion occurs at temperatures between 37°C (98.6°F) and 40°C (104°F). The syndrome is milder than heatstroke and can be treated by replenishing fluids and electrolytes; avoid rapid correction of temperature.

Case 11-1

An 82-year-old woman was found by her neighbor on a hot summer day undressed in her backyard, digging a hole in the lawn. When queried, she spoke incoherently and mentioned her dog that had died years before. She was taken by ambulance to the hospital. At her initial evaluation, her pulse was 88 beats/min, her temperature was 39.2°C (102.6°F), and her blood pressure was 155/80 mm Hg. She appeared confused, was disoriented in time and space, and had extremely dry mucosae. Family members reported that she had a history of type 2 diabetes mellitus and poorly controlled hypertension. In the past year, she had been affected by mild memory loss; however, she lived independently.

Brain CT and MRI were negative for acute changes. Her serum sodium level was 130 mEq/L. Fluids and sodium were replenished accordingly. After a few days, she was less confused but was not able to return to her previous baseline functional status. She was transferred to a nursing home and then to an assisted living facility.

Comment. This is a case of heat exhaustion in an elderly woman with mild cognitive impairment that ultimately became a more severe clinical dementia after the dehydration and hyponatremia. Rapid intervention, with correction of dehydration and electrolyte imbalance, will prevent worsening of symptoms of heat exhaustion and the development of heatstroke.

KEY POINTS

- A direct lightning strike is rare; most injuries are secondary to falling trees or blast injuries. Neurologic manifestations can be preceded by cutaneous damage and metabolic complications.
- Keraunoparalysis is an immediate but rare consequence of lightning strike; transient paralysis of the lower limbs improves in hours without treatment.

times. When core temperature drops below 32°C (89.6°F), amnesia, severe confusion, and bizarre behaviors (eg, paradoxical undressing) may occur. The peripheral nervous system may be affected as well, with damage of the large- and small-nerve fibers (frostbite), causing neuropathic symptoms (eg, numbness, lancinating pain). The prognosis of neuropathic symptoms is usually favorable, with symptoms resolving in a few months.[1]

ELECTRICAL INJURIES

Lightning is a natural atmospheric electrical discharge that occurs between electrically charged regions of a cloud or between clouds (ie, positive versus negative electrical charges of cloud areas). Most lightning (cloud-to-cloud, about 60% to 90%) does not represent a threat to humans. In the United States, most lightning-related injuries occur between May and September in the South and the Midwest. Approximately 30 million cloud-to-ground lightning strikes occur every year, causing about 374 struck-by-lightning deaths (based on a 1993 to 2000 average annualized rate of 0.23 per 1,000,000 deaths).[7] Thus, being struck by lightning is a relatively rare occurrence. The injuries are usually caused by secondary effects (eg, blast injury, falling tree) rather than by direct strike. Neurologic damage involves the central, peripheral, and autonomic nervous systems and may be preceded by cutaneous and metabolic derangements.[8]

It is important to differentiate between immediate injuries and long-term neurologic sequelae of a lightning strike. Not considering direct cardiopulmonary arrest and tympanic membrane damage secondary to the blast, the immediate neurologic disorders are determined by the intensity, location, and absorption of the force causing the symptoms; these may range from pain to coma. Immediately after a lightning strike, a number of neurologic disorders may occur as a result of the extreme electrical discharge; they can be divided into ''immediate and transient'' and ''immediate and prolonged'' (**Table 11-2**).[8] The long-term sequelae include delayed neurologic symptoms, such as parkinsonism and focal dystonias, and secondary injuries after trauma or blasts.[9]

Keraunoparalysis is an immediate and transient symptom of lightning strike. It is characterized by transient weakness of the lower limbs that usually improves within hours (**Case 11-2**). It is important to consider keraunoparalysis after any lightning-induced injury to avoid subjecting the patient to unnecessary surgical procedures; however, neuroimaging is crucial to exclude traumatic injuries or bleeding.[10,11] The mechanism of development

TABLE 11-2 Neurologic Manifestations of Lightning Strike

▶ **Immediate and Transient**
Loss of consciousness
Confusion
Amnesia
Weakness
Keraunoparalysis (lightning-induced paralysis)
▶ **Immediate and Prolonged**
Strokelike syndrome
Seizures
Brain hemorrhage
▶ **Long-term Sequelae**
Parkinsonism
Focal dystonias

Case 11-2

A 32-year-old farmer was found unconscious on the ground while harvesting crops with his family on a cloudy day in September. His brother reported hearing a loud sound ''like an explosion'' just a couple of minutes before they found him in the field. After a few minutes, while being transported to the hospital, he regained consciousness. He reported that he was unable to move or feel his lower extremities. The initial evaluation did not find any neurologic abnormalities or focal signs other than a flaccid paralysis in the lower extremities. Spine and brain imaging did not reveal any significant findings. Within 3 hours, he had improvement in lower extremity strength. In 24 hours, he had complete resolution of his lower extremity symptoms. He was discharged 2 days later, with left-sided tinnitus that did not resolve over the next few months. Further tests found a rupture of the tympanic membrane.

Comment. This is a typical presentation of keraunoparalysis after a lightning strike. The transient nature of the symptoms is a relevant clinical observation that should avoid unnecessary procedures or treatments. However, it is crucial to use neuroimaging (CT or MRI) to exclude acute bleeding, edema, or other secondary consequences of the lightning strike.

KEY POINT

■ Lightning strike does not leave entry marks, but alternating current electrical injury does.

of keraunoparalysis is still not totally understood; however, it seems to be caused by a sympathetic system activation and transient vasospasm that resolves spontaneously. In general, in patients with lightning injury, it is better to wait to make a prognosis until after the first 24 hours of observation.

A fundamental difference exists between injuries from alternating electrical current (eg, after contact with an electrical grid) and lightning injuries. The neurologic injuries of alternating electrical current depend on the duration of exposure and the intensity of the current. A 50-Hz to 60-Hz current can cause neurologic effect, depending on the milliamps: 1 mA can cause tingling, whereas 6 mA to 30 mA can cause forceful contraction and inability to release grip and 50 mA to 150 mA leads to shock, respiratory paralysis, and severe muscle spasm. Usually higher milliamps are associated with cardiac arrest and death. The duration of exposure to the current is extremely short in lightning injuries, with the vast majority of lightning energy flashes occurring around the body surface. Lightning has only brief contact with skin, too brief to burn the skin substantially or leave entry marks, whereas alternating current injuries are usually associated with a prolonged exposure of the current to the skin; the presence of burns and entry marks is common in alternating current injuries due to the longer surface and internal exposure to the current. Nevertheless, the brief and fast contact of a high discharge of energy generated by lightning can explain the peculiarity and the transient nature of some of the symptoms.

IMMERSION-RELATED INJURIES

Scuba diving is a type of underwater diving that takes its name from the self-contained underwater breathing apparatus (scuba) that divers use. Scuba divers carry their own source of pressurized oxygen. The death rate among US divers is approximately 3 per 100,000 to 6 per 100,000, and 70% of the deaths are caused by drowning.[12]

Decompression sickness is the most common mechanism of injury.

KEY POINTS

- Reports of itchiness and joint pain after scuba diving require a neurologic evaluation because type I decompression sickness can evolve to the more severe type II decompression sickness. Information regarding the rate of descent/ascent is crucial for an accurate evaluation.
- Decompression sickness must be treated with 100% oxygen immediately at the onset of symptoms, followed by use of a decompression chamber. About 70% of patients have a good prognosis and no consequences.

When divers breathe compressed air, inert gases dissolve, causing bubbles to form. As a diver descends, the amount of inert gas increases because of exposure to increased pressure. In accordance with the Henry law, more gas is dissolved as a diver descends deeper and over an extended period; thus, a too-quick ascent causes increased bubble formation in veins and tissues.[13]

Decompression sickness can be divided into two types. Type I is characterized by pain in the joints and itching and is usually self-limited, with improvement in a few hours to a day with minimal or no treatment. Type II is a serious neurologic condition that requires rapid treatment (**Table 11-3**).[14] Interestingly, type II decompression sickness targets the spinal cord at the thoracic level (**Figure 11-1**[15]).

The paravertebral veins of the Batson plexus are the most likely area of bubble collection because of the anatomic structure of the plexus; they are prone to stasis. Cerebral involvement in type II decompression sickness is reported in about 30% of cases, typically 1 hour or more after resurfacing (**Table 11-3**). It is crucial to perform an accurate neurologic evaluation whenever a diver reports joint pain or itching; in fact, the symptoms of type I decompression sickness often precede the onset of type II. It is also crucial to collect information on duration, depth, and speed of ascent. If the rate of descent/ascent was miscalculated or was accelerated because of malfunction of the decompression equipment, multiple divers may be affected by decompression sickness.

Migraine, epilepsy, and multiple sclerosis can increase the risk of decompression sickness.[12] Although still controversial, the presence of a patent foramen ovale can increase the risk of paradoxical embolism, and individuals with this condition should be made aware of their increased risk with diving.[12]

Once the diagnosis of decompression sickness is made, the prognosis depends on the promptness of treatment: 100% oxygen has to be administered immediately at the onset of symptoms (during the so-called *oxygen window*). Use of a decompression chamber is the next urgent procedure to be considered.[16] The vast majority (about 70%) of individuals do not have any long-term consequences of decompression sickness; also, the demographic characteristics (young and in good overall health) of most divers favor a

TABLE 11-3 Neurologic Symptoms of Decompression Sickness

▶ **Type I**
Pain
Itching
▶ **Type II**
Weakness
Paralysis
Vertigo
Paresthesia
Vision disturbance
Bladder dysfunction
Bowel dysfunction
Dysphagia
Visual disorders
Ataxia
Hemiparesis
Aphasia
Mental slowness

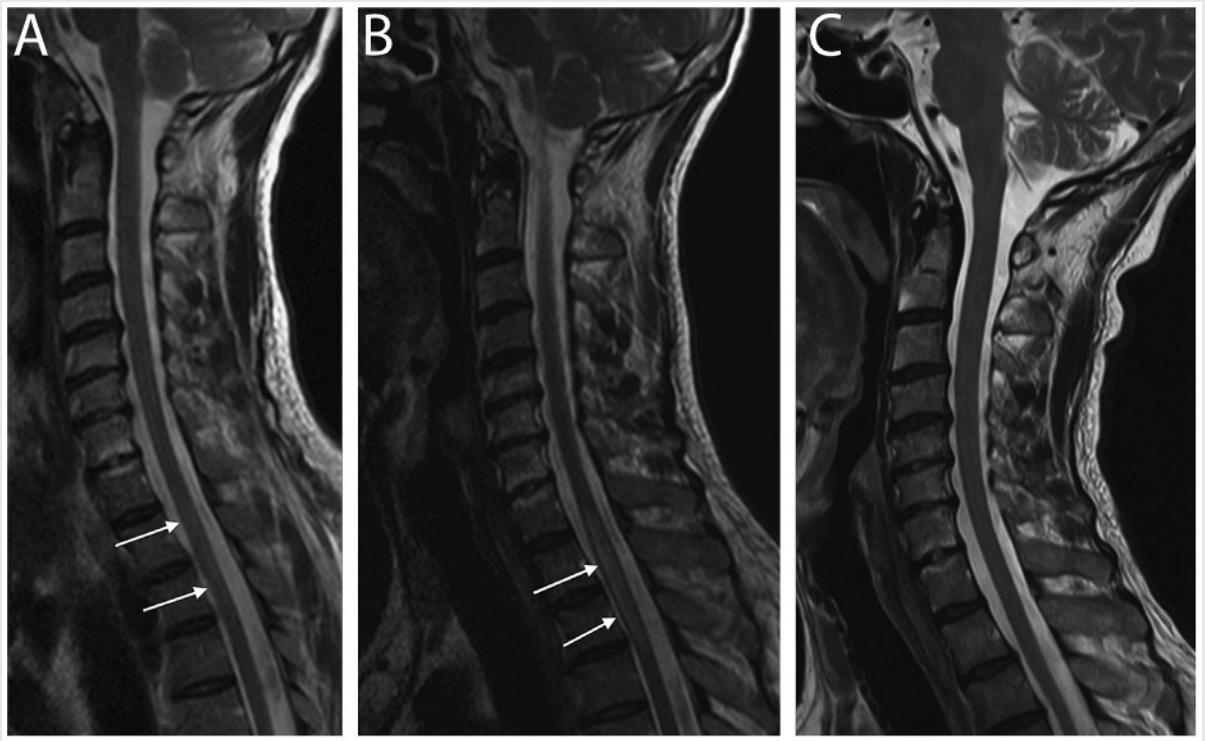

FIGURE 11-1 Thoracic spinal cord involvement in type II decompression sickness. *A*, Sagittal T2-weighted MRI performed 24 hours after a diving accident shows a thoracic lesion appearing as a subtle high signal (*arrows*). The lesion increases in size on the following day (*B, arrows*) and subsequently disappears on day 13 (*C*). This evolution may also be consistent with edema.

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good prognosis. Despite reports of short-term memory loss after decompression sickness, the long-term cumulative effect of diving has yet to be clarified.[14]

Divers who descend more than 600 m (1969 ft) to 700 m (2297 ft) can be susceptible to high-pressure neurologic syndrome. Initially described when divers were breathing helium during descent, the symptoms depend on the rate of descent, duration and depth of the dive, and amount of helium inhaled.[17] The most common symptom seems to be tremor with proximal to distal propagation (**Table 11-4**). EEG changes, including appearance of theta and delta activity in the anterior cortex, disappearance of alpha waves in the temporooccipital area, and a reduction of rapid eye movement (REM) and N3 sleep stage percentages have also been reported.[18]

TABLE 11-4 Manifestations of High-Pressure Neurologic Syndrome

- Action tremor[a]
- Weakness[a]
- Cramps[a]
- Sleep disturbances
- Hallucinations
- Memory loss

[a] Proximal to distal propagation.

KEY POINT

■ Neurologic symptoms of high-altitude exposure are more common between 2500 m (8202 ft) and 3500 m (11,483 ft). Return to a lower level or to sea level will restore the baseline physiologic status.

No treatment is available for high-pressure neurologic syndrome; antiepileptic agents and antidepressants have been studied in animals but not in humans.[17] Mixing helium with other gases during deep descents has been suggested to reduce the occurrence of high-pressure neurologic syndrome.

INJURIES RELATED TO HIGH ALTITUDE

When a significant reduction of oxygen occurs, neurons experience hypoxia-induced dysfunction. However, when the hypoxia is subacute or chronic rather than acute, the pathophysiologic mechanisms of disease are completely different. The most common neurologic complications of hypoxia are caused by high-altitude exposures. The most common neurologic diseases related to high-altitude exposure are acute mountain sickness and high-altitude cerebral edema.[19] Generally, most altitude-related disorders occur between 2500 m (8202 ft) and 3500 m (11,483 ft).[19] The most important mechanism of injury is the speed of ascent or the speed of depressurization. A sudden change in aircraft cabin pressure caused by fast ascension to a high altitude will cause loss of consciousness and death within minutes; in contrast, climbers can gradually and methodically climb high peaks without supplemental oxygen. Acclimatization is the physiologic process helping to increase the delivery of oxygen when climbing; interestingly, it is not a long-lasting mechanism, and the return to a lower level or to sea level will restore the initial physiologic status.[20] The central nervous system is extremely sensitive to acclimatization because of its dependency on oxygen and perfusion. However, the development of acute mountain sickness and high-altitude cerebral edema depends on a number of factors (eg, rate of ascent, individual susceptibility); thus, whenever an individual reports symptoms, even mild symptoms, it is better to consider altitude sickness until proven wrong.

Acute Mountain Sickness

Acute mountain sickness is the most common altitude disorder. Between 40% and 45% of climbers in the Himalayas have symptoms; however, acute mountain sickness can be present at significantly lower altitudes.[19] The clinical features of acute mountain sickness are not specific and include a variety of symptoms or combinations of symptoms (**Table 11-5**). Usually they occur within 8 to 24 hours after a new altitude is reached, at times even during the descent, and they resolve in 4 to 5 days.[19] Acute mountain sickness seems to be caused by mild vasogenic edema. Usually no treatment is needed, although symptomatic treatment of headache can be considered. Acetazolamide, 250 mg every 8 hours, can cause a metabolic acidosis, which increases the respiratory exchange of oxygen. Dexamethasone, which reduces edema without affecting respiration, can be used with acetazolamide if needed.[20] Portable hyperbaric chambers are available for

TABLE 11-5 Neurologic Symptoms of Acute Mountain Sickness[a]

- ▶ Headache
- ▶ Lethargy
- ▶ Fatigue
- ▶ Poor appetite
- ▶ Poor sleep

[a] Occurring between 8 and 24 hours and resolving in 4 to 5 days.

high-altitude expeditions. The best treatment, however, is to avoid a fast rate of ascent and to camp at a slightly lower altitude overnight to support the process of acclimatization (**Case 11-3**).

High-Altitude Cerebral Edema

High-altitude cerebral edema is a life-threatening condition that can be preceded by acute mountain sickness or high-altitude pulmonary edema. It usually occurs at higher altitudes, even after a good acclimatization process. The prevalence among climbers is between 0.5% and 1.0% at 4000 m (13,123 ft) to 5000 m (16,404 ft).[21] High-altitude cerebral edema usually presents 24 to 36 hours after acute mountain sickness and is caused by increased microvascular permeability and extravasation secondary to hypoxia, which creates a severe vasogenic edema, apparently mediated by the chemicals bradykinin, histamine, arachidonic acid, oxygen, and, especially, vascular endothelial growth factor (VEGF) released during the hypoxia, increasing vascular permeability.[22] Neuroimaging does not show any evidence of edema in the gray matter. T2-weighted or diffusion-weighted neuroimaging may reveal increased signal in the splenium or other areas of the corpus callosum. Edema can evolve to petechiae and thrombosis in later stages of the disease. Interestingly, it has been theorized that individuals with larger ventricles and cerebral atrophy are less susceptible to altitude sickness because of their increased ability to accommodate cerebral edema.[23] High-altitude cerebral edema has symptoms similar to those of acute mountain sickness; however, the symptoms rapidly progress to a more severe neurologic picture (**Table 11-6**).

In the presence of ataxia and loss of consciousness after/during a climb, high-altitude cerebral edema should be considered and treated immediately.[21] The symptoms may take up to 14 days to resolve; usually, ataxia is the last symptom to improve. The treatment is similar to that for acute mountain sickness: descent, oxygen, hyperbaric chamber, and dexamethasone.[21]

KEY POINT

- In acute mountain sickness, acetazolamide is commonly used to cause metabolic acidosis; dexamethasone can be used in conjunction with acetazolamide. Portable hyperbaric chambers are needed in climbing expeditions to make treatment readily accessible.

Case 11-3

A 45-year-old man descended from the Mount Etna volcano in Italy during a climbing expedition. After starting the descent from the peak, he experienced shortness of breath and severe headache. His respiratory rate was 48/min. He immediately took acetazolamide and was transported to the base camp. From there, he was transferred immediately by helicopter to a hospital at sea level. The headache did not subside, and dexamethasone was started with acetazolamide. The hyperbaric chamber was prepared; however, 12 hours after onset, his headache started to improve and resolved completely after 5 hours. He was discharged the next day.

Comment. This is a typical case of acute mountain sickness that resolved in about 18 hours. The most important treatment, which is also a common practice in mountain expeditions, is to further reduce the altitude. (In fact, climbers usually spend the night at a lower altitude than they reached during the day to facilitate the process of acclimatization.) If possible, returning to sea level in a short time is warranted. Acetazolamide can be used immediately but does not seem to have a role as a preventive agent. In high-altitude expeditions, a portable hyperbaric chamber enables readily accessible therapy.

KEY POINT

■ Decompression sickness can be caused by decreased pressure at flight altitude, but the symptoms appear less severe than in immersion-related decompression sickness. Administering 100% oxygen and descending to a lower altitude produce immediate improvement.

TABLE 11-6 Neurologic Manifestations of High-Altitude Cerebral Edema Presenting Within 24 to 36 Hours

- ▶ Acute mountain sickness
- ▶ Ataxia
- ▶ Papilledema
- ▶ Abnormal tone
- ▶ Meningism
- ▶ Fever
- ▶ Lethargy
- ▶ Change in behavior
- ▶ Hallucinations
- ▶ Coma

AVIATION- AND SPACE-RELATED INJURIES

Type I and type II decompression sickness (refer to the section on immersion-related injuries) may occur as the result of decreased pressure at flight altitude.[24] The pathophysiologic mechanism and symptoms are similar to those occurring in scuba diving; however, the symptoms are less severe, with more cerebral rather than spinal involvement and different gas composition and bubble load.[24] At altitudes of 3048 m (10,000 ft), alveolar reorganization creates hypoxia, which may lead to reduced performance, blurred vision, fatigue, headache, confusion, behavioral changes, loss of coordination, and, finally, coma. Administration of 100% oxygen and descent to a lower altitude usually lead to immediate improvement.

In addition, some evidence suggests Air Force U-2 pilots who have been exposed to high altitudes (more than 21,336 m [70,000 ft]) may develop decompression sickness and cognitive impairment that seems to be correlated with the presence of a number of radiologic abnormalities. Some pilots were found to have a higher number and increased volume of white matter hyperintensities compared to nonpilot controls. Interestingly, the risk of abnormalities seems to have increased in recent years because of the longer time spent at higher altitude.[25,26]

Pilots are exposed to acceleration, measured as g-force. The main neurologic symptom associated with g-force is peripheral loss of vision, followed by central vision loss. If g-force acceleration continues, the top-down force impairs blood flow, causing hypoperfusion and ischemia, which causes loss of consciousness. G-force–induced loss of consciousness has been reported in 14% of pilots and 70% of individuals exposed to centrifuge-acceleration force; usually 15 seconds of disorientation and confusion precede a 15-second loss of consciousness.[27]

CONCLUSION

Environmental injuries can cause serious neurologic harm. We are exposed to the risk of some types of injuries throughout our lifetime; however, some individuals have more frequent or more intensive exposure in their work setting or through their chosen recreational activities. Therefore, prompt recognition of these disorders is crucial to minimize the neurologic consequences and improve the prognosis.

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CONTINUUM
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Autoimmune Neurology of the Central Nervous System

W. Oliver Tobin, MBBCh, BAO, PhD; Sean J. Pittock, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):627–653.

Abstract

Purpose of Review:

This article reviews the rapidly evolving spectrum ofautoimmune neurologic disorders with a focus on those that involve the central nervous system, providing an understanding of how to approach the diagnostic workup of patients presenting with central nervous system symptoms or signs that could be immune mediated, either paraneoplastic or idiopathic, to guide therapeutic decision making.

Recent Findings:

The past decade has seen a dramatic increase in the discovery of novel neural antibodies and their targets. Many commercial laboratories can now test or these antibodies, which serve as diagnostic markers of diverse neurologic disorders that occur on an autoimmune basis. Some are highly specific for certain cancer types, and the neural antibody profiles may help direct the physician's cancer search.

Summary:

The diagnosis of an autoimmune neurologic disorder is aided by the detection of an objective neurologic deficit (usually subacute in onset with a luctuating course), the presence of a neural autoantibody, and improvement in the neurologic status after a course of immunotherapy. Neural autoantibodies should raise concern for a paraneoplastic etiology and may inform a targeted oncologic valuation (eg, *N*-methyl-D-aspartate [NMDA] receptor antibodies are associated with teratoma, antineuronal nuclear antibody type 1 [ANNA-1, or anti-Hu] are associated with small cell lung cancer). MRI, EEG, functional imaging, videotaped evaluations, and neuropsychological evaluations provide objective evidence of neurologic dysfunction by which the success of immunotherapy may be measured. Most treatment information emanates from retrospective case series and expert opinion. Nonetheless, early intervention may allow reversal of deficits in many patients and revention of future disability.

Key Points

- Unless a high degree of suspicion exists for a single antigenic target in patients presenting with neurologic disorders, such as in neuromyelitis optica, the authors advocate a global screen for a number of potential causative antibodies.

- Indirect tissue immunofluorescence and immunohistochemistry serve as excellent screening tools for the presence of neural antibodies.
- Western blot is best suited for detecting antibodies that bind to cytosolic or nuclear antigens.
- A high rate of false-positive results for neuromyelitis optica IgG exists with use of enzyme-linked immunosorbent assays.
- Ideally, paired samples of serum and CSF should be tested in patients with suspected autoimmune neurologic disease.
- Paraneoplastic antibodies are more strongly predictive of tumor type than of a particular clinical syndrome.
- Some antibody clusters, when present, should alert the clinician to a high probability of systemic malignancy.
- The presence of risk factors for malignancy, such as smoking or a family history, or the presence of a neural antibody with an oncologic association should prompt an evaluation for malignancy.
- Cytologic and molecular classification systems have been proposed to describe antibody-associated diseases.
- The most recent iteration of the diagnostic criteria for neuromyelitis optica spectrum disorder emphasizes the importance of detecting neuromyelitis optica IgG with a sensitive and specific assay in the correct clinical context (optic neuritis, brainstem or area postrema syndrome, myelitis, symptomatic narcolepsy, or diencephalic syndrome with neuromyelitis optica spectrum disorder– typical brain MRI).
- The entity of seronegative neuromyelitis optica spectrum disorder requires a more stringent set of criteria to be filled in the absence of neuromyelitis optica IgG detection.
- Myelin oligodendrocyte glycoprotein–specific antibodies are associated with a distinct phenotype of central nervous system demyelinating disease, including conus-predominant myelitis and bilateral optic neuritis, often occurring simultaneously, associated with ''cotton wool'' brain lesions with poorly defined margins.
- Antibodies to the glial fibrillary acidic protein-α isoform have recently been described as a biomarker of a steroid-responsive autoimmune meningoencephalomyelitis.
- Antibodies directed against targets at or near the *N*-methyl-D-aspartate receptor account for the second most common form of autoimmune encephalitis after acute disseminated encephalomyelitis.
- Viral herpes simplex type 1 encephalitis can be followed by *N*-methyl-D-aspartate receptor encephalitis.
- Rapid-onset cognitive impairment, in particular if associated with a personal or family history of autoimmunity or abnormal CSF findings, should prompt consideration of an autoimmune cause.
- Any treatment of cognitive impairment with immunotherapy should be accompanied by careful objective documentation of cognitive deficits before embarking on an immunotherapy trial to allow an objective demonstration of any treatment response.
- Features that should prompt the clinician to consider an autoimmune cause for seizures include a new-onset seizure disorder with frequent events; new-onset refractory status epilepticus; multiple event types in one individual; antiepileptic drug treatment resistance; CSF abnormalities; and a history of malignancy, smoking, or autoimmune disease.
- CSF abnormalities are not invariable in autoimmune conditions, so the presence of a normal CSF should not dissuade the clinician from considering autoimmune causes.
- Features that should prompt the clinician to consider an autoimmune cause for a movement disorder include a subacute onset and a widespread distribution of symptoms and signs, including involvement of the trunk and head as well as extremities.

- A family history of autoimmune disease, such as autoimmune thyroid disease, lupus, or rheumatoid arthritis, may suggest a predisposition toward neuromyelitis optica spectrum disorder or other antibody-mediated myelopathies.
- The clinical course of a myelopathy can yield clues to the differential diagnosis, with typical transverse myelitis being of subacute onset over days to weeks and conditions such as neurosarcoidosis and paraneoplastic myelopathies having a progressive course from onset.
- The goal of initial treatment of neuromyelitis optica is to determine the maximum response that can be obtained with immunotherapy.
- In patients with a suspected autoimmune neurologic syndrome with no therapeutic response to immunotherapy, the diagnosis should be reevaluated.
- Objective measures of disability and treatment response should be obtained before and after treatment of suspected autoimmune neurologic conditions.
- In patients treated with IVIg, false-positive antibody results can be seen due to the transfused immunoglobulin.
- Patients who have a clinical response when treated with azathioprine tend to have a
- 5-femtoliter or more elevation in mean corpuscular volume in response to treatment.
- Therapeutic drug monitoring is not routinely recommended in patients treated with mycophenolate mofetil; however, in patients with loss of disease control, mycophenolic acid serum levels are useful to guide treatment toward dose escalation or drug switching.

Neurologic Complications of Cardiac and Aortic Disease

James P. Klaas, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):654–668.

Abstract

Purpose of Review:

This article discusses neurologic complications that can arise from cardiac and aortic disease and dysfunction.

Recent Findings:

Advances in the care of patients with cardiac or aortic disease include the use of prolonged cardiac monitoring in cryptogenic stroke and the pproval of the use of left atrial appendage closure devices for stroke prevention in patients with atrial fibrillation who are not candidates for anticoagulation. Continuing controversy surrounds patent foramen ovale closure, and new evidence indicates that cognitive impairment following coronary artery bypass grafting surgery may be less common than previously thought.

Summary:

Dysfunction of the cardiovascular system can cause serious neurologic injury. In some cases, both the initial presenting symptom and the most serious damage done by cardiac or aortic dysfunction may be neurologic. Prompt recognition of the symptoms, combined with recent

advances in both cardiology and neurology, may permit more accurate diagnoses, more effective treatment, and less injury to patients.

Key Points

- Prolonged cardiac monitoring should be considered for patients with cryptogenic stroke.
- Left atrial appendage closure is an emerging stroke prevention treatment option for patients with atrial fibrillation for whom anticoagulation is problematic.
- Randomized controlled trials have not shown a benefit of patent foramen ovale closure over medical therapy for prevention of recurrent stroke or transient ischemic attack.
- Infective endocarditis frequently causes neurologic complications. Stroke is the most common.
- The risk of neurologic complications from infective endocarditis declines rapidly with the initiation of antibiotics.
- Atrial myxomas and papillary fibroelastomas are the most common cardiac tumor types and the types most frequently associated with neurologic complications.
- Atrial fibrillation and heart failure may be independent risk factors for dementia.
- Cognitive impairment as a consequence of coronary artery bypass grafting surgery may be less common than previously thought.
- Aortic aneurysms can cause direct neurologic dysfunction by compressing neuronal structures, such as the left recurrent laryngeal nerve.
- Aortic dissections can be painless, and the initial presenting symptom of a dissection may be neurologic.
- Stroke is the most common neurologic complication of a type A aortic dissection.
- Development of a syndrome resembling progressive supranuclear palsy can rarely develop after surgical repair of ascending aortic dissection or aneurysm.
- Aortic plaques are an underrecognized cause of ischemic stroke.
- Consider screening for cerebral aneurysms in patients with coarctation of the aorta.

Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias

Michelle L. Mauermann, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):669–690.

Abstract

Purpose of Review:

This article reviews the spectrum of neurologic complications associated with lymphoma, leukemia, and paraproteinemic disorders. While leptomeningeal metastasis is the most common complication of lymphoma and leukemia and peripheral neuropathy is the most common complication of paraproteinemic disorders, clinicians need to be familiar with the diverse neurologic complications of these disorders.

Recent Findings:

Lymphomatous nervous system involvement can be difficult to diagnose, especially when it is the presenting symptom. CSF cytology and flow cytometry, as well as the imaging pattern, assist in diagnosis. Neurologic complications are less common in Hodgkin lymphoma; however, some unique paraneoplastic syndromes are associated with Hodgkin lymphoma, including primary central nervous system angiitis, limbic encephalitis, and cerebellar degeneration. Recent reports suggest that anti–metabotropic glutamate receptor 5 (mGluR5) antibodies are associated with limbic encephalitis and that anti-Tr antibodies are associated with cerebellar degeneration in Hodgkin lymphoma. Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome is often misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). A lambda protein, thrombocytosis, and elevated vascular endothelial growth factor (VEGF) can all be helpful clues in diagnosis. Early recognition is important, as the neuropathy responds to radiation therapy or chemotherapy.

Summary:

Neurologic involvement can occur throughout the disease course in lymphoma and leukemia, including at presentation, with systemic progression, and at relapse. In paraproteinemias, the peripheral neuropathy phenotype, monoclonal protein type, and associated autonomic and systemic features aid in identification of an underlying plasma cell disorder.

Key Points

- The majority of patients with non-Hodgkin lymphoma present with nervous system involvement during treatment or shortly following completion.
- Lymphomatous infiltration of the leptomeninges is the most common neurologic complication of non-Hodgkin lymphoma.
- The identification of Reed-Sternberg cells in the CSF is the definitive test for leptomeningeal metastases from Hodgkin lymphoma.
- Epidural metastases occur in 2% to 5% of patients with non-Hodgkin lymphoma and develop from a paravertebral mass invading the epidural space through the intervertebral foramina.
- The MRI in lymphomatosis cerebri demonstrates diffuse white matter disease with little or no contrast enhancement.
- Neurolymphomatosis most frequently involves the cauda equina or sciatic nerve and is
- very painful.
- Treatment of neurolymphomatosis consists of systemic chemotherapy with high-dose IV methotrexate.
- Limbic encephalitis and paraneoplastic cerebellar degeneration are paraneoplastic syndromes seen in Hodgkin lymphoma.
- Limbic encephalitis in Hodgkin lymphoma is associated with antibodies to metabotropic glutamate receptor 5, and paraneoplastic cerebellar degeneration in Hodgkin lymphoma is associated with anti-Tr antibodies.
- Primary angiitis of the central nervous system presents with headache, encephalopathy, and stroke.
- Intravascular lymphoma has a multifocal presentation with systemic symptoms and is due to occlusion of small vessels by lymphoma cells.
- Leptomeningeal metastasis in leukemia is most common in acute lymphoblastic leukemia, and patients are routinely given central nervous system prophylaxis.

- Extramedullary myeloid tumors may be the initial presentation of acute myelogenous leukemia or chronic myelogenous leukemia and frequently affect the thoracic spine, causing spinal cord compression.
- Intracranial hemorrhage is the second most common complication in adult patients with hematologic malignancies, and the risk is highest in acute leukemia.
- Paraproteinemias affect 3% to 4% of the population older than the age of 50 and more than 5% of the population older than the age of 70.
- Peripheral neuropathy is a common complication of paraproteinemias.
- Epidural spinal cord compression occurs in 6% of patients with multiple myeloma and typically presents with back pain with radicular features or lower limb weakness.
- Hyperviscosity can occur in multiple myeloma and Waldenström macroglobulinemia and is treated with plasma exchange in addition to systemic therapy.
- Bing-Neel syndrome is due to perivascular infiltration of lymphocytes and plasma cells surrounding Virchow-Robin spaces (perivascular spaces) and leptomeninges.
- Stroke occurs in 10% of patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome and is associated with thrombocytosis and bone marrow plasmacytosis.
- POEMS syndrome should be considered in patients with treatment-refractory chronic inflammatory demyelinating polyradiculoneuropathy with a lambda monoclonal protein.
- AL amyloid neuropathy causes a length-dependent neuropathy with prominent early involvement of somatic and autonomic fibers.
- AL amyloid myopathy often has a normal creatine kinase.
- IgM neuropathy (distal acquired demyelinating symmetric neuropathy) often presents in older men with sensory ataxia.

Rheumatology and Neurology

Elliot L. Dimberg, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):691–721.

Abstract

Purpose of Review:

This article reviews the various rheumatologic disorders that have neurologic complications and manifestations.

Recent Findings:

Recent advances have improved the understanding of the true epidemiology of many rheumatologic diseases and their complications. Many years of observation have clarified findings even in rarer disorders. Classification and diagnostic criteria have been updated and validated. As newer pharmacologic agents have become available, new information regarding efficacy and toxicity has emerged.

Summary:

Rheumatologic disorders are common, as can be their neurologic complications. In many instances, these complications are treatable, but clinicians' understanding of the underlying disorder, its neurologic risks, and the risk of therapy is required.

Key Points

- Rheumatologic disorders are common and can present with central or peripheral nervous system manifestations; they can also develop at any time during the disease course.
- Central nervous system manifestations of neuropsychiatric lupus are more common than peripheral nervous system presentations. Headache, mood disorders, cognitive dysfunction, seizures, and cerebrovascular disease are most common.
- Chronic inflammation is implicated in accelerated atherosclerosis; in systemic lupus erythematosus, this manifests as increased risk for cardiovascular and cerebrovascular disease independent of other vascular risk factors.
- Rheumatoid arthritis is the most common inflammatory arthritis and affects 1% to 2% of the population. Central nervous system complications are rare but more common with seropositivity, including anti–cyclic citrullinated peptide antibodies, rheumatoid factor, antinuclear antibody, and C-reactive protein, and with longer disease duration.
- Cervical spine subluxation is a common complication of rheumatoid arthritis, with atlantoaxial subluxation being most common, leading to progressive myelopathy; surgical stabilization may be necessary to prevent progression.
- Patients with rheumatoid arthritis may develop vasculitis, which can cause a vasculitic neuropathy, including mononeuritis multiplex or a distal symmetric sensory or sensorimotor peripheral neuropathy; this is an independent predictor of mortality.
- Sensory neuronopathy (ganglionopathy) is a classic presentation of sjögren syndrome, manifesting with non–length-dependent sensory loss, pseudoathetosis, and ataxia due to lymphocytic inflammation of the dorsal root ganglion.
- Longitudinally extensive demyelinating lesions of the spinal cord in patients with Sjögren syndrome are considered to be reflective of primary neuromyelitis optica rather than a central nervous system complication of Sjögren syndrome itself.
- Inflammatory myopathy in the setting of systemic sclerosis is more frequent with anti-PM/Scl antibody positivity; if seen in diffuse cutaneous systemic sclerosis, corticosteroids should be avoided as their use can lead to renal crisis.
- Numerous systemic vasculitides exist, but primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy represent two forms of vasculitis isolated to the central nervous system and peripheral nervous system, respectively.
- Biopsy is the diagnostic procedure of choice for primary angiitis of the central nervous system and nonsystemic vasculitic neuropathy, but its sensitivity is not 100% in either case, requiring high clinical suspicion.
- The vasculitides are categorized according to the size of vessels involved, although neurologic involvement is not specific to the vessel size involved.
- The presence of mixed cryoglobulinemia in the setting of peripheral neuropathy should prompt a search for hepatitis C infection, although a minority of patients with hepatitis C will develop neuropathy.
- Antiphospholipid antibodies are prothrombotic and can cause false-positive Venereal Disease Research Laboratory and rapid plasma reagin tests; they also occur in systemic lupus erythematosus and are associated with other, nonstroke-related neurologic manifestations.
- Pachymeningitis is a classic presentation of IgG4-related disease but requires biopsy confirmation with specific pathologic criteria met for the diagnosis.
- Tumor necrosis factor α inhibitor administration may be complicated by demyelination of the central nervous system, peripheral nervous system, or both.

Renal Disease and Neurology

Sara E. Hocker, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):722–743.

Abstract

Purpose of Review:

Neurologic dysfunction is prevalent in patients with acute and chronic renal disease and may affect the central nervous system, peripheral nervous system, or both. Neurologic manifestations may result directly from the uremic state or as a consequence of renal replacement therapy. Early recognition of neurologic dysfunction may provide opportunities for intervention and reduced morbidity.

Recent Findings:

Advances in the understanding of neurologic complications of renal disease and its treatments have led to more widespread recognition and earlier identification of encephalopathy syndromes such as cefepime neurotoxicity and posterior reversible encephalopathy syndrome (PRES), dramatic reductions in the incidence of dialysis disequilibrium syndrome and dialysis dementia, and improved survival in disorders such as von Hippel-Lindau disease and thrombotic thrombocytopenic purpura.

Summary:

This article summarizes the conditions that affect both the renal and the nervous systems, the effects of renal failure on the nervous system, and the neurologic complications of dialysis.

Key Points

- Neurologicmanifestations of autosomal dominant polycystic kidney disease include saccular cerebral aneurysms, cervicocephalic artery dissections, and dolichoectasia.
- Screening for intracranial aneurysms in autosomal dominant polycystic kidney disease is recommended in patients with a family history of intracranial aneurysm or subarachnoid hemorrhage, previous intracranial aneurysm rupture, high-risk professions (eg, airline pilots), or patient anxiety despite adequate information.
- Neurologicmanifestations of von Hippel-Lindau disease include retinal and central nervous system hemangioblastomas, ataxia, syringobulbia, and syringomyelia.
- Early detection of tumors through presymptomatic screening of at-risk individuals may enhance overall outcome in patients with von Hippel-Lindau disease.
- By middle age, most patients with Fabry disease develop cardiovascular or cerebrovascular disease, which may manifest as transient ischemic attacks, cerebral infarctions, or dolichoectasia.
- In the presence of delayed recognition of thrombotic thrombocytopenic purpura, the pentad of thrombocytopenia, fever, acute renal failure, microangiopathic hemolytic anemia, and neurologic findings will develop and lead to death; however, since the use of therapeutic plasma exchange has become routine, the presence of the full pentad has become rare.
- Hemolytic uremic syndrome is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in which seizures, coma, stroke, pyramidal or extrapyramidal syndromes, dysphasia, and cortical blindness may occur.

- Acidosis and alkalosis both can present with neurologic signs, predominantly altered consciousness.
- Neurologicmanifestations of the uremic state include both central nervous system complications (eg, lethargy, encephalopathy, seizures, acute movement disorders, and coma) and peripheral nervous system complications (eg, neuropathy and myopathy).
- Symptoms of uremia are usually alleviated by dialysis or renal transplantation.
- The use of cefepime in the setting of renal failure may result in neurotoxicity, which commonly presents with reduced consciousness, encephalopathy, and myoclonus and less commonly with nonconvulsive status epilepticus.
- A diagnosis of posterior reversible encephalopathy syndrome should be considered when acute neurologic symptoms develop in patients with renal failure, blood pressure fluctuations, autoimmune disorders, use of cytotoxic drugs, or eclampsia.
- Polyneuropathy may result from uremia alone, or it may develop in diseases that involve the kidney, such as diabetes mellitus, vasculitis, connective tissue diseases, and plasma cell dyscrasias.
- Uremic neuropathy is classically a length-dependent, distal, axonal, sensorimotor, large fiber neuropathy.
- Uremic myopathy presents with proximal limb weakness and muscle wasting with bone pain and tenderness, and the progression mirrors the decline of renal function.
- The relative risk of hospitalization for ischemic or hemorrhagic stroke among patients on dialysis is estimated to be fourfold to tenfold higher than that of patients without chronic kidney disease.
- Dialysis disequilibrium syndrome presents with a variable constellation of symptoms, including headache, irritability, blurred vision, nausea, muscle cramps, encephalopathy, and seizures. It may be prevented or alleviated by adding osmotically active solutes to the dialysate and slowing the rate, increasing the frequency, and shortening the duration of dialysis.
- Poor-quality sleep, which has been associated with restless legs syndrome and snoring, has been documented in the majority of patients with end-stage renal disease.
- End-stage renal disease is a risk factor for Wernicke encephalopathy due to a combination of reduced oral intake and increased loss of the water-soluble vitamin thiamine during dialysis.
- Patients who are dependent on dialysis are at higher risk for the development of subdural hematoma than the general population due to trauma, uremia-related coagulation disturbances, use of anticoagulants for dialysis, and use of rapid ultrafiltration and hypertonic dialysate.
- Mononeuropathies, particularly median neuropathy at the wrist, may be seen in association with dialysis.

Gastroenterology and Neurology

Ronald F. Pfeiffer, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):744–761.

Abstract

Purpose of Review:

Just as gastrointestinal dysfunction may develop in the setting of neurologic disease, neurologic dysfunction may become evident in the setting of gastrointestinal disease. This article describes the range of neurologic features that have been described in three primary gastrointestinal diseases: celiac disease and gluten-related disorders, inflammatory bowel disease, and Whipple

disease. Particular emphasis is placed on the controversial and evolving clinical picture of neurologic dysfunction in disorders of gluten sensitivity.

Recent Findings:

Gluten-related disorders, including both the traditional autoimmunebased celiac disease and the more recently recognized nonautoimmune, nonallergic gluten sensitivity, have been the source of much attention in both medical and lay publications. The possible association between Crohn disease and neurologic disorders also is receiving attention. The recognition that, although Whipple disease is an exceedingly rare disorder, a surprising percentage of the population may be asymptomatic stool carriers of the causative organism makes it important to always be cognizant of the disorder.

Summary:

The range of neurologic dysfunction in gastrointestinal diseases is broad and spans the spectrum from peripheral to central processes. Peripheral neuropathy, myopathy, myelopathy, cerebrovascular events, epilepsy, encephalopathy, and cerebellar dysfunction have all been described. Neurologists should be aware of the possibility that an underlying gastrointestinal disease process may be present in and responsible for the neurologic dysfunction that has prompted referral of an individual for evaluation.

Key Points

- The enteric nervous system contains approximately 100 million neurons, about the same number as the spinal cord.
- Wheat allergy and other allergic gluten-related disorders are characterized by the presence of IgE antibodies.
- Celiac disease is an autoimmune enteropathy involving the adaptive immune system.
- The classic clinical features of celiac disease are diarrhea, malabsorption, weight loss, and gassy distension.
- Gluten sensitivity disorders are not accompanied by anti–tissue transglutaminase antibodies and typically do not display small intestinal pathology.
- The innate immune system may be involved in gluten sensitivity disorders.
- Allergic gluten-related disorders do not display neurologic manifestations.
- Neurologic dysfunction may appear in up to 22.5% of persons with celiac disease.
- Individuals with celiac disease have a 2.5-fold increased risk of developing peripheral neuropathy.
- Purkinje cell loss and lymphocytic infiltration in the cerebellum has been described in gluten ataxia.
- Anti–tissue transglutaminase 6 antibodies have been described in gluten ataxia.
- Patients with gluten ataxia may respond to a gluten-free diet.
- Various neuropsychiatric symptoms may be present in individuals with gluten sensitivity.
- The pathology of ulcerative colitis is confined to the colon; Crohn disease may involve the entire gastrointestinal tract.
- The reported presence of neurologic dysfunction in inflammatory bowel disease ranges from 0.25% to 37.5%.
- Peripheral neuropathy is the most frequent manifestation of neurologic involvement in inflammatory bowel disease.
- Cerebrovascular events, both arterial and venous, are uncommon but potentially devastating neurologic manifestations of inflammatory bowel disease.

- Whipple disease is a multisystem disorder and not simply a gastrointestinal disease.
- Whipple disease is caused by *Tropheryma whippleii*, an Actinobacteria that may dwell in the soil.
- Postmortem examination demonstrates central nervous system involvement in over 90% of patients with Whipple disease, many of whom have no neurologic symptoms.
- Oculomasticatory myorhythmia develops in 20% of patients with Whipple disease and is pathognomonic for the disorder.
- Prolonged 1-year antibiotic treatment of Whipple disease is necessary to prevent relapse.

Liver Disease and Neurology

Robert N. Schwendimann, MD, FAAN; Alireza Minagar, MD, FAAN. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):762–777.

Abstract

Purpose of Review:

Neurologists often encounter patients with acute and chronic liver disease and must be aware of how these diseases can affect the nervous system. This is particularly true when evaluating patients with alterations in cognition and level of consciousness. Wilson disease, while uncommon, is a treatable condition with many neurologic and psychiatric symptoms. Neurologic disorders associated with liver disease may affect not only the brain, but also the spinal cord and peripheral nervous system. This article reviews the association of liver disease and the nervous system and provides new information regarding diagnostic and therapeutic approaches to evaluating patients with liver diseases.

Recent Findings:

Early recognition of hepatic encephalopathy may be possible using a combination of clinical suspicion and various neuropsychological studies. Management of severe hepatic encephalopathy from acute liver failure is important to neurologists involved in neurocritical care. Next-generation genetic testing may aid in the diagnosis of patients suspected of having Wilson disease. The relationship of numerous neurologic findings from hepatocerebral degeneration and from viral hepatitis is more widely recognized.

Summary:

It is important for neurologists to recognize the neurologic symptoms that may occur in patients with acute and chronic liver failure, Wilson disease, and viral hepatitis to inform prompt diagnostic and management decisions.

Key Points

- Hepatic encephalopathy has a wide spectrum of neurologic and psychiatric symptoms ranging from subclinical alterations to coma.
- Hepatic encephalopathy can be caused by acute liver failure, portosystemic shunting with intrinsic liver disease, or chronic liver disease related to cirrhosis and portal hypertension.

- The West Haven criteria for staging of clinical symptoms are a useful way to determine the severity of hepatic encephalopathy. Simpler scales divide hepatic encephalopathy into covert and overt forms.
- Laboratory studies that typically are helpful in patients with more advanced stages of encephalopathy may be of little help in the patient who is cognitively normal or who manifests only minimal hepatic encephalopathy.
- The presence of triphasic waves on EEG recording may be seen in numerous types of metabolic encephalopathies.
- Brain imaging is generally of little use in the diagnosis of hepatic encephalopathy, although patients with chronic liver disease may show T1-weighted hyperintensities in the basal ganglia thought to represent accumulations of manganese.
- Manganese toxicity is believed to be a major factor in the development of symptoms of acquired hepatocerebral degeneration that may mimic many of the symptoms of Wilson disease.
- Hepatic myelopathy must be differentiated from numerous other causes of myelopathy. Liver transplantation may result in some improvement of symptoms.
- Viral hepatitis is a common cause of acute liver failure in developing countries, while in the United States the toxic effect of acetaminophen is the most common cause.
- Aggressive efforts to prevent the development of cerebral edema leading to increased intracranial pressure are necessary to increase the chances of survival in acute liver failure.
- Wilson disease is caused by mutation of the gene ATP7B on chromosome 13q14 coding for the protein ATP7B. Next-generation sequencing of this gene may be less time consuming and more cost effective than older techniques in assessing the presence of this genetic abnormality.
- Kayser-Fleischer rings may be absent in patients with Wilson disease who do not have evidence of neurologic involvement.
- Routine serum copper level is not particularly helpful in screening for Wilson disease since it measures total serum copper, which is bound to ceruloplasmin.
- Perhaps the best single screening test for Wilson disease is the 24-hour urinary copper measurement.
- With early diagnosis and treatment, symptoms of Wilson disease can be controlled. Treatment typically is with drugs such as penicillamine, trientine, and other chelating agents. Oral zinc can also be used to inhibit absorption of copper in the gastrointestinal tract.
- Fifty percent of patients with hepatitis C have mixed cryoglobulinemia.
- Hepatitis C is a worldwide problem that can cause numerous neurologic problems, including cerebrovascular symptoms, problems with cognitive function, inflammatory processes affecting the spinal cord, and peripheral nerve pathology.
- Hepatitis E is an emerging viral infection that may cause neurologic symptoms in up to 5% of cases.

Endocrine Emergencies With Neurologic Manifestations

Makoto Ishii, MD, PhD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):778–801.

Abstract

Purpose of Review:

This article provides an overview of endocrine emergencies with potentially devastating neurologic manifestations that may be fatal if left untreated. Pituitary apoplexy, adrenal crisis, myxedema coma, thyroid storm, acute hypercalcemia and hypocalcemia, hyperglycemic emergencies (diabetic ketoacidosis and hyperglycemic hyperosmolar state), and acute hypoglycemia are discussed, with an emphasis on identifying the signs and symptoms as well as diagnosing and managing these clinical entities.

Recent Findings:

To identify the optimal management of endocrine emergencies, using formal clinical diagnostic criteria and grading scales such as those recently proposed for pituitary apoplexy will be beneficial in future prospective studies. A 2015 prospective study in patients with adrenal insufficiency found a significant number of adrenal crisis–related deaths despite all study patients receiving standard care and being educated on crisis prevention strategies, highlighting that current prevention strategies and medical management remain suboptimal.

Summary:

Early diagnosis and prompt treatment of endocrine emergencies are essential but remain challenging because of a lack of objective diagnostic tools. The optimal management is also unclear as prospective and randomized studies are lacking. Additional research is needed for these clinical syndromes that can be fatal despite intensive medical intervention.

Key Points

- As endocrine emergencies can be successfully managed if accurately and promptly diagnosed, clinical neurologists should be aware of the neurologic manifestations of endocrine emergencies.
- Pituitary apoplexy is a heterogeneous clinical syndrome characterized by sudden hemorrhage or infarction of the pituitary gland and is most commonly associated with a pituitary adenoma.
- Depending on the extent of hemorrhage, necrosis, and edema, the course of pituitary apoplexy can include very mild symptoms of headache, visual disturbances, or pituitary deficiencies developing slowly over weeks to a true medical emergency presenting with acute onset of blindness, coma, and hemodynamic instability that can result in death if untreated.
- Lumbar puncture has limited utility in differentiating pituitary apoplexy from subarachnoid hemorrhage; however, if bacterial meningitis is suspected, CSF cultures should be obtained.
- Empiric corticosteroid replacement should be initiated for patients with acute pituitary apoplexy with hemodynamic instability, altered consciousness, reduced visual acuity, severe visual field deficits, or signs of hypoadrenalism.
- Adrenal insufficiency can be classified as a primary disorder (eg, autoimmune destruction of the adrenal gland) or a secondary disorder (eg, hypopituitarism caused by pituitary apoplexy) or may result from drug-induced adrenal insufficiency (eg, glucocorticoid withdrawal after chronic exogenous glucocorticoid therapy).

- Adrenal crisis occurs when, during an acutely stressful event, a patient with adrenal insufficiency fails to mount a normal physiologic response of increased endogenous cortisol production and is not adequately compensated with exogenous glucocorticoids.
- Fluid resuscitation and steroid replacement are the main therapies of an adrenal crisis.
- Myxedema coma is typically triggered by a systemic illness, such as a pulmonary or urinary infection; congestive heart failure; stroke; trauma; or certain medications in a patient with previously undiagnosed or untreated hypothyroidism.
- The cardinal hallmarks of myxedema coma are hypothermia and depressed mental status or coma.
- The main goal of treatment of myxedema coma should involve airway protection, thyroid hormone therapy, fluid repletion, empiric hydrocortisone because of the relative risk of adrenal insufficiency, correction of any hyponatremia, and treatment (including empiric antibiotics) of any inciting factors.
- Patients with thyroid storm have variable clinical manifestations, with exaggerated signs and symptoms of thyrotoxicosis accompanied by multiorgan decompensation.
- No set serum thyroxine (T4) or triiodothyronine (T3) criteria exist for diagnosing a thyroid storm, but a full laboratory evaluation including thyroid-stimulating hormone, free T3, and free T4 (even with a normal thyroid-stimulating hormone level) should be conducted in all suspected cases.
- The goals of treatment of thyroid storm are to inhibit new thyroid hormone synthesis, inhibit thyroid hormone release, block the peripheral effect of thyroid hormones, and enhance the clearance of thyroid hormones.
- The most common cause of hypercalcemia is an underlying primary hyperparathyroidism caused by a single benign parathyroid adenoma, but hypercalcemia can result from malignancies, endocrinopathies, granulomatous diseases, immobilization, and medications such as thiazide diuretics and lithium.
- Hypercalcemic crisis usually results from an underlying mild to moderate hypercalcemia that evolves into an acute exacerbation of severe hypercalcemia, often with a known precipitating factor such as an illness or use of thiazide diuretics.
- The overall goals of therapy of a hypercalcemic crisis are to lower calcium levels, rehydrate, increase renal calcium excretion, and decrease osteoclast-mediated bone resorption, followed by definitive curative therapy of the hypercalcemia.
- Disorders of parathyroid hormone and vitamin D are the major causes of hypocalcemia, with acquired hypoparathyroidism as a complication of thyroid and neck surgeries being the most common cause of hypocalcemia in adults.
- Typical central nervous system manifestations of hypocalcemia are encephalopathy and seizures, both of which can be the initial manifestation of the hypocalcemia.
- On examination, tetany or neuromuscular irritability caused by hypocalcemia can be demonstrated by eliciting the Chvostek sign (ipsilateral facial contraction after facial nerve percussion) or Trousseau sign (painful carpopedal spasm after inflating a sphygmomanometer placed on the upper arm above the systolic blood pressure for 3 minutes).
- Treatment for patients with acutely symptomatic hypocalcemia consists of IV calcium given as a bolus, followed by a slow continuous infusion, with the goal of maintaining serum calcium levels in the low-normal range.
- As the brain relies almost entirely on glucose for its energy source, insufficient glucose in the brain can have a wide range of potentially devastating neurologic consequences, from altered mental status to focal neurologic deficits that are often, but not always, reversible.

- Diabetic ketoacidosis is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.
- Hyperglycemic hyperosmolar state is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.
- The most common precipitant of diabetic ketoacidosis and hyperglycemic hyperosmolar state is infection, but other causes include omission of or inadequate insulin dosing, pancreatitis, myocardial infarction, stroke, and certain drugs (eg, corticosteroids, thiazide diuretics, sympathomimetics, and antipsychotics).
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state classically present with polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and altered mental status.
- Both diabetic ketoacidosis and hyperglycemic hyperosmolar state can be associated with altered mental status, including lethargy and coma. These are more common in hyperglycemic hyperosmolar state and correlate with hyperosmolality.
- The goals of therapy in hyperglycemic crises are to correct the dehydration, hyperglycemia, and electrolyte abnormalities and to identify and treat the underlying inciting factor.
- The most common cause of hypoglycemia is the inadvertent or deliberate overdose of hypoglycemic agents, but, less commonly, insulin-secreting tumors, Addison disease, renal or hepatic failure, or severe sepsis can cause symptomatic hypoglycemia.

Neurologic Complications of Transplantation

Amy A. Pruitt, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease): 802–821.

Abstract

Purpose of Review:

This article describes the diagnosis and management of neurologic problems during hematopoietic cell and solid organ transplantation using time elapsed since transplantation as a guide to expected complications, including drug toxicities, infections, strokes, autoimmune phenomena, disease recurrence, and secondary neoplasms.

Recent Findings:

Growing clinical experience in the neurology of transplantation has led to appreciation of the diverse clinical and radiographic spectrum of calcineurin inhibitor–related posterior reversible encephalopathy syndrome (PRES) and progressive multifocal leukoencephalopathy. Novel autoimmune phenomena illustrate the delicate balance between adequate immunosuppression and necessary host inflammatory defenses that can lead to organ rejection. The spectrum of infectious complications has changed with the evolution of new conditioning regimens.

Summary:

Neurologic problems remain an important source of morbidity and mortality, both in the immediate transplantation period and for years after the procedure. As perioperative management has reduced the incidence of acute infections, graft versus host disease, and organ rejection,

problems of long-term survivors require neurologic input into multidisciplinary management of chronic neurologic conditions impacting quality of life.

Key Points

- Tacrolimus and cyclosporine have multiple adverse effects and must be included in the differential diagnostic possibilities among the wide variety of central and peripheral nervous system complications that may occur following hematopoietic cell transplantation or solid organ transplantation.
- Posterior reversible encephalopathy syndrome, often caused by tacrolimus or cyclosporine, can occur at any point in the patient's course after hematopoietic cell transplantation or solid organ transplantation, is not necessarily related to drug level, and can present variably with altered sensorium, cortical blindness, seizures, spinal cord involvement, or hydrocephalus.
- Posttransplant acute limbic encephalitis is usually caused by human herpesvirus 6 and is associated with seizures, anterograde amnesia, MRI abnormalities in the hippocampi, and severe graft versus host disease, with early posttransplantation mortality.
- Neutropenia for more than 10 days is the biggest risk factor for invasive aspergillosis, which can present as a sentinel headache or sinus infection or as hemorrhage from aneurysms. CSF or serial serum galactomannan testing is useful. CSF may be neutrophilic or acellular.
- Varicella-zoster infections begin to emerge in the second month posttransplant and are common in both hematopoietic cell transplantation and solid organ transplantation recipients, with manifestations ranging from dermatomal rash to cranial neuritis, myelitis, multifocal stroke, acute retinal necrosis, spinal cord infarction, and a temporal arteritis–mimicking syndrome.
- If the symptoms of varicella-zoster virus have been present for less than 1 week, polymerase chain reaction is the best diagnostic test. However, CSF varicella-zoster virus testing should include anti-varicella IgM and IgG in addition to CSF polymerase chain reaction if symptoms have been present longer than 1 week.
- Chronic graft versus host disease affects multiple organs. The two most distinctive peripheral nervous system manifestations of chronic graft versus host disease are dermatomyositis and polymyositis, although myasthenia gravis, acute inflammatory demyelinating polyradiculoneuropathy, and chronic inflammatory demyelinating polyradiculoneuropathy are also associated with the syndrome.
- A relationship between calcineurin inhibitors and white matter abnormalities on MRI must always be suspected. This consideration will dictate a workup to exclude progressive multifocal leukoencephalopathy and will avoid unnecessary medicines such as multiple sclerosis drugs. Changing the immunosuppressive regimen may improve the clinical and radiographic signs and symptoms.
- The clinical and radiographic picture of progressive multifocal encephalopathy can be quite varied. Variable degrees of enhancement can occur, and immune reconstitution after reduction of immunosuppression can lead to neurologic symptom exacerbation as well as intensified graft versus host disease, threatening the viability of transplanted organs.
- Management of long-term survivors of transplantation becomes surveillance of a chronic condition, the treatment of which predisposes patients to multiple complications, including metabolic syndrome, cataracts, secondary neoplasm, osteoporosis, the need for revaccination, and ongoing risk of rejection or recurrence of original disease.
- Donor organ–associated infections include West Nile virus, lymphocytic choriomeningitis virus, rabies, *Balamuthia mandrillaris*, and *Cytomegalovirus*.

- Cryptococcosis can be difficult to diagnose in solid organ transplantation recipients as many patients have little inflammation and nondiagnostic initial CSF. Immune reconstitution inflammatory syndrome can occur when immunosuppression is reduced, with ensuing raised intracranial pressure and meningeal inflammation.
- Posttransplant lymphoproliferative disorder, the most common brain neoplasm in transplant recipients, is a spectrum of B-cell proliferations ranging from polyclonal hyperplasia to fulminant multifocal parenchymal disease. The fulminant disorder can occur shortly after transplantation, while more indolent neoplasia can develop several years posttransplantation.
- Important neurologic conditions relevant to liver transplantation include both preoperative neurologic problems and those due to the transplantation procedure, including hyperammonemic encephalopathy, raised intracranial pressure, seizures, stroke, osmotic demyelination, and hepatic myelopathy.
- Cardiac transplant recipients have the highest risk of posttransplantation stroke and the highest risk for toxoplasmosis.

Nutrients and Neurology

Neeraj Kumar, MD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):822–861.

Abstract

Purpose of Review:

This article provides an update on the clinical presentation and management of neurologic disease related to key nutrient deficiencies.

Recent Findings:

Major advances have been made in understanding the pathway related to vitamin B12 absorption and distribution. It is now known that deficiencies of vitamin B12 and copper have similar neurologic manifestations. Bariatric surgery is a risk factor for both. Alcoholism is just one of the many causes of thiamine deficiency. Early neurologic complications following bariatric surgery are often due to thiamine deficiency. Encephalopathy in the setting of alcoholism that persists despite thiamine replacement should prompt consideration of niacin deficiency. Pyridoxine deficiency and toxicity both have neurologic sequelae. Vitamin D deficiency and the risk for multiple sclerosis has been an area of ongoing research.

Summary:

Optimal functioning of the nervous system is dependent on a constant supply of certain vitamins and nutrients. This article discusses neurologic manifestations related to deficiency of these key nutrients.

Key Points

- Early neurologic complications following bariatric surgery may be related to thiamine deficiency, while delayed complications are often due to copper or vitamin B_{12} deficiency.

- Marasmus is due to caloric insufficiency and results in growth failure and emaciation in early infancy.
- Kwashiorkor presents between 2 and 3 years of age. Its underlying cause is protein deficiency.
- Food-bound cobalamin malabsorption refers to reduced liberation of cobalamin from food proteins and results from achlorhydria, gastritis, gastrectomy, and the use of proton pump inhibitors or antacids. It is the most common cause of vitamin B_{12} deficiency and may affect up to 20% of older adults.
- Many patients with clinically expressed or disabling cobalamin deficiency have intrinsic factor–related malabsorption such as that seen in pernicious anemia.
- Vitamin B_{12} deficiency is not universal in vegetarians but does develop more rapidly with malabsorption in vegetarians.
- Clues to possible vitamin B_{12} deficiency in a patient with polyneuropathy include a relatively sudden onset of symmetric symptoms, findings suggestive of an associated myelopathy, the onset of symptoms in the hands, concomitant involvement of upper and lower limbs, and the presence of a risk factor for vitamin B_{12} deficiency or laboratory markers of vitamin B_{12} deficiency.
- The bulk of evidence suggests that vitamin B_{12} supplementation does not result in improved cognition or slowed cognitive decline despite normalization of vitamin B_{12} levels.
- Although a widely used screening test, serum vitamin B_{12} measurement has technical and interpretive problems and lacks specificity and sensitivity for the diagnosis of vitamin B_{12} deficiency.
- Vitamin B_{12} bound to transcobalamin (holotranscobalamin) is the fraction of total vitamin B_{12} available for tissue uptake. Holotranscobalamin concentration and transcobalamin saturation (holotranscobalamin to total transcobalamin) has been proposed by some as potentially useful alternative indicators of vitamin B_{12} status.
- A common approach in the diagnosis of pernicious anemia as a cause of vitamin B_{12} deficiency is to combine the specific but insensitive intrinsic factor antibody test with the sensitive but nonspecific serum gastrin or pepsinogen I level.
- Patients with pernicious anemia have a higher frequency of thyroid disease, diabetes mellitus, carcinoid, and iron deficiency and should be screened for these conditions.
- Acquired folate deficiency rarely exists in the pure state.
- Small intestinal bacterial overgrowth may be associated with increased folate levels due to bacterial synthesis.
- Serum folate falls within 3 weeks after decrease in folate intake or absorption, red blood cell folate declines weeks later, and clinically significant depletion of folate stores may be seen within months.
- For unclear reasons, neurologic manifestations involving the spinal cord or peripheral nerves, such as those seen in vitamin B_{12} deficiency, are relatively rare in folate deficiency.
- Plasma homocysteine levels are commonly elevated in patients with clinically significant folate deficiency.
- Serum folate fluctuates daily and does not correlate with tissue stores. Red blood cell folate is more reliable than plasma folate because its levels are less affected by short-term fluctuations in intake.
- Alcoholism is just one of many causes of thiamine deficiency, and thiamine deficiency is increasingly being recognized in individuals who are not alcoholics.
- Wernicke encephalopathy often results from severe short-term thiamine deficiency, while peripheral neuropathy is more often a consequence of prolonged mild to moderate thiamine deficiency.

- Patients with Wernicke encephalopathy may have none of the manifestations related to the classic triad, although one or more components of the triad do generally appear later in the course.
- h It is important to recognize that a patient who does not recover fully and spontaneously from intoxication may have Wernicke encephalopathy.
- Korsakoff syndrome is an amnestic-confabulatory syndrome characterized by severe anterograde and retrograde amnesia that follows Wernicke encephalopathy; Korsakoff syndrome emerges as ocular manifestations and encephalopathy subside. Rarely, Korsakoff syndrome may be present without Wernicke encephalopathy.
- Alcoholic neuropathy is a slowly progressive, painful, predominantly sensory neuropathy, with preferential involvement of small fiber function. In contrast, thiamine deficiency–related neuropathy is often a more rapidly progressive sensorimotor neuropathy, with large fiber–predominant sensory loss.
- Wernicke encephalopathy is largely a clinical diagnosis.
- A normal serum thiamine level does not exclude Wernicke encephalopathy.
- IV glucose infusion in patients with thiamine deficiency may consume the available thiamine and precipitate acute Wernicke encephalopathy. Patients who are at risk should therefore receive parenteral thiamine before administration of glucose or parenteral nutrition.
- A commonly used thiamine replacement regimen is 200 mg IV every 8 hours. Higher doses of thiamine may be required in Wernicke encephalopathy, particularly when it occurs in the setting of alcoholism.
- Unexplained progressive encephalopathy in alcoholics that is not responsive to thiamine or escalating doses of benzodiazepines should raise the possibility of pellagra.
- The two most prevalent forms of pyridoxine-dependent epilepsy include the autosomal recessive disorders associated with antiquitin deficiency and pyridoxal 5"-phosphate oxidase deficiency.
- Excess consumption of vitamin B_6 has been associated with a predominantly sensory ganglionopathy. It is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and a positive Romberg sign.
- Vitamin D status is assessed by 25-hydroxyvitamin D levels.
- Mutations in *TTPA*, the gene that encodes α-tocopherol transfer protein, results in ataxia with vitamin E deficiency. Additional disorders associated with vitamin E deficiency include hypobetalipoproteinemia, abetalipoproteinemia, and chylomicron retention disease.
- The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable dorsal column and peripheral nerve involvement. The phenotype is similar to that of Friedreich ataxia.
- Hyperlipidemia increases the plasma carriers for vitamin E. Hyperlipidemia can, therefore, independently increase serum vitamin E without reflecting similar alterations in tissue levels of the vitamin.
- The most common cause of acquired copper deficiency is a prior history of gastric surgery for peptic ulcer disease or bariatric surgery.
- Excessive zinc ingestion is a well-recognized cause of copper deficiency.
- Other nutrient deficiencies, notably vitamin B_{12} deficiency, can coexist with copper deficiency.
- The most common manifestation of acquired copper deficiency is that of a myelopathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.
- A rise in ceruloplasmin is accompanied by an increase in serum copper in conditions such as pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, myocardial infarctions, uremia, and various inflammatory and infectious diseases.

Environmental Neurologic Injuries

Rodolfo Savica, MD, PhD. Continuum (Minneap Minn). June 2017;23(3 Neurology of Systemic Disease):862–871.

Abstract

Purpose of Review:

This article discusses neurologic complications resulting from environmental injuries and the treatment modalities for these conditions.

Recent Findings:

Recent advances include improved management of altitude sickness. Relatively uncommon conditions, such as keraunoparalysis (lightning-induced paralysis) and high-pressure neurologic syndrome, are areas of ongoing study.

Summary:

Environmental injuries may be associated with serious neurologic sequelae. This article reviews thermal and electrical injuries as well as injuries related to aviation, altitude, and diving. Recognition of signs and symptoms of such complex injuries and exposures will permit accurate diagnoses and improved outcomes.

Key Points

- Approximately 20% of cases of high-temperature syndromes may have long-term consequences.
- Heat exhaustion occurs at temperatures between 37 °C (98.6°F) and 40°C (104°F). The syndrome is milder than heatstroke and can be treated by replenishing fluids and electrolytes; avoid rapid correction of temperature.
- A direct lightning strike is rare; most injuries are secondary to falling trees or blast injuries. Neurologic manifestations can be preceded by cutaneous damage and metabolic complications.
- Keraunoparalysis is an immediate but rare consequence of lightning strike; transient paralysis of the lower limbs improves in hours without treatment.
- Lightning strike does not leave entry marks, but alternating current electrical injury does.
- Reports of itchiness and joint pain after scuba diving require a neurologic evaluation because type I decompression sickness can evolve to the more severe type II decompression sickness. Information regarding the rate of descent/ascent is crucial for an accurate evaluation.
- Decompression sickness must be treated with 100% oxygen immediately at the onset of symptoms, followed by use of a decompression chamber. About 70% of patients have a good prognosis and no consequences.
- Neurologic symptoms of high-altitude exposure are more common between 2500 m (8202 ft) and 3500 m (11,483 ft). Return to a lower level or to sea level will restore the baseline physiologic status.

- In acute mountain sickness, acetazolamide is commonly used to cause metabolic acidosis; dexamethasone can be used in conjunction with acetazolamide. Portable hyperbaric chambers are needed in climbing expeditions to make treatment readily accessible.
- Decompression sickness can be caused by decreased pressure at flight altitude, but the symptoms appear less severe than in immersion-related decompression sickness. Administering 100% oxygen and descending to a lower altitude produce immediate improvement.

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Response to Medical Errors

Adam Webb, MD

ABSTRACT

Despite improvements in patient safety science over the past 15 years since the Institute of Medicine's publication of *To Err Is Human*, medical errors remain a major contributor to adverse patient outcomes and mortality. In the aftermath of a harmful medical error, providers often face dilemmas regarding how to best report and disclose errors.

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Case

A neurologist provided consultation in the emergency department for a patient with diplopia, generalized weakness, and respiratory distress, suspicious for a myasthenia gravis crisis. While he was writing the consult note, the emergency department physician asked him to urgently see a patient who had just arrived with ongoing generalized tonic-clonic seizures. After examining that patient, he returned to the computer workstation and entered an order for IV lorazepam and a CT of the head. Later, while still in the emergency department, he heard an emergency code called in the CT scanner. While in CT, the patient with myasthenia gravis developed hypoxia and respiratory failure requiring emergent intubation. The neurologist realized that he had accidentally entered orders for the lorazepam and head CT on the wrong patient. While it was likely that the patient with myasthenia gravis would have eventually required mechanical ventilation, it is also likely that the large dose of lorazepam and flat positioning in the CT scanner worsened the respiratory symptoms and precipitated intubation. The neurologist contemplated two issues:

- Should he report this medical error to risk management?
- Should he disclose this medical error to the patient and the patient's family?

DISCUSSION

An error is defined as either the failure of a planned action to be completed as intended (error of execution) or the use of a wrong plan to achieve an aim (error of planning).[1–3] Errors can be distinguished from complications, which are nonpreventable adverse events resulting from medical interventions. Medical errors are often subdivided based on whether their consequences reach the patient or not. Those not reaching the patient, whether by chance, specific intervention, or safety barrier, are referred to as *near misses*. Those reaching the patient but not inflicting harm are often referred to as *harmless*

hits. Medical errors reaching the patients and inflicting harm are referred to as *harmful errors*. According to James Reason's often-cited "Swiss cheese" model of human error, errors occur when the system surrounding a provider allows a human error to penetrate a series of safeguards and reach the patient. The holes in the Swiss cheese represent defects in the design and organization of the care delivery system.[3]

Few studies specifically examine the epidemiology of medical errors in neurologic practice.[4] As demonstrated in this case, neurologists are prone to the same slips and lapses as all human beings. Neurologists practice in both inpatient and outpatient settings, with potential differences in the types of medical errors committed in each setting. Studies of malpractice claims in neurology, which are imperfect gauges to study errors, suggest that the highest risks for neurologists include errors in care provided in the emergency department, diagnostic errors, and medication errors.[5] Neurologists commonly prescribe certain classes of drugs that are prone to adverse drug events. Anticoagulants and antiseizure medications rank among the top five drug classes associated with adverse drug events.[6] Others include antihypertensives, antibiotics, and opiates.[7]

Ethical Considerations

When a medical error occurs, several ethical principles should influence the response, including the principles of beneficence, nonmaleficence, patient autonomy, and justice. From a practical standpoint, physicians are faced with these questions.

Should the physician report this medical error to risk management? The US health care system must develop a culture in which all medical errors are reported and investigated.[8] Generally speaking, medical errors are underreported.[9] Several factors may explain the underreporting of medical error: (1) the importance of error and incident reporting is not emphasized in medical training, (2) providers may believe someone else is responsible for identifying and reporting errors, (3) providers may assume error reporting will not lead to positive change and may, in fact, lead to a punitive response. However, the ethical principle of beneficence, which requires physicians to optimize benefit for their patients, should compel physicians to help design systems of care that provide the safest and most effective care possible.

Recent efforts to promote a culture of safety as well as a just culture in health care environments facilitate a physician's ability to act beneficently to a patient who has been affected by medical error. The principles of a just culture promote respectful inquiry into adverse events with a focus on system issues that did not prevent the error from occurring in the first place. A just culture acknowledges that, despite our best efforts, human error will inevitably occur and recommends comforting providers rather than blaming them in the case of simple error. Providers are held accountable and coached for voluntary behaviors that increase risk, such as failure to follow safety protocols, and are only punished for truly reckless actions. Transparency in reporting of errors combined with thoughtful root cause analysis can catalyze system improvements and thereby improve patient outcomes.

Should the physician disclose this medical error to the patient and the patient's family? Physicians should disclose harmful errors to patients and families for many reasons. First and foremost, error disclosure is both an ethical and a professional duty. The American Medical Association *Code of Medical*

Ethics plainly articulates this obligation.[10] The ethical argument for error disclosure centers on the virtue of honesty and the principles of respect for patient autonomy, beneficence, nonmaleficence, and justice. Providers should be truthful in their interactions with patients. Patients have a right to information about the care they receive, including the etiology of adverse events whether due to their medical condition or medical error. Respect for adult patients possessing a right to self-determination requires physicians to understand that patients should not be asked to make health care choices without a full accounting of relevant medical information, including the cause and consequences of iatrogenic harm.[4] Failure to disclose errors compromises the fundamental trust on which the physician-patient relationship is based, actively harming the patient and violating the obligation to promote well-being (beneficence) and avoid harm (nonmaleficence). Finally, the principle of justice, which grapples with allocation of resources, dictates that patients should understand the circumstances under which they might deserve compensation.

The realization that an error has harmed a patient is a psychologically painful one for the provider. Physicians often feel conflicted about disclosing medical errors because doing so may create cognitive dissonance, whereby providers are forced to reconcile their self-identity as competent and caring professionals with the fact that they inflicted harm on a patient, albeit unintentionally. This conflict may lead to a defense mechanism of normalization or rationalization of errors. As this case demonstrates, the provider believed the patient was likely to require intubation anyway. Although the error may have precipitated respiratory failure and intubation, it did not ultimately change the outcome. Rationalization, along with the very understandable fear providers typically experience after committing an error, may lead to underreporting and nondisclosure of errors. Additionally, these psychological reactions may foster an approach to disclosure wherein the physician offers the patient a perfunctory explanation of what happened, conveying only a minimum of information without an outright admission of error.[11]

Legal and Regulatory Considerations

One of the most often cited barriers to transparency and disclosure of harmful medical errors is a fear of malpractice litigation. This fear often promotes silence and leads to the contradiction between what providers feel they should do and what they actually do after they have made a harmful error.[12] The traditional "deny and defend" approach to malpractice claims management has fostered this fear and impeded both patient safety efforts and transparent communication between providers and patients. This approach also creates a confusing and ultimately demoralizing environment in which nonmeritorious claims are often settled and indefensible errors are defended.[13] Providers are concerned that apologies and frank admissions of error could be used to prove liability in a medical malpractice claim. To encourage transparency, some states have enacted laws protecting aspects of the communications around medical error. However, the legal regimes of most states offer only partial protections. The majority of states have evidentiary laws protecting only the apology part of the statement (eg, "I'm sorry you were hurt") without extending protection to the explanation part of the statement (eg, "I ordered the wrong medication").

On the frontier of health care's journey toward transparency is the development of disclosure, apology, and offer programs.[8] In these programs, health care systems openly identify when errors have occurred, promptly disclose them to patients, apologize for the error, and make an offer of compensation where appropriate. The University of Michigan, a self-insured academic health care system, established one of the earliest and best such programs.[13] It completely restructured its patient safety and malpractice claims management programs around the following principles:

- Compensate patients quickly and fairly when unreasonable medical care caused injury
- If care was either reasonable or did not adversely affect clinical outcome, support caregivers and the organization vigorously
- Reduce patient injuries (and therefore claims) by learning through patients' experiences

This restructuring nurtured an institutional culture focused on patient safety and transparency and ultimately led to a significant decrease in malpractice claims as well as settlement and litigation costs. Because the institution, rather than the individual physician, offers a settlement with the injured patient, these settlements are not reportable to the National Practitioner Data Bank.[14]

Practical Considerations

Another barrier to physician disclosure of medical errors is that most physicians do not know how to disclose effectively. Few providers received formal instruction on error disclosure in either medical school or residency. Disclosure training is now making its way into academic curricula through role modeling, simulation training, reflection, and discussion. Training is associated with a greater sense of preparedness and confidence when faced with a disclosure.[15,16] Those not trained in error disclosure during medical training may find just-in-time teaching and coaching effective in preparing for disclosure immediately after the error occurs.[17] Error disclosure should include a review of the facts leading to the harm, an explicit apology or expression of regret, information about any possible or realized harm to the patient, and information about the investigation to be undertaken to learn from the causes of the error. The physician should promise to follow up and must keep this promise.

Case Continued

The neurologist consulted with the risk management team and was encouraged to disclose the error after receiving just-in-time disclosure training. Once the patient was extubated, the neurologist apologized for the error; the patient appreciated the neurologist's honesty, felt that the neurologist was trustworthy, and was not upset about the error itself. The neurologist was initially scared to disclose and apologize, but after the conversation he felt relieved and less conflicted about the situation. The neurologist upheld the virtue of honesty, demonstrated immense respect for the patient, and allowed the patient to make appropriate medical decisions with full information.

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Safety Considerations During Transitions of Care From Inpatient to Outpatient Settings

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ABSTRACT

Hospital admissions are times of intense change. New medications are started, treatment regimens are modified, and care plans that will continue in the outpatient setting are initiated. After discharge, most patients receive care from different providers than those seen in the hospital. This situation will increase as inpatient-based practice patterns, such as neurohospitalist practices, become more prevalent. Communication failures during the transition from hospital to clinic increase the risk of adverse events. Providers must realize that successful transition can impact the patient's health as significantly as treatment of the admitting diagnosis. The transition should be carefully planned and standardized. This article discusses common pitfalls encountered during the transition period and highlights methods to improve patient care and safety.

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Case

An 81-year-old woman with dementia and epilepsy was admitted from a skilled nursing facility for confusion, dizziness, and recurrent falls over the previous week. Her outpatient medications included donepezil, phenytoin, and lacosamide. Her temperature was 37°C (98.6°F), blood pressure 132/70 mm Hg, heart rate 72 beats/min, and respiratory rate 20/min. Neurologic examination revealed impaired attention, vertical and horizontal nystagmus, and truncal ataxia. Her phenytoin level was 29 mg/L (stated therapeutic level: 10 mg/L to 20 mg/L). Noncontrast brain CT scan demonstrated mild generalized atrophy. She was diagnosed with phenytoin toxicity. Phenytoin was discontinued, and her symptoms resolved within 48 hours.

Four months earlier, the patient had also been admitted for phenytoin toxicity. During that admission, phenytoin was discontinued, lacosamide was continued, and she was discharged to a skilled nursing facility. The patient did not have an appointment scheduled with her outpatient provider at the time of discharge. Several weeks following discharge, the primary care provider refilled the patient's prescription of phenytoin. The primary care provider had been unaware of the patient's previous admission for phenytoin toxicity.

DISCUSSION

This case illustrates several common problems encountered at hospital discharge: failure to engage the primary care provider, lack of follow-up care, and errors in medication management.[1,2] American hospitals complete over 35 million patient discharges annually, and the number is expected to rise.[3] McLeod[4] noted that half of patients experience a medical error at discharge. This alarming number of errors can be curbed by formalizing the transition process and targeting the sources of transition failures. The National Transitions of Care Coalition (NTOCC) provides seven essential intervention categories that providers can use as a framework to develop a transition-of-care strategy.[5] What follows is a discussion of the seven categories and recommendations on their implementation.

Medications Management

Medication errors are the most common type of error at hospital discharge.[6] Studies have shown that patients on anticoagulants and those on more than five medications are at greatest risk.[7] Accurate medication management is, therefore, an important goal of transition planning. Medication management begins with reviewing patient medications at intake, including over-the-counter medications and nutritional and herbal supplements. Adherence to medication schedules avoids adverse effects from interruption of time-critical medications, such as dopaminergic therapy in Parkinson disease. Polypharmacy should be identified and reduced where possible. When medications are discontinued, prescriptions can be canceled to prevent inadvertent refills after discharge. Medication management includes initiation of new medications before discharge. Sauer and colleagues[8] noted that patients with stroke and atrial fibrillation who started anticoagulant therapy prior to discharge had greater compliance with therapy at 90 days (91% versus 53%) and 1 year (90% versus 68%) after discharge than those patients for whom anticoagulant therapy was only recommended. Other studies of patients poststroke showed that initiation of secondary prevention therapies before discharge was the strongest predictor of adherence with antihypertensive agents, lipid-lowering agents, and antithrombotic agents at 1, 2, and 10 years after stroke.[9,10] Hohmann and colleagues[11] demonstrated that the provision of discharge summaries that included a report listing each medication, detailing the reason for its use, and highlighting which medications were initiated and stopped during the hospital stay improved medication compliance among patients with stroke at 3 months when compared to the use of a simple medication list.

Transition Planning

Transition planning is the process of managing the patient's transition to the clinic setting. Hospitals may create multidisciplinary teams and adopt standard checklists to address each intervention category. Additionally, the team should coordinate with providers in other settings. The product of the process is a discharge summary. Multiple studies have shown that dedicated transition teams using standard checklists and printed summaries increase postdischarge compliance, decrease medical errors, and improve patient follow-up.[12–14]

Patient and Family Engagement/Education

Patients and their caregivers consistently identify lack of information as a primary concern during hospital stays.[15] In addition to causing patient frustration, lack of information correlates with poor adherence to treatment regimens.[16] During transition, education should include details of the plan of care, indications that a condition may be worsening, and instructions on self-management skills. In a survey of patients poststroke, Haynes and colleagues[17] identified provider contact information and patient understanding of a follow-up plan as important elements after hospital discharge.

Information Transfer and Health Care Provider Engagement

Transfers of care, known as handoffs, occur frequently in hospital medicine and are areas of potential medical risk.[18] In 2007, the Joint Commission developed a National Patient Safety Goal that standardized inpatient handoffs.[19] In contrast, handoffs between the hospital and the outpatient setting are not standardized and contribute to poor communication between providers in the hospital and outpatient primary care providers.[20] A study of over 900 primary care providers revealed that 23% were unaware that their patients were admitted to the hospital, and only 42% received discharge summaries within 2 weeks of patient discharge.[21] Lack of communication between providers is a leading cause of medication discrepancies.[22] Lindquist and colleagues[23] identified a potential solution: when hospitalists communicate with primary care providers before discharge and primary care providers contact patients within 24 hours after discharge, patients are 70% less likely to experience a medication error.

Follow-up Care and Shared Accountability Across Providers and Organizations

Follow-up care and shared accountability involve providers in the hospital and primary care providers identifying each other and sharing accountability as patients move between levels of care. A need exists for providers to clearly delineate responsibilities, share detailed information in a timely manner, and schedule follow-up appointments close to the date of discharge.[24] Confusion about who will follow up on test results is experienced by the majority of providers during transitions of care and can be resolved by direct communication.[25] Prompt follow-up appointments also improve transitions. A study of patients discharged from an emergency department noted that a length of time between discharge and a scheduled clinic appointment of greater than 2 weeks was associated with a decrease in appointment-keeping compliance.[26]

Steps That May Have Improved This Patient's Care Transition After the Previous Hospitalization

Several steps could have been taken to improve this patient's transition of care. During the previous admission, a discharge summary detailing diagnoses, treatments, pending evaluations, and any medications started or stopped along with the reasons for doing so should have been reviewed with and provided to the patient and family. Copies provided to the primary care provider and skilled nursing facility would have ensured widespread understanding. Direct communication from the inpatient team would have alerted the primary care provider

to cancel the phenytoin prescription and allowed a follow-up appointment to be secured. These interventions may have prevented readmission for phenytoin toxicity.

CONCLUSION

Transition of care from the inpatient to the outpatient setting occurs millions of times annually throughout the United States. It is a complex process with the potential for significant medical risk. Institutions that develop formal standardized processes and dedicate multidisciplinary teams to manage this transition can decrease adverse outcomes and improve patient care.

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Coding for Medication-related Poisoning and Adverse Effects

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ABSTRACT

Accurate coding is important for proper reimbursement and documentation of care provided. This article provides an overview of coding considerations for patient encounters associated with medication use, abuse, or poisoning.

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Relationship Disclosure: Dr Yu serves on the neuroscience steering board of Epic Systems.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Yu reports no disclosure.

INTRODUCTION

The *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) diagnosis codes consist of a string of three to seven alphanumeric characters, with the first character always a letter.[1] The first three characters specify the category of diagnosis. Characters four through six can be letters or numbers and specify the etiology, anatomic site, and severity of the diagnosis.

Codes for poisoning, adverse events, and underdosing of medications range from T36 to T50 and can be found in Chapter 19: Injury, Poisoning and Certain Other Consequences of External Causes (S00–T88).[2] All *ICD-10-CM* codes in Chapter 19 require use of a seventh character to specify whether the encounter was an initial or subsequent encounter or for treatment of sequelae of the diagnosis. Initial encounter characters are used for any encounters occurring in the acute phase of illness, whereas subsequent encounter characters are used for encounters in the subacute phase. *ICD-10-CM* does not define specific time periods for use of these codes.

POISONING BY AND ADVERSE EFFECTS OF MEDICATIONS

Neurologists may be called upon to evaluate patients experiencing adverse effects of medications or symptoms related to inadvertent overdosing or underdosing of substances, including prescribed medications, over-the-counter medications, or illicit substances. In the case of an adverse effect of a prescribed medication, the adverse effect is coded first, followed by coding for the substance causing the adverse effect and then the condition being treated. Encounters involving poisoning are coded in a different order first by the substance, followed by the adverse effects. A seventh character is required to specify initial encounter (A), subsequent encounter (D), or sequelae (S).

Codes for individual substances are found in categories T36 to T50. These codes are further divided by intent into accidental poisoning, intentional self-harm, assault, adverse effect, or underdosing. Note that underdosing codes are

used to indicate that the patient has taken less than the recommended dose, either because of noncompliance or error. For example, codes related to mixed antiepileptic drugs are subdivided as follows:

- T42.5X, Poisoning by, adverse effect of and underdosing of antiepileptics
- T42.5X1, Poisoning by mixed antiepileptics, accidental (unintentional)
- T42.5X2, Poisoning by mixed antiepileptics, intentional self-harm
- T42.5X3, Poisoning by mixed antiepileptics, assault
- T42.5X4, Poisoning by mixed antiepileptics, undetermined
- T42.5X5, Adverse effect of mixed antiepileptics
- T42.5X6, Underdosing of mixed antiepileptics

Case 1

A 35-year-old woman with a history of myasthenia gravis and depression was hospitalized with altered mental status, drooling, diaphoresis, and respiratory depression. Her husband found an empty bottle of pyridostigmine and a suicide note at her bedside. On examination, she had a depressed level of consciousness, bradycardia, miosis, and generalized weakness.

The correct diagnosis codes for this patient are:

- T44.0X2A, Poisoning by anticholinesterase agents, intentional self-harm, initial encounter
- G92, Toxic encephalopathy
- G70.1, Toxic myoneural disorders

Case 2

A 52-year-old man with a history of partial epilepsy well controlled on carbamazepine was evaluated in the office as an annual follow-up. Previsit laboratory testing showed a normal carbamazepine level, but his serum sodium was 124 mEq/L (normal 133 mEq/L to 146 mEq/L). He was asymptomatic. Follow-up laboratory testing and possible changes to his medication regimen were discussed.

The correct diagnosis codes for this patient are:

- E87.1, Hypo-osmolality and hyponatremia
- T42.1X5A, Adverse effect of iminostilbenes, initial encounter [carbamazepine is an iminostilbene]
- G40.109, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus

CONCLUSION

Using the most specific diagnosis code or codes for the situation at hand is important for reimbursement, quality reporting, and patient care. When coding for poisoning, the type of ingestion, either intentional or accidental, should be noted, if possible. When coding for adverse effects of medication, the symptom or adverse effect and condition being treated are coded along with the code for the specific medication. Neurologists should remember always to use a seventh digit to specify type of encounter when using codes for poisoning or adverse effects of medication.

REFERENCES

1. Centers for Medicare & Medicaid Services, National Center for Health Statistics. International classification of diseases, tenth revision, clinical modification (ICD-10-CM). *cdc.gov/nchs/icd/icd10cm.htm*. Accessed March 29, 2017.
2. Centers for Medicare & Medicaid Services. ICD-10. *cms.gov/medicare/coding/icd10/index.html*. Updated April 4, 2017. Accessed May 9, 2017.

CONTINUUM

Neurology of Systemic Disease

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Self-Assessment and CME Tally Sheet

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1. a b c d e	**21.** a b c d e
2. a b c d e	**22.** a b c d e
3. a b c d e	**23.** a b c d e
4. a b c d e	**24.** a b c d e
5. a b c d e	**25.** a b c d e
6. a b c d e	**26.** a b c d e
7. a b c d e	**27.** a b c d e
8. a b c d e	**28.** a b c d e
9. a b c d e	**29.** a b c d e
10. a b c d e	**30.** a b c d e
11. a b c d e	**31.** a b c d e
12. a b c d e	**32.** a b c d e
13. a b c d e	**33.** a b c d e
14. a b c d e	**34.** a b c d e
15. a b c d e	**35.** a b c d e
16. a b c d e	**36.** a b c d e
17. a b c d e	**37.** a b c d e
18. a b c d e	**38.** a b c d e
19. a b c d e	**39.** a b c d e
20. a b c d e	**40.** a b c d e

PATIENT MANAGEMENT PROBLEM RESPONSES

1. a b c d e	**7.** a b c d e
2. a b c d e	**8.** a b c d e
3. a b c d e	**9.** a b c d e
4. a b c d e	**10.** a b c d e
5. a b c d e	**11.** a b c d e
6. a b c d e	**12.** a b c d e

Postreading Self-Assessment and CME Test

D. Joanne Lynn, MD, FAAN; Joseph E. Safdieh, MD, FAAN

The *Continuum* Postreading Self-Assessment and CME Test is an integral part of the issue that is intended to stimulate thought and help participants assess general understanding of the material presented in this issue. The Postreading Self-Assessment and CME Test is also approved by the American Board of Psychiatry and Neurology (ABPN) to meet the Lifelong Learning (CME), Self-Assessment (SA) (part 2) component for Maintenance of Certification.

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▶ 1. A 56-year-old man who is 3 months' post–cadaveric kidney transplant develops fever, headache, confusion, visual complaints, and nuchal rigidity over several weeks. Funduscopic examination shows findings consistent with retinitis. His brain MRI shows ventriculomegaly and diffuse ependymal enhancement best visualized on the diffusion-weighted images. Which of the following is the mostly likely etiology for this patient's condition?

A. Cytomegalovirus (CMV)
B. progressive multifocal leukoencephalopathy
C. tuberculosis
D. varicella-zoster virus
E. West Nile virus

▶ 2. A 58-year-old man with long-standing rheumatoid arthritis and neck pain develops acute quadriparesis after intubation in the emergency department during an acute episode of anaphylaxis caused by a newly prescribed antibiotic. Which of the following is the most likely etiology of the quadriparesis?

A. atlantoaxial subluxation
B. nitrous oxide myelopathy
C. spinal cord infarction
D. subaxial subluxation
E. vertical subluxation

▶ 3. A 53-year-old man with Hodgkin lymphoma develops several months of progressive confusion, paranoid ideation, and memory loss. Brain MRI shows increased T2 signal in the bilateral hippocampi. Antibodies against which of the following targets are most likely to be associated with this syndrome?

A. glutamic acid decarboxylase
B. glycine receptor
C. metabotropic glutamate receptor 5
D. voltage-gated calcium channel
E. Yo

▶ 4. A 68-year-old woman presents with a 1-week history of progressive diplopia and gait instability. She has been undergoing chemotherapy for breast cancer, complicated by intractable vomiting. Her family notes that she has seemed confused over the past 2 days. On examination, she demonstrates disorientation to date, 0/3 delayed recall, nystagmus, bilateral dysmetria, and an ataxic gait. MRI of the brain demonstrates nonenhancing T2 hyperintensities in the periaqueductal gray matter and lateral to the third ventricle bilaterally. Which of the following is the most likely diagnosis?

A. beriberi
B. metastatic disease
C. pellagra
D. subacute combined degeneration
E. Wernicke-Korsakoff syndrome

▶ 5. A 32-year-old high school teacher with no significant past medical history develops uncharacteristic anxiety and agitation. Over several days, she develops cognitive changes with decreased memory and becomes less active; she spends most of her time sitting in the living room chair. After she has a seizure witnessed by her husband, she is taken to the hospital. There she is noted to have a central hypoventilation respiratory pattern and intermittent orofacial and upper limb dyskinesia. At times, her dyskinesia resembles someone trying to play the piano. What is the most common neoplasm associated with this clinical syndrome?

A. breast carcinoma
B. Hodgkin lymphoma
C. neuroblastoma
D. small cell lung cancer
E. teratoma

▶ 6. Which of the following is the most common neurologic complication of inflammatory bowel disease?

A. encephalopathy
B. myelopathy
C. myopathy
D. peripheral neuropathy
E. stroke

▶ 7. A 68-year-old woman undergoes evaluation after suffering a right occipital infarct 3 days ago. She has a history of well-controlled hypertension and has been afebrile. Workup thus far has revealed a wedge-shaped right occipital infarct and cutoff of the P1 segment of the right posterior cerebral artery on brain magnetic resonance angiography (MRA). MRA of the neck, transthoracic echocardiogram, and 24-hour cardiac telemetry are normal. Which of the following is the most appropriate next diagnostic step?

A. conventional cerebral angiogram
B. CT perfusion
C. EEG
D. long-term cardiac rhythm monitoring
E. no additional investigation is indicated

▶ 8. A 32-year-old woman presents with 2 days of rapidly worsening headache and visual loss. The patient has a known history of a nonfunctioning pituitary macroadenoma that has been stable on annual imaging for the past 4 years. On examination, she is afebrile and has bitemporal hemianopia as well as mild nuchal rigidity. Which of the following is the most likely diagnosis?

A. bacterial meningitis
B. cavernous sinus thrombosis
C. mucormycosis
D. pituitary apoplexy
E. subarachnoid hemorrhage

▶ 9. Joint pain is a hallmark of which of these environmentally induced disorders?

A. acute radiation syndrome
B. decompression sickness type I
C. electrical injury
D. high-pressure neurologic syndrome
E. hypothermia

▶ 10. The face of the giant panda sign on T2-weighted images has been described as a brain MRI finding in which of the following hepatic diseases?

A. Budd-Chiari syndrome
B. hemochromatosis
C. hepatitis A
D. non-Wilsonian hepatocerebral degeneration
E. Wilson disease

▶ 11. Treatment with which of the following antiepileptic medications would most likely require supplemental dosing after dialysis?

A. carbamazepine
B. lamotrigine
C. levetiracetam
D. phenytoin
E. valproic acid

▶ 12. Which of the following features of aortic atheromas suggests a higher risk of embolization?

A. calcification
B. high lipid content
C. nonmobile
D. smaller size (less than 4 mm)
E. smooth contour

▶ 13. Central nervous system prophylaxis is used routinely in the treatment of which of the following types of lymphoma?

A. Burkitt lymphoma
B. follicular lymphoma
C. Hodgkin lymphoma
D. mantle cell lymphoma
E. small lymphocytic lymphoma

▶ 14. Which of the following is the most common central nervous system manifestation in patients with systemic lupus erythematosus?

A. cerebrovascular disease
B. cognitive impairment
C. headache
D. mood disorders
E. seizures

▶ 15. Which of the following neurologic complications is associated with toxicity of vitamin A?

A. dementia
B. intracranial hypertension
C. myelopathy
D. peripheral neuropathy
E. seizures

▶ 16. A 56-year-old man presents to the emergency department after having a witnessed generalized tonic-clonic seizure in the waiting room of the medicine clinic. He had been experiencing tingling in his fingers and around his lips for the prior week as well as painful finger spasms. He underwent total thyroidectomy 1 month ago for thyroid cancer. He has no prior neurologic history, and his only medication is levothyroxine. On examination, he is alert and fully oriented with normal cognitive function. When percussing his parotid region on either side, ipsilateral facial contractions are noted. Which of the following is the most likely diagnosis?

A. hypocalcemia
B. hypoglycemia
C. hypokalemia
D. hyponatremia
E. hypothyroidism

▶ 17. A 60-year-old man with moderate chronic renal failure is admitted to the hospital for treatment of a urinary tract infection. On the third day, he becomes confused and appears sedated. The following day, he develops myoclonus and is witnessed to have a generalized seizure. Which of the following medications is most likely to cause this constellation of symptoms?

A. cefazolin
B. cefepime
C. ceftaroline
D. ceftriaxone
E. cephalexin

▶ 18. A 46-year-old man presents with cognitive deterioration over the past 2 months. He has a long-standing history of alcoholism and has been treated over the past year for multiple dental infections in the setting of poor oral hygiene. He also has been experiencing abdominal pain and diarrhea. On physical examination, he has a reddish-brown rash on his face, chest, and the dorsum of his hands and feet. Neurologic examination reveals the inability to perform serial 7's and poor recall. Deficiency of which of the following nutrients is most likely responsible for his presentation?

A. cobalamin
B. folate
C. niacin
D. pyridoxine
E. thiamine

▶ 19. A 24-year-old woman presents with headaches, nausea, and ataxia and is found to have a cerebellar hemangioblastoma. Her family history is notable for a pheochromocytoma in her mother. Periodic screening for which of the following conditions should be performed in this patient?

A. Fanconi syndrome
B. glomerular nephritis
C. lymphoma
D. renal cell carcinoma
E. vertebrobasilar aneurysm

▶ 20. Which of the following clinical features should prompt a clinician to consider an autoimmune cause for seizures?

A. frontal lobe epileptic focus
B. normal CSF examination
C. olfactory aura
D. positive family history of epilepsy
E. resistance to antiepileptic drug treatment

▶ 21. Which of the following is the most likely mechanism of stroke occurring as a complication of inflammatory bowel disease?

A. atherosclerosis
B. cardiac embolism
C. hypercoagulability
D. lipohyalinosis
E. reversible cerebral vasoconstriction syndrome

▶ 22. A 65-year-old man with a long history of alcoholism and chronic liver disease presents for evaluation of fluctuating neurologic symptoms, including lethargy, disorientation, and apathy. His wife describes recent episodes of inappropriate behavior, such as walking around the house naked when his adult daughter is visiting. His examination shows lethargy, disorientation for time, asterixis, and mild dyspraxia. What grade of hepatic encephalopathy under the West Haven criteria does he demonstrate?

A. grade I
B. grade II
C. grade III
D. grade IV
E. minimal

▶ 23. Which of the following is the most common neurologic manifestation of type A aortic dissection?

A. cerebral infarction
B. Horner syndrome
C. recurrent laryngeal nerve palsy
D. spinal cord ischemia
E. subarachnoid hemorrhage

▶ 24. A 56-year-old man with chronic liver disease due to viral hepatitis develops painful peripheral neuropathy. Electrodiagnostic studies are consistent with a predominantly axonal distal symmetric sensory neuropathy. Laboratory evaluation is remarkable for the presence of mixed cryoglobulinemia. Which of the following etiologies of viral hepatitis is most likely present in this patient?

A. hepatitis A
B. hepatitis B
C. hepatitis C
D. hepatitis D
E. hepatitis E

▶ 25. A 49-year-old woman develops a progressive encephalomyelitis syndrome over 3 weeks. She is hospitalized because of the development of rigidity and myoclonus in her lower extremities that prevent safe ambulation. This is associated with painful spasms in her legs and low back. Admission physical examination by her internist discloses a firm nonmobile 3-cm diameter mass in her left breast. Which of the following antibodies are most likely to be associated with this clinical presentation?

A. amphiphysin
B. antineural nuclear autoantibody type 2 (ANNA-2)
C. Ma
D. *N*-methyl-D-aspartate (NMDA) receptor
E. Purkinje cell antibody (PCA)-1 (anti-Yo)

▶ 26. A 20-year-old man presents with 24 hours of acute-onset polyuria, polydipsia, vomiting, generalized weakness, and confusion. For the past 2 weeks, he has been aggressively training for a football tryout and has been taking steroids and amphetamines that he obtained from a classmate. In the emergency department, his finger-stick blood glucose reads as over 400 mg/dL, and his initial labs demonstrate hyperglycemia, metabolic acidosis, and the presence of ketone bodies in his serum. Which of the following is the most appropriate initial step in management of this patient?

A. emergent dialysis
B. fluid resuscitation
C. glucagon administration
D. insulin administration
E. IV methylprednisolone

▶ 27. A 54-year-old man presents with 3 weeks of numbness in his hands and feet as well as worsening balance. He has a history of peptic ulcer disease and takes omeprazole. On examination, he has reduced pinprick in a stocking-glove distribution, reduced vibratory and joint position sense at the toes, bilateral Babinski signs, and a positive Romberg sign. Deficiency of which of the following nutrients is most likely responsible for his presentation?

A. cobalamin
B. folate
C. niacin
D. pyridoxine
E. thiamine

▶ 28. A 68-year-old man is evaluated for a sensorimotor predominantly demyelinating neuropathy. His examination shows hepatosplenomegaly, hypothyroidism, and areas of dermal hyperpigmentation. His laboratory studies are remarkable for thrombocytosis and a lambda light chain monoclonal gammopathy. Which of the following disorders is the most likely cause of his peripheral neuropathy?

A. AL amyloidosis
B. chronic inflammatory demyelinating polyradiculopathy (CIDP)
C. neurolymphomatosis
D. polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
E. Waldenström macroglobulinemia

▶ 29. A 50-year-old man with diabetes mellitus reports feeling nauseated while on an airplane. The flight has been delayed by 2 hours, during which time the airplane was sitting on the tarmac awaiting clearance for takeoff. He then becomes diaphoretic and tremulous and develops palpitations. He notifies the flight attendant, and a physician who happens to be on the flight is summoned. Over the next 3 minutes, the patient becomes unresponsive. Which of the following is the most likely diagnosis?

A. acute stroke
B. diabetic ketoacidosis
C. hypercalcemia
D. hyperglycemic hyperosmolar state
E. hypoglycemia

▶ 30. A 41-year-old man develops an acute confusional state with dense anterograde and patchy retrograde amnesia 1 month after hematopoietic stem cell transplantation for treatment of chronic lymphocytic leukemia associated with moderately severe graft versus host disease. He is unable to remember his chronic lymphocytic leukemia diagnosis and asks why he has a central venous access catheter in place. He is witnessed to have several complex partial seizures. Laboratory evaluation is remarkable for moderate hyponatremia. A brain MRI is abnormal, with hyperintense signal in the medial temporal lobes bilaterally on T2-weighted images that do not enhance on postcontrast T1-weighted images. CSF shows a mild pleocytosis. What is the most likely etiology of this patient's syndrome?

A. Cytomegalovirus
B. enterovirus
C. human herpesvirus 6
D. JC virus
E. varicella-zoster virus

▶ 31. Which of the following is the most common neurologic manifestation of Sjögren syndrome?

A. aseptic meningitis
B. encephalopathy
C. myelopathy
D. myopathy
E. peripheral neuropathy

▶ 32. Which of the following solid organ transplantations are associated with the highest risk for *Toxoplasma gondii* infection?

A. heart
B. kidney
C. liver
D. lung
E. pancreas

▶ 33. A 15-year-old girl presents with bilateral optic neuritis and features of myelitis localizable to the conus. Her brain MRI is remarkable for multiple lesions with a ''cotton wool'' appearance with poorly demarcated margins. Which of the following antibodies is most likely to be found in this patient?

A. antineuronal nuclear antibody type 1 (ANNA-1) (anti-Hu)
B. anti-Ma
C. antibodies to myelin oligodendrocyte glycoprotein (MOG)
D. Purkinje cell antibody (PCA)-tr
E. recoverin (anti-CAR)

▶ 34. Which of the following vitamins can cause peripheral neuropathic symptoms in both a state of deficiency or excess?

A. vitamin B_1
B. vitamin B_6
C. vitamin B_{12}
D. vitamin D
E. vitamin E

▶ 35. A 35-year-old man presents with 2 months of progressive cognitive deterioration, weight loss, and diarrhea. On examination, he has impaired delayed recall, poor attention, impaired upgaze, and pendular convergence nystagmus with synchronous contractions of the jaw muscles. Which of the following is the most likely diagnosis?

A. neuro-Behçet disease
B. neurosarcoidosis
C. neurosyphilis
D. progressive supranuclear palsy
E. Whipple disease

▶ 36. A 61-year-old man develops dyspnea on exertion and pedal edema. Abnormalities noted on his examination include periorbital purpura, hepatomegaly, and macroglossia. He also has multiple features of autonomic failure, including orthostatic hypotension, erectile dysfunction, and gastroparesis. Which of the following diagnostic procedures, in combination with bone marrow biopsy, would be the most useful to confirm the etiology of this disease?

A. abdominal subcutaneous fat aspiration
B. liver biopsy
C. muscle biopsy
D. pericardial biopsy
E. salivary gland biopsy

▶ 37. Keraunoparalysis is transient paralysis caused by which of the following environmental-related conditions?

A. acute mountain sickness
B. decompression sickness
C. hyperthermia
D. hypothermia
E. lightning strike

▶ 38. A 44-year-old man presents with acute left-sided weakness. He has been febrile for the past week. He has a history of IV drug abuse. On examination, he is febrile and has a cardiac murmur and left lower face and arm weakness. MRI of the brain demonstrates an acute right frontal infarct. Magnetic resonance angiography (MRA) of the brain demonstrates two small distal middle cerebral artery aneurysms. Erythrocyte sedimentation rate is 86 mm/hr. Transthoracic echocardiogram demonstrates vegetations on the mitral valve. Which of the following is the most appropriate next therapeutic step?

A. antibiotics
B. anticoagulation
C. aspirin
D. endovascular occlusion of the distal aneurysms
E. mitral valve replacement

▶ 39. A 45-year-old man presents with diplopia and right eye pain for 3 weeks. On examination, he has proptosis and ophthalmoparesis of the right eye. MRI of the brain demonstrates patchy pachymeningeal enhancement as well as thickening and enhancement of right periorbital muscles. What is the most likely diagnosis?

A. antiphospholipid antibody syndrome
B. Behçet disease
C. IgG4-related disease
D. mixed connective tissue disease
E. polyarteritis nodosa

▶ 40. A 77-year-old woman is brought to the emergency department with lethargy that has been worsening over the past 3 days. She has reported feeling cold and unwell for the prior 2 weeks. On examination, she is hypothermic to 34.8°C (94.6°F). She has nonpitting edema in her limbs and face, is severely lethargic and barely arousable, and has generalized hyporeflexia. Which of the following endocrine disorders is most likely?

A. addisonian crisis
B. hyperglycemic hyperosmolar state
C. myxedema coma
D. pituitary apoplexy
E. thyroid storm

Postreading Self-Assessment and CME Test—Preferred Responses

D. Joanne Lynn, MD, FAAN; Joseph E. Safdieh, MD, FAAN

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the course material. The comments and references included with each question are intended to encourage independent study.

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▶ 1. The preferred response is **A (Cytomegalovirus [CMV])**. CMV infection may occur in recipients of CMV-positive solid organs with withdrawal of prophylaxis or even despite prophylaxis. Central nervous system CMV infections are associated with meningeal, retinal, and ependymal complications. A pattern of ventricular enlargement and ependymal enhancement on brain MRI consistent with ventriculitis may suggest the diagnosis. For more information, refer to **pages 813–814** of the *Continuum* article ''Neurologic Complications of Transplantation.''

▶ 2. The preferred response is **A (atlantoaxial subluxation)**. Long-standing rheumatoid arthritis can cause inflammatory degenerative changes at the upper cervical spine that are associated with instability. The most common deformity is atlantoaxial subluxation, in which bony destruction occurs at C1-C2 with associated atlantoaxial ligament pannus formation. During intubation, neck hyperextension may lead to exacerbation of the subluxation and spinal cord damage. Patients with upper cervical spine involvement due to rheumatoid arthritis should be intubated with extreme care to avoid neck hyperextension. Other less common rheumatoid arthritis–associated cervical spine processes include subaxial subluxation and vertical subluxation. For more information, refer to **pages 699–700** of the *Continuum* article ''Rheumatology and Neurology.''

▶ 3. The preferred response is **C (metabotropic glutamate receptor 5)**. This clinical presentation is consistent with limbic encephalitis, which when seen in Hodgkin lymphoma is also known as Ophelia syndrome and associated with antibodies to metabotropic glutamate receptor 5. Treatment of the underlying lymphoma often leads to significant or full recovery. For more information, refer to **page 675** of the *Continuum* article ''Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias.''

▶ 4. The preferred response is **E (Wernicke-Korsakoff syndrome)**. The most likely diagnosis is Wernicke-Korsakoff syndrome due to thiamine deficiency in the setting of malnutrition caused by underlying cancer and chemotherapy. The ataxia, nystagmus, and cognitive symptoms are consistent with the diagnosis. MRI features of T2 hyperintensities in the diencephalic and mesencephalic paraventricular region are not always present but are also consistent with the diagnosis. Metastatic disease would almost always be associated with enhancing lesions and are typically at the gray-white junction. Beriberi is also associated with thiamine deficiency but typically presents with peripheral neuropathy. For more information, refer to **page 841** of the *Continuum* article ''Nutrients and Neurology.''

▶ 5. The preferred response is **E (teratoma)**. The clinical presentation described is most consistent with autoimmune encephalitis associated with antibodies to the *N*-methyl-D-aspartate (NMDA) receptor. Features that suggest this diagnosis as the specific cause of the encephalitis are hypoventilation and orofacial/upper limb dyskinesia. This syndrome is associated with neoplasms in approximately 40% of cases. The most common tumor found is a teratoma, which can be found outside of the ovaries in a minority of cases. Removal of the teratoma is associated with an improved outcome. For more information, refer to **pages 641–642** of the *Continuum* article ''Autoimmune Neurology of the Central Nervous System.''

▶ 6. The preferred response is **D (peripheral neuropathy)**. Neurologic complications from inflammatory bowel disease are less common than other systemic complications. The most common neurologic complication is peripheral neuropathy. Other less common neurologic complications include encephalopathy, myelopathy, myopathy, and stroke. For more information, refer to **page 752** of the *Continuum* article ''Gastroenterology and Neurology.''

▶ 7. The preferred response is **D (long-term cardiac rhythm monitoring)**. The patient had a recent stroke that can be classified as cryptogenic. Many of these strokes are presumed to be cardioembolic, and short-term cardiac monitoring has a low sensitivity for detecting paroxysmal atrial fibrillation. Longer-term monitoring is indicated to increase the likelihood of detecting atrial fibrillation. A cerebral angiogram is unlikely to add more information. For more information, refer to **page 655** of the *Continuum* article ''Neurologic Complications of Cardiac and Aortic Disease.''

▶ 8. The preferred response is **D (pituitary apoplexy)**. This patient has a known nonsecreting pituitary macroadenoma and has developed the sudden onset of headache and bitemporal hemianopia. This should immediately raise suspicion for pituitary apoplexy, which can exert pressure on the optic chiasm leading to the visual field abnormality. Although there is nuchal rigidity, the lack of fever and the presence of the bitemporal hemianopia is not consistent with bacterial meningitis. For more information, refer to **page 779** of the *Continuum* article ''Endocrine Emergencies With Neurologic Manifestations.''

▶ 9. The preferred response is **B (decompression sickness type I)**. Decompression sickness is caused by dissolution of inert gases into the blood and tissues with formation of gas bubbles. Type I is characterized by joint pain and itching. Type II is manifested as spinal cord and cerebral dysfunction. A detailed neurologic evaluation should be performed for any diver who reports type I decompression sickness symptoms as they often proceed to type II decompression sickness symptoms. For more information, refer to **pages 865–867** of the *Continuum* article ''Environmental Neurologic Injuries.''

▶ 10. The preferred response is **E (Wilson disease)**. MRI findings in Wilson disease include abnormal signal in the basal ganglia, thalamus, and midbrain. The face of the giant panda sign is a classic MRI finding in Wilson disease, consisting of T2-weighted hyperintensity in the tegmentum with hypointensity of the superior colliculi and sparing of the red nucleus and pars reticulata. This finding is seen in a minority of cases but is helpful for diagnosis when present. Chronic hepatic disease from various causes is associated with hyperintensity of the globus pallidus on T1-weighted images, likely due to manganese deposition. For more information, refer to **page 772** of the *Continuum* article ''Liver Disease and Neurology.''

▶ 11. The preferred response is **C (levetiracetam)**. Levetiracetam, topiramate, and gabapentin are highly water-soluble antiepileptic medications and are small molecules, with minimal plasma protein binding; they are removed to a significant degree during dialysis. For this reason, supplemental dosing is required after dialysis for these medications. Agents such as carbamazepine, lamotrigine, phenytoin, and valproic acid are more highly protein bound and less likely to be removed by dialysis. For more information, refer to **pages 735–736** of the *Continuum* article ''Renal Disease and Neurology.''

▶ 12. The preferred response is **B (high lipid content)**. Aortic atheromas may be an underrecognized cause of ischemic stroke. Aortic atheromas that are noncalcified, lipid rich, larger than 4 mm, ulcerated, and mobile have a higher risk of embolization. For more information, refer to **page 665** of the *Continuum* article ''Neurologic Complications of Cardiac and Aortic Disease.''

▶ 13. The preferred response is **A (Burkitt lymphoma**). Central nervous system prophylaxis is used routinely in Burkitt lymphoma and lymphoblastic lymphoma as the incidence of nervous system involvement is highest for these two lymphoma types. For more information, refer to **pages 670–671** of the *Continuum* article ''Neurologic Complications of Lymphoma, Leukemia and Paraproteinemias.''

▶ 14. The preferred response is **C (headache)**. Neuropsychiatric lupus can have protean manifestations in the central nervous system (CNS) or the peripheral nervous system. The most common CNS manifestation in patients with lupus is headache. All of the other listed choices are also known CNS manifestations in patients with lupus but are not as common as headache. For more information, refer to **pages 695–696** of the *Continuum* article ''Rheumatology and Neurology.''

▶ 15. The preferred response is **B (intracranial hypertension)**. Vitamin A toxicity is associated with the development of pseudotumor cerebri. This is an important complication of vitamin A to recognize because hypervitaminosis A can be caused by use of certain acne creams and medications that contain tretinoins. Other neurologic manifestations of vitamin A toxicity include irritability, headache, and insomnia. For more information, refer to **page 848** of the *Continuum* article ''Nutrients and Neurology.''

▶ 16. The preferred response is **A (hypocalcemia)**. This patient is likely hypocalcemic due to inadvertent removal of parathyroid tissue during the recent thyroidectomy. Hypocalcemia can cause seizures, neuromuscular irritability (manifested by the Chvostek sign in this patient), and paresthesia. Seizures can also occur due to hyponatremia and hypoglycemia, but the other neurologic symptoms would be atypical. Acute severe hypothyroidism causes lethargy and hypothermia. For more information, refer to **page 793** of the *Continuum* article ''Endocrine Emergencies With Neurologic Manifestations.''

▶ 17. The preferred response is **B (cefepime)**. Cefepime is a fourth-generation cephalosporin with activity against gram-positive and gram-negative organisms. Approximately 85% is excreted by the kidneys. Treatment with cefepime may cause a syndrome of neurotoxicity manifested by encephalopathy, myoclonus, and seizures in the setting of renal failure. For more information, refer to **pages 734–735** of the *Continuum* article ''Renal Disease and Neurology.''

▶ 18. The preferred response is **C (niacin)**. Although uncommon, the most likely explanation for the constellation of signs and symptoms in this patient is pellagra, the syndrome of niacin deficiency. The patient likely has poor nutritional status, and chronic infection can contribute to the depletion of niacin stores. Pellagra causes gastrointestinal symptoms, rash, and poorly characterized encephalopathic symptoms. None of the other choices cause this combination of symptoms. For more information, refer to **page 845** of the *Continuum* article ''Nutrients and Neurology.''

▶ 19. The preferred response is **D (renal cell carcinoma)**. This patient's clinical presentation and family history are consistent with Von Hippel-Lindau disease, which is an autosomal dominant syndrome caused by mutation of the *VHL* tumor suppressor gene. Patients with this condition are at risk for developing several different types of benign and malignant tumors. Hemangioblastomas of the central nervous system are the most common type of tumor. Clear cell renal cell carcinoma is another significant tumor in this population and a frequent cause of death. Screening should be performed for renal cell carcinoma, central nervous system hemangioblastoma, retinal angioma, and pheochromocytoma. For more information, refer to **page 725** of the *Continuum* article ''Renal Disease and Neurology.''

▶ 20. The preferred response is **E (resistance to antiepileptic drug treatment)**. Features that might raise suspicion of an autoimmune etiology for a seizure disorder include antiepileptic drug treatment resistance; new-onset refractory status epilepticus; multiple event types in the same individual; and a history of smoking, malignancy, or autoimmune disease. CSF is often abnormal, but normal CSF does not exclude an autoimmune etiology. For more information, refer to **pages 642–643** of the *Continuum* article ''Autoimmune Neurology of the Central Nervous System.''

▶ 21. The preferred response is **C (hypercoagulability)**. Vascular complications have been described in association with inflammatory bowel disease. The mechanism is most likely related to hypercoagulability, as serum levels of prothrombotic factors such as factors V and VIII and fibrinogen are elevated and antithrombin III levels are reduced. For more information, refer to **page 754** of the *Continuum* article ''Gastroenterology and Neurology.''

▶ 22. The preferred response is **B (grade II)**. The West Haven criteria are used to grade the severity of hepatic encephalopathy. The grades are derived from changes in the level of consciousness, behavior, and intellectual function. Grade II criteria include disorientation for time, lethargy or apathy, inappropriate behavior, dyspraxia, and asterixis. For more information, refer to **pages 762–763** of the *Continuum* article ''Liver Disease and Neurology.''

▶ 23. The preferred response is **A (cerebral infarction)**. Type A aortic dissection involves the ascending aorta. The most common neurologic manifestation of type A aortic dissection is cerebral infarction. A clue may be the occurrence of chest or back pain with the stroke. Other less common complications of type A aortic dissection include a Horner syndrome, recurrent laryngeal nerve palsy, and spinal cord ischemia. For more information, refer to **page 664** of the *Continuum* article ''Neurologic Complications of Cardiac and Aortic Disease.''

▶ 24. The preferred response is **C (hepatitis C)**. Chronic hepatitis C infection is associated with systemic inflammatory responses, including elevated levels of inflammatory cytokines and B-cell proliferation with many potential health complications. Mixed cryoglobulinemia develops in approximately 50% of patients, and this may cause several different types of peripheral neuropathy. Other neurologic complications include increased risk of stroke from accelerated atherosclerosis or cerebral vasculitic changes and encephalomyelitis. For more information, refer to **page 774** of the *Continuum* article ''Liver Disease and Neurology.''

▶ 25. The preferred response is **A (amphiphysin)**. Several different neuronal antibodies are associated with syndromes of abnormal tone, including stiff person syndrome and progressive encephalomyelitis with rigidity and myoclonus. Glutamic acid decarboxylase 65 (GAD65) is one antibody commonly encountered with these conditions. Other antibodies associated with stiff person syndrome include those directed against amphiphysin, glycine receptor, and gephyrin. Amphiphysin antibodies have been associated with breast carcinoma and small cell lung cancer. For more information, refer to **page 643** of the *Continuum* article ''Autoimmune Neurology of the Central Nervous System.''

▶ 26. The preferred response is **B (fluid resuscitation)**. This patient is experiencing an episode of diabetic ketoacidosis likely precipitated by amphetamines and steroids. The most appropriate initial step in the management of diabetic ketoacidosis is aggressive fluid resuscitation. Fluids should be administered before insulin as acute insulin therapy in a patient with diabetic ketoacidosis who is dehydrated can cause cardiovascular collapse. For more information, refer to **pages 796–797** of the *Continuum* article ''Endocrine Emergencies With Neurologic Manifestations.''

▶ 27. The preferred response is **A (cobalamin)**. This patient presents with a syndrome compatible with myeloneuropathy. Cobalamin (vitamin B_{12}) deficiency causes a myeloneuropathy. This patient is at higher risk of vitamin B_{12} malabsorption because of the use of a proton pump inhibitor. Folate can also cause a myeloneuropathy, but it is very rare and much less common than cobalamin deficiency. Deficiency states of niacin or pyridoxine may cause peripheral neuropathy, among other symptoms, but not myeloneuropathy. For more information, refer to **page 831** of the *Continuum* article ''Nutrients and Neurology.''

▶ 28. The preferred response is **D (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes [POEMS] syndrome)**. POEMS is a paraneoplastic syndrome, and the acronym is derived from its common features. The neuropathy is typically a length-dependent sensorimotor demyelinating neuropathy. The CSF profile is similar to that of CIDP with albuminocytologic dissociation, but clinically the distal involvement is typically more severe. Clinical features also include a monoclonal plasma cell disorder and, variably, Castleman disease, sclerotic bone lesions, and elevated vascular endothelial growth factor. For more information, refer to **pages 683–684** of the *Continuum* article ''Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias.''

▶ 29. The preferred response is **E (hypoglycemia)**. This patient has diabetes mellitus and experiences an episode of unconsciousness preceded by tremulousness, palpitations, and diaphoresis. Although this presentation is not pathognomonic for any one condition, the most likely etiology based on the choices listed is hypoglycemia. Patients with acute hypoglycemia tend to manifest initially with acute sympathetic autonomic symptoms and can progress to seizure or coma. Diabetic patients on treatment are at high risk for hypoglycemia, and, in this patient, it is possible that the long delay on the plane altered his normal oral intake of food. For more information, refer to **page 797** of the *Continuum* article ''Endocrine Emergencies With Neurologic Manifestations.''

▶ 30. The preferred response is **C (human herpesvirus 6)**. The syndrome of posttransplant acute limbic encephalitis (PALE) is composed of confusion, amnesia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), mild pleocytosis, and MRI abnormalities involving the hippocampus and other medial temporal lobe structures. Seizures may occur. The most common etiology of this infection is human herpesvirus 6 type B. For more information, refer to **page 805** of the *Continuum* article ''Neurologic Complications of Transplantation.''

▶ 31. The preferred response is **E (peripheral neuropathy)**. Sjögren syndrome is most commonly associated with peripheral nervous system manifestations, most commonly presenting as a peripheral polyneuropathy. Mononeuropathy, mononeuritis multiplex, autonomic neuropathy, and trigeminal sensory neuropathy can occur. Central nervous system manifestations of Sjögren syndrome are uncommon and can include encephalopathy and aseptic meningitis. For more information, refer to **page 702** of the *Continuum* article ''Rheumatology and Neurology.''

▶ 32. The preferred response is **A (heart)**. Toxoplasmosis is an infectious risk in cardiac transplantation as the parasite can be harbored in the donor myocardium. Infection usually becomes symptomatic within the first 3 months after transplantation. For more information, refer to **page 818** of the *Continuum* article ''Neurologic Complications of Transplantation.''

▶ 33. The preferred response is **C (antibodies to myelin oligodendrocyte glycoprotein [MOG])**. Recent reports describe a distinct non–multiple sclerosis central nervous system demyelinating disorder that is associated with serum antibodies to MOG. The distinctive features for this MOG antibody–associated central nervous system inflammatory disease include conus predominant myelitis, bilateral optic neuritis, and ''cotton wool'' brain lesions with poorly defined margins. This antibody assay could help to differentiate this disorder from multiple sclerosis, acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (NMO) spectrum disorders. For more information, refer to **page 641** of the *Continuum* article ''Autoimmune Neurology of the Central Nervous System.''

▶ 34. The preferred response is **B (vitamin B_6)**. Vitamin B_6 (pyridoxine) deficiency is associated with peripheral neuropathy, and excess can cause a sensory ganglionopathy. Both of these states cause neuropathic symptoms including numbness. This is not a characteristic of any of the other listed vitamins. For more information, refer to **page 847** of the *Continuum* article ''Nutrients and Neurology.''

▶ 35. The preferred response is **E (Whipple disease)**. This patient presents with gastrointestinal and cognitive symptoms and on examination has vertical gaze involvement as well as findings consistent with oculomasticatory myorhythmia. This is pathognomonic for Whipple disease with neurologic involvement. None of the other options would be associated with this clinical picture (particularly the oculomasticatory myorhythmia), although progressive supranuclear palsy involves impairment of vertical eye movements. For more information, refer to **pages 756–757** of the *Continuum* article ''Gastroenterology and Neurology.''

▶ 36. The preferred response is **A (abdominal subcutaneous fat aspiration)**. This patient's clinical symptoms of congestive heart failure, hepatomegaly, periorbital purpura, and macroglossia are consistent with immunoglobulin light chain (AL) amyloidosis. Bone marrow biopsy in combination with abdominal subcutaneous fat aspiration will detect amyloid in the majority of patients. For more information, refer to **pages 684–686** of the *Continuum* article ''Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias.''

▶ 37. The preferred response is **E (lightning strike)**. Keraunoparalysis is a transient weakness of the lower limbs that usually improves within hours. It is thought to be caused by vasospasm secondary to lightning-induced activation of the sympathetic system. For more information, refer to **pages 864–865** of the *Continuum* article ''Environmental Neurologic Injuries.''

▶ 38. The preferred response is **A (antibiotics)**. This patient presents with a stroke as a complication of likely endocarditis. He is febrile and has a heart murmur, an elevated erythrocyte sedimentation rate, and a vegetation detected on echocardiography. The initial treatment of endocarditis is with antibiotics. Aspirin and anticoagulation are inappropriate as they do not treat the underlying mechanism and may increase hemorrhage risk. Valve replacement is indicated for recurrent infarcts despite appropriate antibiotic therapy. For more information, refer to **page 659** of the *Continuum* article ''Neurologic Complications of Cardiac and Aortic Disease.''

▶ 39. The preferred response is **C (IgG4-related disease)**. The patient is presenting with a syndrome consistent with orbital inflammation (also called orbital pseudotumor) and associated pachymeningeal enhancement. Of the choices listed, the most likely etiology is IgG4-related disease, which is described to cause this presentation. All of the listed choices can have neurologic manifestations, but none are specifically associated with the described clinical syndrome. For more information, refer to **pages 716–717** of the *Continuum* article ''Rheumatology and Neurology.''

▶ 40. The preferred response is **C (myxedema coma)**. This patient presents with severe lethargy, edema, and, importantly, hypothermia. Of the choices listed, the most likely diagnosis is myxedema coma. For more information, refer to **pages 786–787** of the *Continuum* article ''Endocrine Emergencies With Neurologic Manifestations.''

Patient Management Problem

Sara E. Hocker, MD

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Relationship Disclosure: Dr Hocker serves in an advisory role for SAGE Therapeutics and receives research/grant support from the Mayo Clinic.

Unlabeled Use of Products/Investigational Use Disclosure: Dr. Hocker reports no disclosure.

The following Patient Management Problem was chosen to reinforce the subject matter presented in the issue. It emphasizes decisions facing the practicing physician. As you read through the case you will be asked to complete 12 questions regarding history, examination, diagnostic evaluation, therapy, and management. For each item, select the single best response.

To obtain CME credits for this activity, subscribers must complete this Patient Management Problem online at *aan.com/continuum/cme*. A tally sheet is provided with this issue to allow the option of marking answers before entering them online. A faxable scorecard is available only upon request to subscribers who do not have computer access or to nonsubscribers who have purchased single back issues (send an email to ***ContinuumCME@aan.com***).

US Participants: Upon completion of the Patient Management Problem, US participants may earn up to *2 AMA PRA Category 1 Credits*™. US participants have up to 3 years from the date of publication to earn CME credits. No CME will be awarded for this issue after June 30, 2020.

Canadian Participants: This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, on April 1, 2017. Refer to the CME tab on *ContinuumJournal.com* for dates of accreditation. Canadian participants should visit MAINPORT (*www.mainport.org*) to record learning and outcomes. Canadian participants can claim a maximum of 2 hours (credits are automatically calculated).

LEARNING OBJECTIVES

Upon completion of this activity, the participant will be able to:

- List the protean manifestations of serotonin syndrome
- Recognize the complications of serotonin syndrome
- Initiate appropriate therapy for serotonin syndrome

Case

A 74-year-old man with hyperlipidemia, coronary artery disease, and depression undergoes emergent abdominal aortic aneurysm repair. He is extubated in the postanesthesia care unit and then admitted to the surgical intensive care unit. Postoperatively, he is started on a fentanyl infusion at 50 mcg/h for pain control and given ondansetron as needed for nausea. Approximately 48 hours after surgery, he becomes very restless over a period of several hours and appears to be shivering. His blood pressure is 177/96 mm Hg, pulse is 113 beats/min and regular, and respiratory rate is 22 breaths/min. His temperature is 38.1°C (100.6°F). On examination, he is diaphoretic and has a frequent intermittent tremor of the trunk and upper extremities. He is alert and conversant and follows simple commands but is markedly inattentive and disoriented. His pupils are 6 mm bilaterally and reactive to light. Neurologic examination is otherwise unrevealing.

▶ 1. Which of the following is the most likely diagnosis?

A. malignant hyperthermia
B. neuroleptic malignant syndrome
C. nonconvulsive status epilepticus
D. sepsis
E. serotonin syndrome

▶ 2. Which of the following additional clinical features would suggest serotonin toxicity?

A. diarrhea
B. flushed skin
C. hyperreflexia
D. hypotonicity
E. temperature higher than 38°C (100.4°F)

Upon clinical suspicion of serotonin toxicity, the patient's medication history and administration record are reviewed. Paroxetine, which the patient was taking daily at home, and ondansetron are discontinued, and further nausea is treated with droperidol. Over a period of hours, he becomes progressively hyperthermic and disoriented and develops frequent, multifocal, shocklike jerks of his muscles. His nurse reports that he is having loose stools.

▶ 3. Which of the following additional examination findings is likely to be found at this stage?

A. clonus
B. disproportionately increased tone in the upper extremities
C. dystonic posturing
D. sialorrhea
E. waxy flexibility

▶ 4. Which of the following is the next best step in the management of this patient?

A. bolus IV lorazepam
B. discontinue fentanyl
C. neuromuscular paralysis
D. order cyproheptadine
E. therapeutic normothermia

▶ 5. Which of the following additional clinical findings should raise the highest suspicion for an alternative diagnosis?

A. akathisia
B. dry mucous membranes
C. extensor plantar responses bilaterally
D. extensor posturing provoked by noxious stimulation
E. repetitive head rotation

Despite discontinuation of fentanyl, the patient becomes unresponsive and undergoes intubation and initiation of mechanical ventilation. He is started on lorazepam as needed to suppress the myoclonus and also started on cyproheptadine. His temperature is 41.3°C (106.3°F). His heart rate is now 133 beats/min and blood pressure is 190/102 mm Hg. He has had no urine output for 2 hours. Results of his laboratory evaluation are shown in **PMP Table 1**.

Continued on page 903

Continued from page 902

PMP TABLE 1 Laboratory Evaluation Results

▶ **Complete Blood Cell Count**	
Hgb	9.2 gd/L
Platelet count	146,000/mm^3
WBC	12,000/mm^3
▶ **Chemistry Panel**	
Sodium	140 mmol/L
Chloride	103 mmol/L
Potassium	4.4 mmol/L
Bicarbonate	21 mmol/L
Blood urea nitrogen	35 mg/dL
Creatinine	1.6 mg/dL
▶ **Other**	
ALT	120 U/L
AST	90 U/L
Creatine kinase	8013 IU/L
aPTT	50 seconds

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Hgb = hemoglobin; WBC = white blood cell.

During repeat examination, the patient has a generalized tonic-clonic seizure, after which he is again unresponsive. He does not open eyes to painful stimulus. When the eyes are passively opened, the pupils are 6 mm and reactive bilaterally. He has ocular clonus and intermittent multifocal myoclonus of the extremities. Tone is markedly increased throughout. It is difficult to illicit reflexes, but with any passive motion, he develops sustained clonus in the lower extremities.

▶ 6. Which of the following interventions is most likely to result in correction of the laboratory abnormalities?

A. aggressive hydration
B. dexmedetomidine infusion
C. initiation of cyproheptadine
D. propofol infusion
E. therapeutic normothermia

▶ 7. Which of the following is the most appropriate management of this patient's seizure?

A. benzodiazepine administration
B. fosphenytoin loading
C. high-dose magnesium
D. propofol infusion
E. therapeutic normothermia

▶ 8. Which of the following is the most appropriate option for the treatment of this patient's hypertension?

A. amlodipine
B. clonidine
C. enalaprilat
D. esmolol
E. labetalol

The patient is started on an IV esmolol infusion for blood pressure control. An IV midazolam infusion is also started to blunt the hyperadrenergic component of the syndrome, and he is paralyzed with a onetime dose of vecuronium to eliminate excessive muscle activity, thereby helping control hyperthermia. He is sandwiched between cooling blankets below and above his body. Ice packs are placed over the femoral arteries and under the axillae. With these measures, his temperature is rapidly reduced to 38.6°C (101.5°F). He is given 1 liter of fluid and started on a maintenance rate of 200 mL/h. After 24 hours, the midazolam is held for a ''sedation holiday.'' On examination, he opens eyes to pain, fixates on the examiner, and tracks. He does not follow commands. Pupils are of normal size and reactive to light. He localizes pain in the upper extremities and briskly withdraws the lower extremities. Tone is mildly increased in the arms and moderately increased in the legs. He is diffusely hyperreflexic and has a few beats of clonus in the lower extremities. Rare multifocal myoclonic jerks are observed. Blood pressure, pulse, and temperature are normal.

▶ 9. Which of the following is the most likely expected time to recovery after removal of the serotonergic drugs in this patient?

A. 0 to 12 hours
B. 12 to 24 hours
C. 24 to 96 hours
D. 5 to 8 days
E. 9 to 12 days

▶ 10. The patient's wife expresses concern about his continued unresponsiveness and asks about the patient's neurologic prognosis should he survive, stating that he would not wish to survive with significant cognitive impairment. How should she be counseled?

A. he has a high probability of developing epilepsy
B. he is expected to make a good neurologic recovery
C. mild cognitive impairment is expected
D. outcomes are highly variable and cannot be reliably predicted
E. severe cognitive impairment is expected

Forty-eight hours later (postoperative day 7), the patient is reliably following commands and is extubated. The myoclonus has fully resolved, and his neurologic examination has normalized. His acidosis and disseminated intravascular coagulation has resolved, and his kidney function is improving.

▶ 11. Which of the following is most appropriate regarding cyproheptadine therapy in this patient at this time?

A. continue for a total of 7 more days
B. continue for a total of 14 more days
C. continue for a total of 21 more days
D. continue for 30 more days
E. discontinue the drug

Cyproheptadine is discontinued. The patient continues to recover over several days. He and his wife express concern about discontinuing his selective serotonin reuptake inhibitor (SSRI). They state he has a history of severe depression and had an excellent response to paroxetine.

▶ 12. How should this patient be counseled regarding future SSRI use?

A. all serotonergic drugs should be avoided indefinitely
B. any future SSRI use should be avoided and his physician consulted regarding an alternative class of antidepressant
C. the patient is now considered to have an allergy to paroxetine and should try an alternative SSRI under the direction of his physician
D. resuming paroxetine in 2 to 4 weeks is probably safe if concomitant use of other serotonergic drugs is avoided
E. serotonin norepinephrine reuptake inhibitors (SNRIs) have a lower risk of resulting in recurrence of serotonin syndrome

The patient is discharged home and resumes his paroxetine after 3 weeks. He does not experience any recurrence of symptoms.

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Relationship Disclosure: Dr Hocker serves in an advisory role for SAGE Therapeutics and receives research/grant support from the Mayo Clinic.

Unlabeled Use of Products/Investigational Use Disclosure: Dr. Hocker reports no disclosure.

Patient Management Problem—Preferred Responses

Sara E. Hocker, MD

Following are the preferred responses for the Patient Management Problem in this *Continuum* issue. The case, questions, and answer options are repeated, and the preferred response is given, followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the material. The comment and references included with each question are intended to encourage independent study.

To obtain CME credits for this activity, subscribers must complete this Patient Management Problem online at *aan.com/continuum/cme*.

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LEARNING OBJECTIVES

Upon completion of this activity, the participant will be able to:

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- Recognize the complications of serotonin syndrome
- Initiate appropriate therapy for serotonin syndrome

Case

A 74-year-old man with hyperlipidemia, coronary artery disease, and depression undergoes emergent abdominal aortic aneurysm repair. He is extubated in the postanesthesia care unit and then admitted to the surgical intensive care unit. Postoperatively, he is started on a fentanyl infusion at 50 mcg/h for pain control and given ondansetron as needed for nausea. Approximately 48 hours after surgery, he becomes very restless over a period of several hours and appears to be shivering. His blood pressure is 177/96 mm Hg, pulse is 113 beats/min and regular, and respiratory rate is 22 breaths/min. His temperature is 38.1°C (100.6°F). On examination, he is diaphoretic and has a frequent intermittent tremor of the trunk and upper extremities. He is alert and conversant and follows simple commands but is markedly inattentive and disoriented. His pupils are 6 mm bilaterally and reactive to light. Neurologic examination is otherwise unrevealing.

▶ 1. Which of the following is the most likely diagnosis?

A. malignant hyperthermia
B. neuroleptic malignant syndrome
C. nonconvulsive status epilepticus
D. sepsis
E. serotonin syndrome

The preferred response is **E (serotonin syndrome)**. The combination of dysautonomia (fever, hypertension, and tachycardia), mydriasis, diaphoresis, tremor, and encephalopathy following exposure to serotonergic drugs is most suggestive of serotonin syndrome. The differential diagnosis of serotonin syndrome includes malignant hyperthermia, neuroleptic malignant syndrome, anticholinergic poisoning, sepsis, cefepime neurotoxicity, encephalitis, and nonconvulsive status epilepticus.[1] Serotonin syndrome can typically be readily distinguished from these diagnoses on clinical grounds. Infection must be considered in this patient who has been hospitalized for more than 48 hours. His acute change in mental status and elevated respiratory rate, heart rate, and temperature should prompt urgent evaluation for suspected infection. Additionally, the intermittent tremor could be interpreted as rigors.[2] The other diagnoses listed are unlikely. Mydriasis, fever, and altered mental status may accompany anticholinergic toxicity; however, the patient is not stated to have received an anticholinergic drug. Hyperactive bowel sounds, neuromuscular abnormalities, and diaphoresis distinguish serotonin syndrome from the anticholinergic toxidrome, in which sweating is absent and bowel sounds are decreased.[1] Malignant hyperthermia develops within minutes of receiving a volatile anesthetic agent or succinylcholine (a neuromuscular blocking agent); however, it has been over 48 hours since his surgery. While the clinical manifestations of the neuroleptic malignant syndrome overlap significantly with those of serotonin syndrome, it is defined by its association with a class of medications that block dopamine transmission, to which this patient has not been clearly exposed. It is reasonable to consider nonconvulsive status epilepticus as it has a highly variable presentation, and both mydriasis and the acute alteration in mental status with associated increased sympathetic tone are suggestive; however, the fact that the patient is alert and following commands in the setting of bilateral tremor makes it less likely.

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801–810. doi:10.1001/jama.2016.0287.

▶ 2. Which of the following additional clinical features would suggest serotonin toxicity?

A. diarrhea
B. flushed skin
C. hyperreflexia
D. hypotonicity
E. temperature higher than 38°C (100.4°F)

The preferred response is **C (hyperreflexia)**. The Hunter Serotonin Toxicity Criteria were developed and published in 2003 to assist in the diagnosis of serotonin syndrome. These criteria are both sensitive (84%) and specific (97%) for the diagnosis of serotonin syndrome. These decision rules incorporate seven variables (spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor, and hyperreflexia) into a set of five specific rules that reliably predict serotonin toxicity. To summarize, the following combinations of clinical signs support a diagnosis of serotonin syndrome when they occur in the presence of a serotonergic agent: (1) spontaneous clonus, (2) inducible clonus and either agitation or diaphoresis, (3) ocular clonus and either agitation or diaphoresis, (4) tremor and hyperreflexia, (5) hypertonicity and temperature higher than 38°C (100.4°F), and either ocular clonus or inducible clonus. The patient is described as having a tremor, making hyperreflexia the answer (decision rule 4).[1]

1. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96(9):635–642. doi:10.1093/qjmed/hcg109.

Upon clinical suspicion of serotonin toxicity, the patient's medication history and administration record are reviewed. Paroxetine, which the patient was taking daily at home, and ondansetron are discontinued, and further nausea is treated with droperidol. Over a period of hours, he becomes progressively hyperthermic and disoriented and develops frequent, multifocal, shocklike jerks of his muscles. His nurse reports that he is having loose stools.

▶ 3. Which of the following additional examination findings is likely to be found at this stage?

A. clonus
B. disproportionately increased tone in the upper extremities
C. dystonic posturing
D. sialorrhea
E. waxy flexibility

The preferred response is **A (clonus)**. Clonus (spontaneous, inducible, and ocular) is the most important sign in the Hunter Serotonin Toxicity Criteria.[1] Tone, hyperreflexia, and clonus may be considerably greater in the lower extremities than in the upper extremities.[2] Sialorrhea may be present in neuroleptic malignant syndrome. Dystonic posturing may be present in neuroleptic malignant syndrome or malignant catatonia. Waxy flexibility is a feature of catatonia. Sialorrhea, dystonic posturing, and waxy flexibility are not associated with serotonin syndrome.

1. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96(9):635–642. doi:10.1093/qjmed/hcg109.
2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.

▶ 4. Which of the following is the next best step in the management of this patient?

A. bolus IV lorazepam
B. discontinue fentanyl
C. neuromuscular paralysis
D. order cyproheptadine
E. therapeutic normothermia

The preferred response is **B (discontinue fentanyl)**. The most important step in the management of serotonin syndrome is the removal of all precipitating drugs. Despite discontinuing ondansetron and paroxetine, the patient is continuing to deteriorate. Fentanyl has serotonergic activity. In a retrospective review of 33 intensive care unit patients with serotonin syndrome, antidepressants were the serotonergic medications most often used before admission, and opioids (principally fentanyl) and antiemetics were the most frequently prescribed new serotonin-enhancing medications.[1] Temperature control, paralysis, and sedation are supportive measures only, as serotonin syndrome is not believed to resolve spontaneously as long as precipitating agents continue to be administered. Benzodiazepines blunt the hyperadrenergic component of the syndrome.[2] The purpose of neuromuscular paralysis is to eliminate excessive muscle activity, thereby helping control hyperthermia. Non-depolarizing agents, such as vecuronium, should be used as succinylcholine may increase the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Cyproheptadine is a serotonin and histamine antagonist that also has anticholinergic and sedative effects. It is recommended for serotonin syndrome, although its efficacy has not been clearly established.[3] In summary, while all of the listed answers are reasonable answers, the best immediate step is elimination of all drugs with known serotonergic activity. These drugs include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), opiate analgesics, over-the-counter cough medicines, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products. The addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has also been associated with the development of the syndrome.

1. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014;21(1):108–113. doi:10.1007/s12028-013-9914-2.
2. Nisijima K, Shioda K, Yoshino T, et al. Diazepam and chlormethiazole attenuate the development of hyperthermia in an animal model of the serotonin syndrome. Neurochem Int 2003;43(2):155–164. doi:10.1016/S0197-0186(02)00213-9.
3. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.

▶ 5. Which of the following additional clinical findings should raise the highest suspicion for an alternative diagnosis?

A. akathisia
B. dry mucous membranes
C. extensor plantar responses bilaterally
D. extensor posturing provoked by noxious stimulation
E. repetitive head rotation

The preferred response is **D (extensor posturing provoked by noxious stimulation)**. Extension of the extremities to painful stimulus may be indicative of a structural problem. Abnormal flexion or extension to pain should prompt immediate neuroimaging to exclude a structural lesion as well as consideration for elevated intracranial pressure related to a central nervous system infection. Dry mucous membranes can be seen in serotonin syndrome. While typically seen with structural central nervous system lesions, bilateral Babinski signs may also accompany serotonin syndrome as part of the neuromuscular hyperactivity that may also manifest as tremor, muscle rigidity, myoclonus, and hyperreflexia. Patients may also manifest a head-turning behavior characterized by repetitive rotation of the head with the neck held in moderate extension. Anxiety, agitation, and akathisia are common early signs of serotonin syndrome.[1]

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120.

Despite discontinuation of fentanyl, the patient becomes unresponsive and undergoes intubation and initiation of mechanical ventilation. He is started on lorazepam as needed to suppress the myoclonus and also started on cyproheptadine. His temperature is 41.3°C (106.3°F). His heart rate is now 133 beats/min and blood pressure is 190/102 mm Hg. He has had no urine output for 2 hours. Results of his laboratory evaluation are shown in **PMP Table 1.**

PMP TABLE 1 Laboratory Evaluation Results

- **Complete Blood Cell Count**
  - Hgb 9.2 g/dL
  - Platelet count 146,000/mm^3
  - WBC 12,000/mm^3
- **Chemistry Panel**
  - Sodium 140 mmol/L
  - Chloride 103 mmol/L
  - Potassium 4.4 mmol/L
  - Bicarbonate 21 mmol/L
  - Blood urea nitrogen 35 mg/dL
  - Creatinine 1.6 mg/dL
- **Other**
  - ALT 120 U/L
  - AST 90 U/L
  - Creatine kinase 8013 IU/L
  - aPTT 50 seconds

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Hgb = hemoglobin; WBC = white blood cell.

During repeat examination, the patient has a generalized tonic-clonic seizure, after which he is again unresponsive. He does not open eyes to painful stimulus. When the eyes are passively opened, the pupils are 6 mm and reactive bilaterally. He has ocular clonus and intermittent multifocal myoclonus of the extremities. Tone is markedly increased throughout. It is difficult to illicit reflexes, but with any passive motion, he develops sustained clonus in the lower extremities.

▶ 6. Which of the following interventions is most likely to result in correction of the laboratory abnormalities?

A. aggressive hydration
B. dexmedetomidine infusion
C. initiation of cyproheptadine
D. propofol infusion
E. therapeutic normothermia

The preferred response is **E (therapeutic normothermia)**. The laboratory evaluation is consistent with metabolic acidosis, rhabdomyolysis, acute kidney injury, and disseminated intravascular coagulopathy, all of which are primarily the result of hyperthermia. The most effective intervention is therapeutic normothermia. His temperature should be rapidly normalized. Hydration is necessary for the management of rhabdomyolysis but is unlikely to result in correction of all of the laboratory abnormalities in the setting of ongoing hyperthermia. Cyproheptadine, which has been started in this patient, may provide some benefit, possibly shortening the duration of symptoms; however, as stated previously, its efficacy has not been rigorously established. Both propofol and dexmedetomidine are alternative methods of sedation that are reasonable options; however, sedation with benzodiazepines is preferred because they have been shown to blunt the hyperadrenergic component of the syndrome.[1]

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.

▶ 7. Which of the following is the most appropriate management of this patient's seizure?

A. benzodiazepine administration
B. fosphenytoin loading
C. high-dose magnesium
D. propofol infusion
E. therapeutic normothermia

The preferred response is **E (therapeutic normothermia)**. A generalized tonic-clonic seizure in the setting of hyperthermia and in the absence of a history of epilepsy is considered to be a provoked seizure. Treatment consists of eliminating the trigger, and initiation of an antiseizure drug is not recommended.[1] All of the other listed answers are medications with antiseizure properties. It is reasonable to obtain an EEG if the patient is sedated or stuporous after a generalized tonic-clonic seizure to exclude nonconvulsive status epilepticus.[2]

1. Bergey GK. Management of a first seizure. Continuum (Minneap Minn) 2016;22(1 Epilepsy):38–50. doi:10.1212/CON.0000000000000271.
2. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(1):3–23. doi:10.1007/s12028-012-9695-z.

▶ 8. Which of the following is the most appropriate option for the treatment of this patient's hypertension?

A. amlodipine
B. clonidine
C. enalaprilat
D. esmolol
E. labetalol

The preferred response is **D (esmolol)**. Management of patients with hypertension and tachycardia should include short-acting agents such as nitroprusside or esmolol.[1] Esmolol has a half-life of 9 minutes. All of the other listed options are long-acting antihypertensive agents. Often, however, the hypertension and tachycardia are controlled with sedation alone.

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120.

The patient is started on an IV esmolol infusion for blood pressure control. An IV midazolam infusion is also started to blunt the hyperadrenergic component of the syndrome, and he is paralyzed with a onetime dose of vecuronium to eliminate excessive muscle activity, thereby helping control hyperthermia. He is sandwiched between cooling blankets below and above his body. Ice packs are placed over the femoral arteries and under the axillae. With these measures, his temperature is rapidly reduced to 38.6°C (101.5°F). He is given 1 liter of fluid and started on a maintenance rate of 200 mL/h. After 24 hours, the midazolam is held for a ''sedation holiday.'' On examination, he opens eyes to pain, fixates on the examiner, and tracks. He does not follow commands. Pupils are of normal size and reactive to light. He localizes pain in the upper extremities and briskly withdraws the lower extremities. Tone is mildly increased in the arms and moderately increased in the legs. He is diffusely hyperreflexic and has a few beats of clonus in the lower extremities. Rare multifocal myoclonic jerks are observed. Blood pressure, pulse, and temperature are normal.

▶ 9. Which of the following is the most likely expected time to recovery after removal of the serotonergic drugs in this patient?

A. 0 to 12 hours
B. 12 to 24 hours
C. 24 to 96 hours
D. 5 to 8 days
E. 9 to 12 days

The preferred response is **C (24 to 96 hours)**. In many cases of serotonin syndrome, the symptoms resolve within 24 hours of discontinuation of the serotonergic drugs and initiation of therapy,[1] but symptoms may persist in patients taking drugs with long elimination half-lives. The elimination half-life of paroxetine is 15 to 21 hours,[2] so although it was discontinued, it is expected to have some activity for 3 to 4 days after discontinuation. The patient was previously on paroxetine at home, and it was the addition of ondansetron (elimination half-life 4.6 hours; prolonged in hepatic impairment[2]) and fentanyl (elimination half-life 3 to 12 hours[2]) that precipitated the syndrome. These may take up to 60 hours to clear the system. His organ injuries (kidney and liver) may also result in reduced metabolism and excretion of the drugs and their metabolites.[3]

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.
2. Micromedex [database on the Internet]. Ann Arbor (MI): Truven Health Analytics. Subscription required to view. *www.micromedexsolutions.com*. Accessed June 12, 2016.
3. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014;21(1):108–113. doi:10.1007/s12028-013-9914-2.

▶ 10. The patient's wife expresses concern about his continued unresponsiveness and asks about the patient's neurologic prognosis should he survive, stating that he would not wish to survive with significant cognitive impairment. How should she be counseled?

A. he has a high probability of developing epilepsy
B. he is expected to make a good neurologic recovery
C. mild cognitive impairment is expected
D. outcomes are highly variable and cannot be reliably predicted
E. severe cognitive impairment is expected

The preferred response is **B (he is expected to make a good neurologic recovery)**. A spectrum of severity exists in serotonin syndrome, ranging from mild to lethal. Death is usually a result of the metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulopathy that develop as a consequence of prolonged severe hyperthermia. Survivors typically make a full neurologic recovery; in those who do have persistent disability, it typically results from underlying comorbid disease and critical illness. For example, in a retrospective study of 33 patients with serotonin syndrome, full functional recovery was noted in 55% at 3 months. In that study, the functional impairment in all patients with persistent disability was caused by underlying primary disease and comorbidities rather than by complications related to serotonin syndrome.[1]

1. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014;21(1):108–113. doi:10.1007/s12028-013-9914-2.

Forty-eight hours later (postoperative day 7), the patient is reliably following commands and is extubated. The myoclonus has fully resolved, and his neurologic examination has normalized. His acidosis and disseminated intravascular coagulation has resolved, and his kidney function is improving.

▶ 11. Which of the following is most appropriate regarding cyproheptadine therapy in this patient at this time?

A. continue for a total of 7 more days
B. continue for a total of 14 more days
C. continue for a total of 21 more days
D. continue for 30 more days
E. discontinue the drug

The preferred response is **E (discontinue the drug)**. Doses of 12 mg to 32 mg may be used in adults during a 24-hour period. This dose will bind 85% to 95% of serotonin receptors. A reasonable course is to begin with an initial dose of 12 mg of cyproheptadine followed by 2 mg scheduled every 2 hours. As the patient improves, this may be transitioned to 8 mg every 6 hours for ease of administration.[1] Little guidance exists for when to discontinue cyproheptadine; however, it is reasonable to discontinue it when the patient is no longer experiencing symptoms or demonstrating signs of serotonin syndrome and all previously administered serotonergic drugs are expected to have been metabolized and excreted, as is the case with this patient.

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–1120. doi:10.1056/NEJMra041867.

Cyproheptadine is discontinued. The patient continues to recover over several days. He and his wife express concern about discontinuing his SSRI. They state he has a history of severe depression and had an excellent response to paroxetine.

▶ 12. How should this patient be counseled regarding future SSRI use?

A. all serotonergic drugs should be avoided indefinitely
B. any future SSRI use should be avoided and his physician consulted regarding an alternative class of antidepressant
C. the patient is now considered to have an allergy to paroxetine and should try an alternative SSRI under the direction of his physician
D. resuming paroxetine in 2 to 4 weeks is probably safe if concomitant use of other serotonergic drugs is avoided
E. SNRIs have a lower risk of resulting in recurrence of serotonin syndrome

The preferred response is **D (resuming paroxetine in 2 to 4 weeks is probably safe if concomitant use of other serotonergic drugs is avoided)**. Data to guide resumption of antidepressants following an episode of serotonin syndrome are limited; however, a retrospective study of 33 intensive care unit patients with serotonin syndrome found that all but one of the 32 survivors had been restarted on a serotonergic agent (typically an antidepressant) upon last follow-up with no recurrences of serotonin syndrome. The average interval from diagnosis of serotonin syndrome to reintroduction of a serotonergic drug was 21.6 days.[1] While serotonin syndrome has been reported to occur after only one dose of an SSRI, it is important to remember that it was the addition of other serotonergic drugs that precipitated the syndrome in this patient. Cases must be judged on an individual basis; however, future avoidance of any antidepressant with serotonergic activity is probably an overreaction for the majority of cases and may result in substantial harm for patients who depend on antidepressants for treatment of depression and other neurologic or psychiatric conditions.

Caution should be exercised going forward when any drug is added to the medication regimen of a patient who has experienced serotonin syndrome, and the addition of a second serotonergic drug in a patient already receiving one should be avoided. Careful consideration of the risk of recurrent serotonin syndrome should be weighed against the potential for benefit when the addition of a serotonergic drug is being considered and an alternative drug class selected when possible. Serotonin syndrome is an adverse drug reaction and not an allergy. It can result from therapeutic drug use, intentional self-poisoning, or interactions between multiple drugs with serotonergic activity. No evidence supports the statement that SNRIs have a lower risk of recurrent serotonin syndrome than SSRIs.

1. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014;21(1):108–113. doi:10.1007/s12028-013-9914-2.

The patient is discharged home and resumes his paroxetine after 3 weeks. He does not experience any recurrence of symptoms.

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Neurology of Systemic Disease
List of Abbreviations

AChR	Acetylcholine receptor
ACR	American College of Rheumatology
ADEM	Acute disseminated encephalomyelitis
AED	Antiepileptic drug
AF	Atrial fibrillation
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AIDS	Acquired immunodeficiency syndrome
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANA	Antinuclear antibody
ANCA	Antineutrophil cytoplasmic antibody
ANNA-1	Antineuronal nuclear antibody type 1
ANNA-2	Antineuronal nuclear antibody type 2
ARCH	Aortic Arch Related Cerebral Hazard [trial]
ATPase	Adenosine triphosphatase
BUN	Blood urea nitrogen
CASPR2	Contactin associated protein-like 2
CCP	Cyclic citrullinated peptide
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CK	Creatine kinase
CLIPPERS	Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CMAP	Compound muscle action potential
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Coenzyme A
CREST	Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia [syndrome]
CSF	Cerebrospinal fluid
CT	Computed tomography
DADS	Distal acquired demyelinating symmetric [neuropathy]
DKA	Diabetic ketoacidosis
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
FDA	US Food and Drug Administration
FDG	Fludeoxyglucose
FDG-PET	Fludeoxyglucose positron emission tomography
FLAIR	Fluid-attenuated inversion recovery
GABA	γ-Aminobutyric acid
GAD65	Glutamic acid decarboxylase 65
GFAP	Glial fibrillary acidic protein
GVHD	Graft versus host disease
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
ICD-10-CM	*International Classification of Diseases, Tenth Revision, Clinical Modification*
IFE	Immunofixation electrophoresis
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
IgM	Immunoglobulin M
IM	Intramuscular
INR	International normalized ratio
IRIS	Immune reconstitution inflammatory syndrome
ISHEN	International Society for Hepatic Encephalopathy and Nitrogen Metabolism
IV	Intravenous
IVIg	Intravenous immunoglobulin
MAG	Myelin-associated glycoprotein
MCA	Middle cerebral artery
MCV	Mean corpuscular volume
mGluR5	Metabotropic glutamate receptor 5
MGUS	Monoclonal gammopathy of undetermined significance
MOG	Myelin oligodendrocyte glycoprotein
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Multiple sclerosis
MTHFR	Methylenetetrahydrofolate reductase
NMDA	*N*-methyl-D-aspartate
NMO	Neuromyelitis optica
NORSE	New-onset refractory status epilepticus
NSAID	Nonsteroidal anti-inflammatory drug
NTOCC	National Transitions of Care Coalition
PALE	Posttransplant acute limbic encephalitis
PCA-1	Purkinje cell cytoplasmic antibody type 1
PCR	Polymerase chain reaction
PEP	Protein electrophoresis
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PET	Positron emission tomography
PFO	Patent foramen ovale
PML	Progressive multifocal leukoencephalopathy
PNPO	Pyridoxal 5'-phosphate oxidase
PNS	Peripheral nervous system
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes [syndrome]
PRES	Posterior reversible encephalopathy syndrome
RA	Rheumatoid arthritis
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
REM	Rapid eye movement
RLS	Restless legs syndrome
RNA	Ribonucleic acid
RoPE	Risk of Paradoxical Embolism [score]
RPR	Rapid plasma reagin
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SIFE	Serum immunofixation
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SNAP	Sensory nerve action potential
SNRI	Serotonin norepinephrine reuptake inhibitor
SPEP	Serum protein electrophoresis
SSA	Sjögren syndrome A
SSB	Sjögren syndrome B
SSRI	Selective serotonin reuptake inhibitor
T3	Triiodothyronine
T4	Thyroxine
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
UIFE	Urine immunofixation
UPEP	Urine protein electrophoresis
VDRL	Venereal Disease Research Laboratory [test]
VEGF	Vascular endothelial growth factor
VGKC	Voltage-gated potassium channel
VZV	Varicella-zoster virus